Obesity Reviews

WILEY | WORLD OBESITY

REVIEW OPEN ACCESS

Efficacy of Weight-Lowering Agents on Fat Distribution: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials

Xiuqi Qiao[1,2] | Weihao Wang[1] | Jiaming Cao[1,2] | Lixin Guo[1,2] | Qi Pan[1,2]

[1]Department of Endocrinology, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, China | [2]Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China

Correspondence: Lixin Guo (glx1218@163.com) | Qi Pan (panqi621@126.com)

Received: 12 June 2024 | **Revised:** 9 September 2025 | **Accepted:** 2 January 2026

Keywords: antiobesity agents | body fat distribution | network meta-analysis

ABSTRACT

Background: Pharmacotherapy offers a potential solution for individuals with overweight and obesity to decrease their body weight. However, there is limited knowledge of the effects of antiobesity agents on the distribution of body fat.

Methods: The PubMed, Embase, and Cochrane Library databases were reviewed for randomized controlled trials (RCTs) of weight-lowering drugs between inception and May 23, 2023. The main results were visceral and subcutaneous adipose tissue (VAT and SAT). Secondary outcomes were altered body weights and waist circumferences. For the statistical analysis, STATA 14.0 was utilized, and the frequentist method was used for random-effect network meta-analyses.

Results: A total of 39 articles including 41 RCTs with 2741 patients were included. GLP-1 receptor agonists and SGLT-2 inhibitors were observed to lower VAT (−0.90 [−1.32 to −0.47] and −0.66 [−1.22 to −0.10]) after a mean of 29.4 weeks, whereas only GLP-1 receptor agonists reduced SAT (−1.01 [−1.58 to −0.43]). Naltrexone-bupropion, GLP-1 receptor agonists, SGLT-2 inhibitors, and metformin were found to reduce body weight (−5.60 [−8.64 to −2.56] kg, −4.73 [−5.58 to −3.88] kg, −3.20 [−4.69 to −1.72] kg, and −1.93 [−3.01 to −0.85] kg). Lastly, waist circumference was decreased by GLP-1 receptor agonists, metformin, SGLT-2 inhibitors, and naltrexone–bupropion.

Conclusion: This analysis demonstrated that GLP-1 receptor agonists may have advantages over other antiobesity agents in reducing VAT and SAT. SGLT-2 inhibitors were more helpful to reduce VAT. The clinical significance relates to physicians being able to choose appropriate weight-loss agents in accordance with a patient's fat distribution.

1 | Introduction

According to World Health Organization estimates, worldwide, 39% of adults are overweight, and 13% are obese [1], with prevalence rising to over 40% in certain regions [2]. Obesity and overweight are major worldwide health concerns [3] that are linked to a broad spectrum of ailments, including type 2 diabetes (T2DM) and cardiovascular diseases [4, 5]. The hallmark of T2DM, apart from obesity and atherosclerosis, is insulin resistance. The distribution of fat plays a pivotal role in determining an individual's insulin sensitivity [6]. Visceral adipose tissue (VAT), found deep inside the abdominal cavity, and subcutaneous adipose tissue (SAT), placed beneath the skin, are the two main locations of adipose tissue in the body. Each has specific metabolic features [7]. Research has implicated VAT in the pathogenesis of numerous conditions,

The systematic review and meta-analysis protocols were registered on PROSPERO (CRD 42023437434) (Title: Effect of anti-obesity agents on fat distribution) (https://www.crd.york.ac.uk/PROSPERO/#recordDetails).

such as insulin resistance and disrupted glucose and lipid metabolism [7]. Moreover, an increase in VAT is a significant factor in assessing overall cardiovascular risk, elevating the likelihood of developing arterial hypertension and ischemic heart disease [7].

Five pharmacological treatments (orlistat, lorcaserin, liraglutide, naltrexone-bupropion, and phentermine-topiramate) have received approval for the long-term therapy of obesity in adult patients and are included in the 2016 guidelines released by the American Association of Clinical Endocrinology [4]. In 2020, however, lorcaserin was withdrawn due to cancer risk [8]. Semaglutide, a once weekly subcutaneous injection at a dosage of 2.4 mg, received FDA approval in 2021 as an auxiliary treatment together with a calorie-restricted diet and enhanced physical activity for the ongoing weight management [9]. Moreover, the antidiabetic drugs pramlintide, metformin, and SGLT-2 inhibitors have shown potential in the management of obesity [10]. Research shows that levocarnitine can significantly reduce body weight, BMI, and waist circumference, supporting its potential as an adjunct therapy for obesity management [11]. Although several drugs are FDA-approved for obesity, our review adopts a broader perspective to include other promising agents that are frequently used or investigated for their weight-loss and metabolic benefits, particularly focusing on their effects on VAT and SAT.

A research demonstrated that liraglutide effectively decreases visceral adipose tissue (VAT) [12]. Additionally, the study identified a significant correlation between VAT reduction and decreased levels of glycated hemoglobin following treatment. Various weight-reduction medications have the potential to alter body fat distribution by modulating lipid metabolism in different adipose depots, thereby ameliorating metabolic disturbances and macrovascular complications [13]. The influence of weight-reduction drugs on fat distribution has received little attention despite its significance in terms of insulin resistance, T2DM, and the risks of cardiovascular and cerebrovascular disease. Therefore, a network meta-analysis and systematic review of randomized controlled trials (RCTs) were conducted using antiobesity drugs, with an emphasis on fat distribution results.

2 | Methods

The analysis was conducted in line with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) criteria [14].

2.1 | Search Strategy

To ascertain the effects of antiobesity medicines on body fat distribution, the PubMed, Embase, and Cochrane Library databases were reviewed to May 23, 2023, using the Population, Intervention, Comparator, Outcomes, and Study (PICOS) design framework. The search technique included the following: keywords, Boolean operators (AND/OR), truncation symbols, and medical subject heading (MeSH) phrases. SGLT-2 inhibitors, metformin, pramlintide, GLP-1 receptor agonists, levocarnitine, naltrexone-bupropion, orlistat, lorcaserin, phentermine-topiramate, RCTs, and fat distribution were among the terms that were searched. A detailed study plan is provided in the Supporting Information. With EndNote X9, duplicated records were eliminated. Reviewers worked in pairs and used EndNote X9 to screen titles and abstracts before moving on to full-text papers. Information on the settings and designs of the studies, indicators, baseline patient data, interventions, and findings was collected. Disagreements were settled through discussion or consultation with a third investigator.

2.2 | Inclusion Criteria and Data Extraction

Eligible RCTs compared the effects of pharmacological agents with weight-reducing properties against a placebo or another active agent. This included FDA-approved antiobesity medications (e.g., orlistat, liraglutide, naltrexone-bupropion, phentermine-topiramate, and semaglutide) as well as other drugs that have been investigated for adipose tissue reduction (e.g., pramlintide, metformin, and SGLT-2 inhibitors, levocarnitine). Studies were required to report absolute or percentage changes in VAT and SAT between baseline/pretreatment and posttreatment without language restriction. To expand the search range, no restrictions were set on dose or duration of treatment, as well as clinical population. The exclusion of the trials was based on (i) studies using animals in place of human trials; (ii) conference abstracts, editorials, commentaries, letters, interviews, or reviews; (iii) the absence of a control group, as in studies containing one experimental group; and (iv) insufficient VAT and SAT data.

2.3 | Data Gathering and Registered Procedures

Studies meeting the criteria above were gathered as potential candidates. The selected papers provided the data source and setting, participants, total number, study design, intervention, study duration, body mass index (BMI), and markers of fat distribution, such as VAT and SAT, weight, and waist circumference.

Ethical approval for the investigation was waived because the data were collected from articles written by other researchers. The procedures for the meta-analysis and systematic review were registered on PROSPERO (CRD 42023437434).

2.4 | Risk-of-Bias Assessment

Bias risk was determined independently by two reviewers with the Cochrane Collaboration technique. The tool used seven source types and six domains, namely, bias linked to performance (blinding personnel and participants), detection (blinding to outcome), selection (randomization and concealment of allocation), attrition (incomplete outcomes), reporting (selective coverage), and others (e.g., funding sources). There were three classifications for each risk of bias analysis domain: low, unclear, and high. If the study used appropriate randomization and concealment, the selection bias risk was deemed minimal. If the

research was blinded to both participants and the individuals administering the therapy, a low risk of performance bias was considered. Blinding in outcome evaluation with no subjective influence from the evaluator suggested low detection bias risk. If the data were complete or if the missing information was comparable between the groups or deemed insufficient to affect the outcome, attrition bias was considered low. By comparing protocols and research reports, it was possible to ascertain whether an outcome had been reported selectively by accounting for the likelihood of reporting bias.

2.5 | Statistical Analysis

To evaluate the relative influences of antiobesity medications on fat distribution, a frequentist random-effect network meta-analysis was combined with a network meta-analysis. Data analysis was done via STATA 14, and RevMan 5.4 was utilized to generate graphs representing bias risk and network evidence.

Because some continuous variables had different units in different articles, the standardized mean difference (SMD) with standard deviation (SD) was applied for assessment of the influence of antiobesity agents on fat distribution including VAT and SAT. An SMD represents the difference between groups in terms of the number of standard deviations. For example, an SMD of −0.5 would indicate that the mean value in the treatment group is 0.5 standard deviations lower than the mean in the control group. The mean difference (MD) with SD was used to assess the influences of antiobesity agents on weight and waist circumference. The study outcomes all needed the number of participants for each study arm, the SD of the mean change, and the abstraction of the mean change from baseline. When variance estimates were not provided as an SD, the SD was computed for mean change using the recommended strategies.

The consistency and inconsistency of the included studies were examined. In each closed loop of evidence, the concurrence between direct and indirect estimates was determined with node-splitting techniques. A $p > 0.05$ was observed as a sign of strong consistency, but a $p \leq 0.05$ denoted inconsistent results. When significant differences were detected, the underlying causes were found by examining the relevant study in more detail.

Several sensitivity tests were undertaken to determine the reliability of the final results, including (i) exclusion of studies that did not report BMI at baseline; (ii) exclusion of studies with fewer than 50 patients; (iii) exclusion of studies lasting fewer than 24 weeks; and (iv) exclusion of all research that used DXA. The asymmetry of the funnel plot was examined to determine small-study effects, including publication bias.

Each treatment's rank probability was calculated using the surface under the cumulative ranking (SUCRA) curve. SUCRA, which was equal to 1 or 0 when the therapy was the best or worst, respectively, was a percentage that represented the probability of the treatment being the most successful in the absence of uncertainty regarding the result. Higher SUCRA values indicate that a treatment regimen is at the highest level or highly effective, resulting in the optimal intervention for the outcome measure.

3 | Results

3.1 | Literature Search

Of the 631 retrieved articles, 95 satisfied the requirements for inclusion. Following the exclusion of 56 articles, a total of 39 eligible studies [12, 15–52] were finally enrolled in the analysis, comparing placebo with six antiobesity agents (SGLT-2 inhibitors, orlistat, naltrexone-bupropion, levocarnitine, metformin, and GLP-1 receptor agonists). Of these, the studies by Pasquali et al. [15] and Kadowaki et al. [16] included two different RCTs. Figure 1 depicts a flowchart of the study selection procedure. The mean values for age, length of therapy, and starting weight were 50.8 years, 29.4 weeks, and 86.8 kg, respectively. The trial sample size ranged from 18 to 360. Table S1 contains the characteristics of these studies, including the total number, BMI, participants, research duration, data source and setting, and intervention. Of the 41 RCTs, 15 RCTs consisted of patients with T2DM, 7 RCTs consisted of participants with polycystic ovary syndrome (PCOS), and 13 RCTs consisted of patients with overweight or obesity.

3.2 | Risk of Bias

Figures S1 and S2 display the bias risk for each study. The primary issues were the low reported degrees of blinding for the outcome assessors, investigators, and participants. Out of the 41 trials, 21 (51.2%) had a low bias risk in terms of randomization, whereas 20 (48.8%) had a low likelihood of bias in terms of allocation concealment. Blinding for participants and investigators was reported in 28 trials (68.3%), and blinding for outcome evaluation was reported in 24 trials (58.5%). A low likelihood of attrition bias was detected in 34 trials (82.9%), whereas minimal risk from selective outcome reporting was found in 37 studies (90.2%).

3.3 | Main Outcomes

VAT data were reported in 40 trials consisting of 2689 patients (Figure 2A). Compared with placebo, administration of SGLT-2 inhibitors and GLP-1 receptor agonists resulted in markedly lower VAT (−0.90 [−1.32 to −0.47] and −0.66 [−1.22 to −0.10], respectively), whereas no statistically significant changes were found following orlistat, naltrexone–bupropion, metformin, and levocarnitine treatment (Figure 3A). The SUCRA score indicated that SGLT-2 inhibitors and GLP-1 receptor agonists were among the top three most effective drugs (Figure S3A).

SAT data were reported in 28 trials consisting of 1682 patients (Figure 2B). Figure 3B illustrates that only GLP-1 receptor agonists decreased SAT when compared to a placebo (−1.01 [−1.58 to −0.43]), whereas no statistically significant effects were observed for SGLT-2 inhibitors, orlistat, naltrexone-bupropion, metformin, and levocarnitine. The SUCRA value indicated

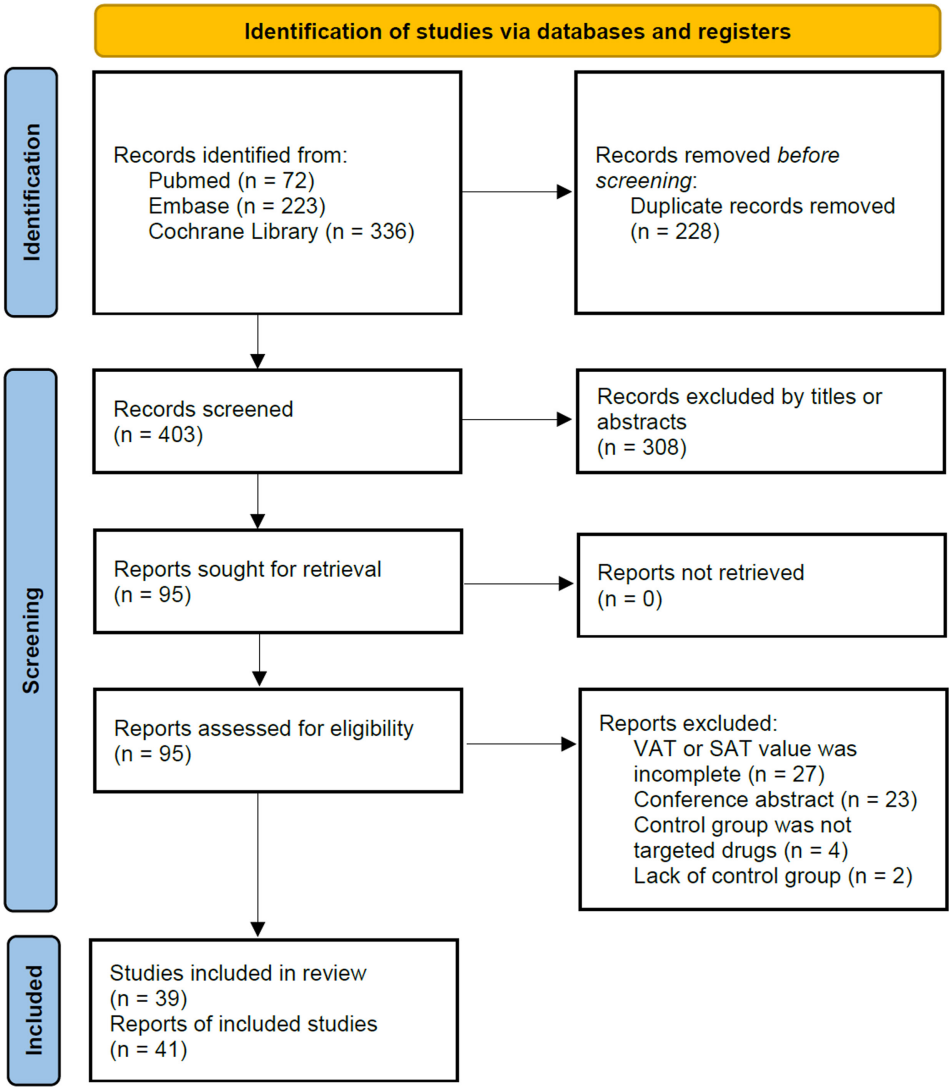

FIGURE 1 | Flowchart of the study selection process.

that the most effective drugs were GLP-1 receptor agonists (Figure S3B).

3.4 | Secondary Outcomes

Weight measurements were documented in a total of 33 investigations, involving a sample size of 2235 individuals (Figure 2C). Weight loss was observed after naltrexone-bupropion, GLP-1 receptor agonists, SGLT-2 inhibitors, and metformin treatment (−5.60 [−8.64 to −2.56] kg, −4.73 [−5.58 to −3.88] kg, −3.20 [−4.69 to −1.72] kg, and −1.93 [−3.01 to −0.85] kg, respectively) relative to the placebo, whereas no marked weight changes were reported following orlistat and levocarnitine treatment (Figure 3C). GLP-1 receptor agonists, SGLT-2 inhibitors, and naltrexone-bupropion were found to be most effective according to the SUCRA score (Figure S3C).

Waist circumference was reported in 26 trials consisting of 1860 patients (Figure 2E). Waist circumference was found to be reduced by medication with GLP-1 receptor agonists, naltrexone-bupropion, SGLT-2 inhibitors, and metformin compared to placebo (−4.89 [−5.42 to −4.36] cm, −3.50 [−6.41 to −0.59] cm, −2.96 [−4.99 to −0.92] cm, and −1.18 [−1.41 to −0.95] cm, respectively), whereas levocarnitine had no statistically significant effect (Figure 3D). The SUCRA score revealed that naltrexone-bupropion, SGLT-2 inhibitors, and GLP-1 receptor agonists ranked as the three most efficacious medications (Figure S3D).

3.5 | Heterogeneity and Inconsistency Tests

Using the node-splitting method, we examined overall network inconsistencies and heterogeneity. No significant inconsistencies between direct and indirect observations were detected. Similarly, no local inconsistencies were observed (Figure S5).

Loop inconsistency analysis revealed that 95% CI of the closed loop formed by each intervention for VAT, SAT, weight, and waist circumference was approximately 0 (Figure S6), indicating essential consistency between direct and indirect comparisons.

In sensitivity analyses, after excluding studies, results similar to the primary analyses were found (Figure S7). After (i) exclusion

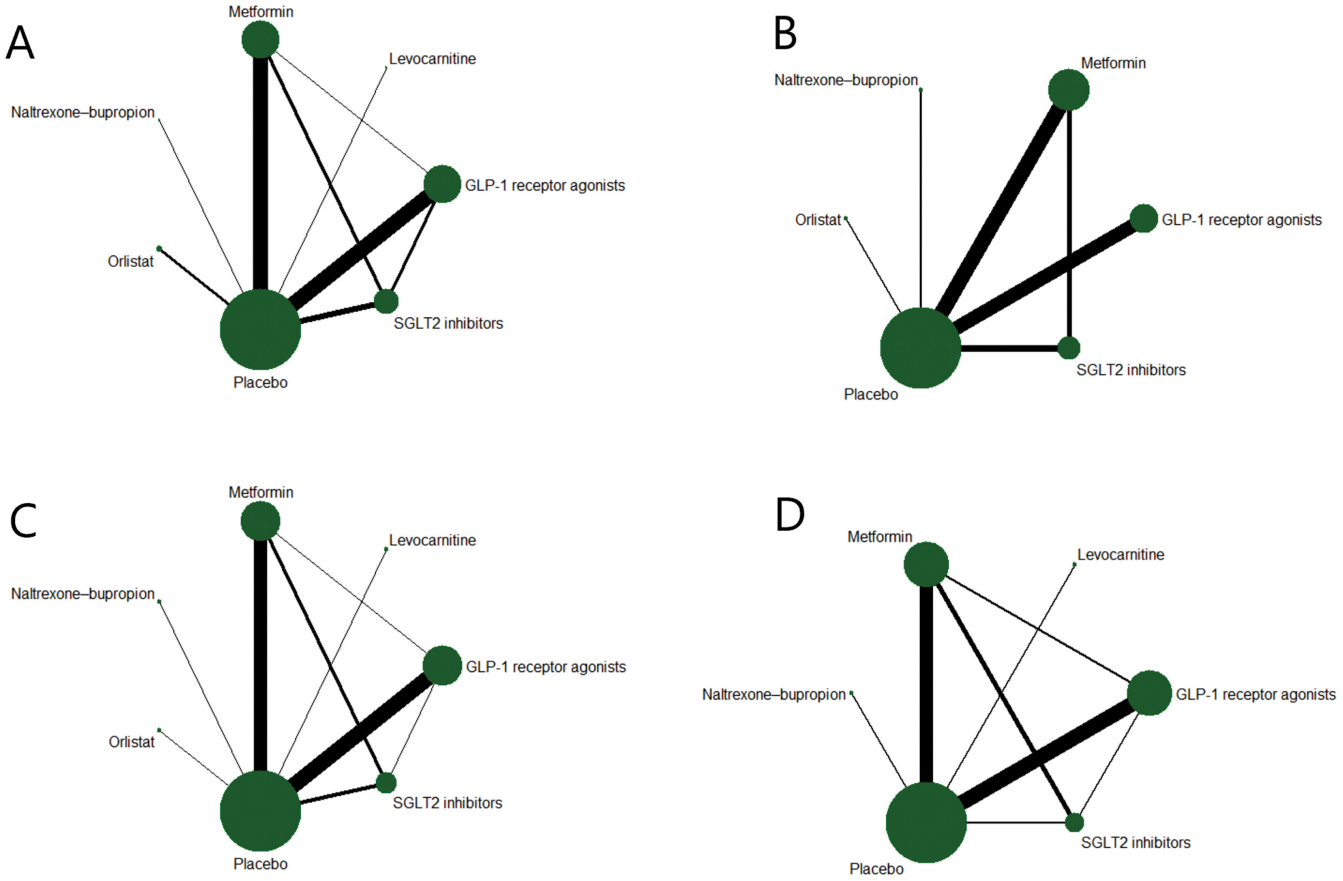

FIGURE 2 | A network plot showing the trials assessing antiobesity medications for various outcomes. (A) VAT, (B) SAT, (C) weight, and (D) waist circumference. Circle sizes are proportional to participant numbers in specific treatment types. Line thickness indicates numbers of studies using the drugs. Metformin and GLP-1 receptor agonists were the treatments most often compared to placebo.

of studies that did not report BMI at baseline; (ii) exclusion of studies with fewer than 50 patients; (iii) studies with a treatment duration shorter than 24 weeks were excluded; and (iv) all research that used DXA were excluded, the GLP-1 receptor agonists and SGLT-2 inhibitors decreased VAT, whereas only GLP-1 receptor agonists reduced SAT. Upon analyzing the funnel plot symmetry, no indications of small study effects were found (Figure S8).

4 | Discussion

Here, a network meta-analysis was used to investigate the impact of antiobesity medications on the distribution of body fat. Although only six types of antiobesity drugs (SGLT-2 inhibitors, orlistat, naltrexone-bupropion, levocarnitine, metformin, and GLP-1 receptor agonists) were analyzed, it was found that GLP-1 receptor agonists markedly decreased both VAT and SAT, as well as body weight and waist circumference relative to other antidiabetic drugs or the placebo.

There is increasing evidence linking VAT with the development of numerous health conditions. Excessive VAT has been found to interfere with adipocytokine production, contributing to the characteristic pathologies of nonalcoholic steatohepatitis and metabolic syndrome [14]. Furthermore, the active metabolic activity of VAT has been identified as a significant source of cellular inflammation in individuals suffering from obesity and coronary heart disease [53]. Karllson et al. [54] reported that VAT could independently predict T2DM risk. Hence, it is recommended to select drugs that modulate both glucose metabolism and reduce VAT for patients with T2DM. Here, preliminary evidence is provided to suggest that GLP-1 receptor agonists can alter fat distribution patterns.

Multiple hypotheses have been proposed to elucidate the processes by which GLP-1 receptor agonists impact the distribution of fat and promote weight reduction. Findings suggest that diabetic patients with obesity have greater densities of GLP-1 receptors on intra-abdominal, relative to subcutaneous fat cells. This higher receptor expression suggests that GLP-1 may induce fat cell lipolysis by activating these receptors. Notably, studies have indicated that GLP-1 at high concentrations enhances adipocyte lipolysis, whereas at lower concentrations, it can stimulate adipocyte lipogenesis. Second, GLP-1 slows emptying of the stomach through interaction with gastrointestinal GLP-1 receptors [55].

Our findings indicated that SGLT-2 inhibitors effectively reduced VAT but not SAT. Each sensitivity analysis corresponded with the overall results. The results contradicted a prior meta-analysis that found that when the follow-up period was more than 6 months, therapy with SGLT-2 inhibitors significantly decreased VAT and SAT [56]. Furthermore, another study indicated

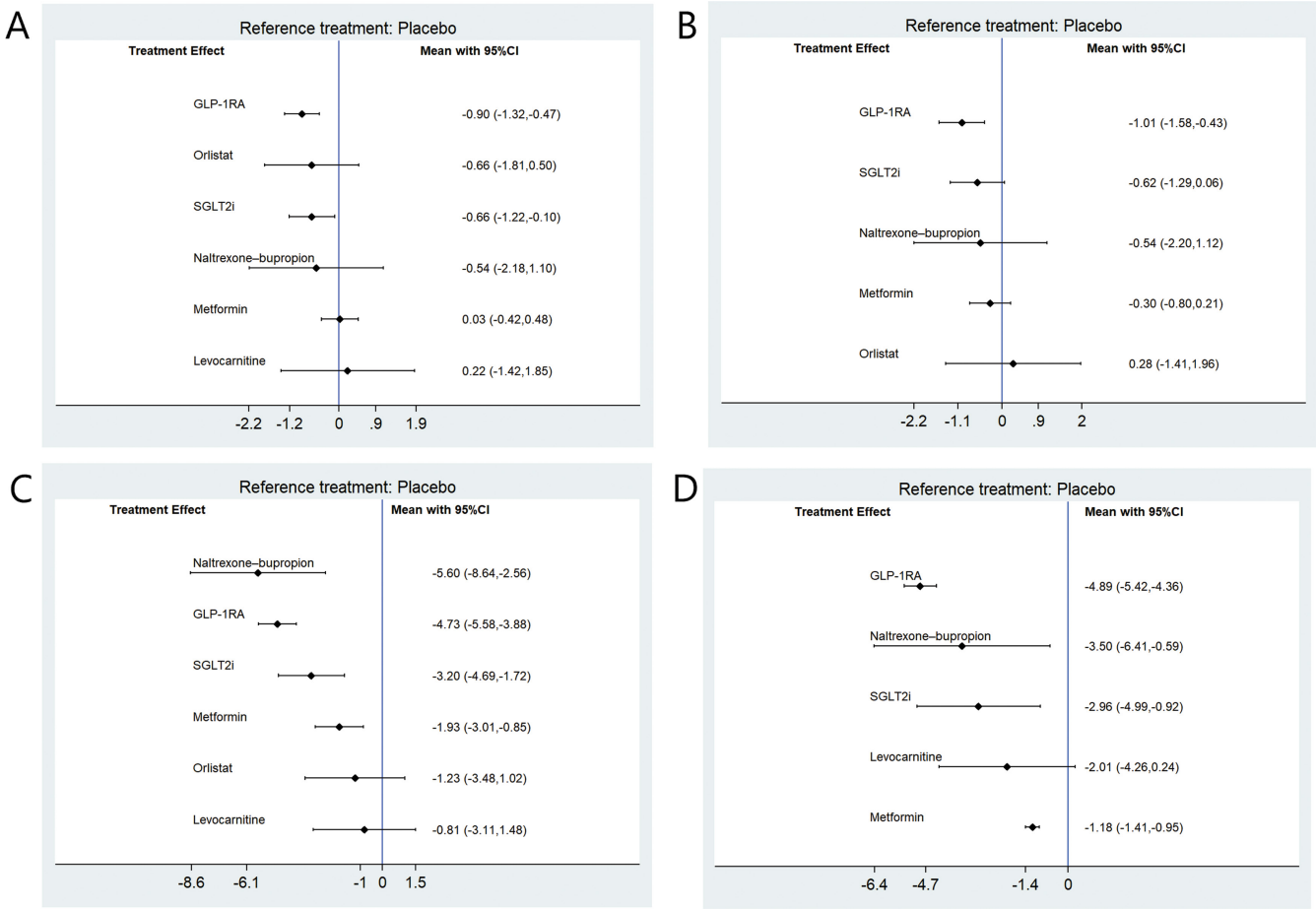

FIGURE 3 | Network meta-analysis results for the outcomes compared with placebo. (A) VAT, (B) SAT, (C) weight, and (D) waist circumference. The study utilized the standardized mean difference (SMD) along with 95% confidence intervals for the assessment of medication effectiveness in terms of reducing fat distribution. It also utilized the mean difference (MD) along with 95% confidence intervals to evaluate the impact of weight and waist circumference.

that treatment with SGLT-2 inhibitors led to weight loss in the first week of treatment, which stabilized after 6 months [57]. Because this analysis included four trials in which patients received follow-up times of less than six months, it is likely that these shorter treatment times account for the discrepancies between our findings and these earlier reports.

It is not known whether SGLT-2 inhibitors decrease fat tissue. However, in animal experiments, SGLT-2 inhibitors can activate the liver-brain-adipose axis and initiate the glycogen depletion signal, which in turn stimulates lipolysis [58]. Lauritsen et al. [59] indicated that SGLT-2 inhibitors decrease GLUT4 expression in adipose tissue, perhaps due to a reduction in glycerol synthesis and a change in substrate use away from lipid storage and glucose oxidation. Undoubtedly, SGLT-2 inhibitors' cardioprotective effects are linked to a reduction in adipose tissue and various pleiotropic effects that reduce indicators associated with cardiovascular disease risk [60].

The results of GLP-1 receptor agonists' effects on VAT align with those of a prior network meta-analysis [61], showing that GLP-1 receptor agonists significantly decreased VAT. Other medication possibilities that were included in this investigation were naltrexone-bupropion and phentermine-topiramate. It was observed that the approved medications' effects on weight reduction in the current research aligned with results from an earlier network meta-analysis [62]. The combination of phentermine-topiramate, naltrexone-bupropion, and GLP-1 receptor agonists resulted in the greatest decrease in body weight in that study. Although the current data support these conclusions, the trial demonstrating that phentermine–topiramate decreased VAT and SAT was not included here.

This is the first network meta-analysis to justify the effectiveness of antiobesity medications on VAT and SAT. It discusses the most recent data highlighting the advantages of weight-lowering medications on fat distribution. The current study has some limitations. Although the inclusion of experimental controls that were not exclusively placebos may have introduced substantial heterogeneity into the analysis, no marked inconsistencies were seen between indirect and direct evidence. The period of follow-up in the studies varied. Nevertheless, the sensitivity analyses revealed no significant variations in outcomes across different follow-up periods. GLP-1 receptor agonists and SGLT-2 inhibitors demonstrated comparable results after excluding studies with brief treatment durations. In addition, only a few studies of 41 RCTs recorded the changes of lean mass and we did not evaluate fat distribution within the context of lean mass loss

(or gains), which can impact health. Further large-sample RCTs are needed for verification of these results.

5 | Conclusions

As one of the most widespread health concerns globally, the public health and economic burdens of obesity have garnered growing attention from patients, regulatory bodies, and biopharmaceutical companies. Research and development efforts are actively pursuing weight-reduction medications that target various points in its pathophysiology. Given the strong association between fat distribution and metabolic syndrome, according to this network meta-analysis, SGLT-2 inhibitors and GLP-1 receptor agonists are useful in lowering VAT, which may have therapeutic advantages. Doctors can choose appropriate weight-loss drugs according to the patient's fat distribution. To provide further support for lowering the risk of long-term consequences in obesity, more clinical research focusing on fat distribution is required.

Author Contributions

X.Q. consulted literature and wrote the manuscript. L.G. and Q.P. designed the review. W.W. and C.M. assisted with writing and revising the manuscript. All authors contributed to the article and approved the submitted version.

Acknowledgments

No AI or AI-assisted technologies were used in the writing of this manuscript.

Funding

This work was supported by the Capital's Funds for Health Improvement and Research (2024-1-4053), the CAMS Innovation Fund for Medical Sciences (2021-I2M-1-050), the Noncommunicable Chronic Diseases-National Science and Technology (2024ZD0531900 and 2024ZD0531905), and the National High Level Hospital Clinical Research Funding (BJ-2024-144).

Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. "Obesity and Overweight," https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.

2. M. Watanabe, R. Risi, F. de Giorgi, et al., "Obesity Treatment Within the Italian National Healthcare System Tertiary Care Centers: What Can We Learn?" *Eating and Weight Disorders* 26, no. 3 (2021): 771–778.

3. NCD Risk Factor Collaboration, "Trends in Adult Body-Mass Index in 200 Countries From 1975 to 2014: A Pooled Analysis of 1698 Population Based Measurement Studies With 19·2 Million Participants," *Lancet* 387 (2016): 1377–1396.

4. W. T. Garvey, J. I. Mechanick, E. M. Brett, et al., "American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive Clinical Practice Guidelines for Medical Care of Patients With Obesity," *Endocrine Practice* 22, no. suppl 3 (2016): 1–203.

5. G. A. Bray, G. Frühbeck, D. H. Ryan, and J. P. H. Wilding, "Management of Obesity," *Lancet* 387 (2016): 1947–1956.

6. S. E. Kahn, R. L. Hull, and K. M. Utzschneider, "Mechanisms Linking Obesity to Insulin Resistance and Type 2 Diabetes," *Nature* 444, no. 7121 (2006): 840–846.

7. A. Shuster, M. Patlas, J. H. Pinthus, and M. Mourtzakis, "The Clinical Importance of Visceral Adiposity: A Critical Review of Methods for Visceral Adipose Tissue Analysis," *British Journal of Radiology* 85 (2012): 1–10.

8. J. Sharretts, O. Galescu, S. Gomatam, E. Andraca-Carrera, C. Hampp, and L. Yanoff, "Cancer Risk Associated With Lorcaserin—The FDA's Review of the CAMELLIA-TIMI 61 Trial," *New England Journal of Medicine* 383 (2020): 1000–1002.

9. "FDA Approves New Drug Treatment for Chronic Weight Management, First Since 2014," https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treatment-chronic-weight-management-first-2014.

10. D. H. Bessesen and L. F. van Gaal, "Progress and Challenges in Anti-Obesity Pharmacotherapy," *Lancet Diabetes and Endocrinology* 6 (2018): 237–248.

11. F. Hamedi-Kalajahi, M. Zarezadeh, M. Malekahmadi, et al., "The Effect of the L-Carnitine Supplementation on Obesity Indices: An Umbrella Meta-Analysis," *International Journal for Vitamin and Nutrition Research* 95, no. 2 (2025): 40033.

12. H. J. van Eyk, E. H. M. Paiman, M. B. Bizino, et al., "A Double-Blind, Placebo-Controlled, Randomised Trial to Assess the Effect of Liraglutide on Ectopic Fat Accumulation in South Asian Type 2 Diabetes Patients," *Cardiovascular Diabetology* 18 (2019): 87.

13. L. Zhao, C. Zhu, M. Lu, et al., "The Key Role of a Glucagon-Like Peptide-1 Receptor Agonist in Body Fat Redistribution," *Journal of Endocrinology* 240, no. 2 (2019): 271–286.

14. A. Schaffler, J. Schölmerich, and C. Büchler, "Mechanisms of Disease: Adipocytokines and Visceral Adipose Tissue–Emerging Role in Nonalcoholic Fatty Liver Disease," *Nature Clinical Practice. Gastroenterology & Hepatology* 2 (2005): 273–280.

15. R. Pasquali, A. Gambineri, D. Biscotti, et al., "Effect of Long-Term Treatment With Metformin Added to Hypocaloric Diet on Body Composition, Fat Distribution, and Androgen and Insulin Levels in Abdominally Obese Women With and Without the Polycystic Ovary Syndrome," *Journal of Clinical Endocrinology and Metabolism* 85, no. 8 (2000): 2767–2774.

16. T. Kadowaki, J. Isendahl, U. Khalid, et al., "STEP 6 Investigators. 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 and Endocrinology* 10, no. 3 (2022): 193–206.

17. J. Bolinder, Ö. Ljunggren, J. Kullberg, et al., "Effects of Dapagliflozin on Body Weight, Total Fat Mass, and Regional Adipose Tissue Distribution in Patients With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin," *Journal of Clinical Endocrinology and Metabolism* 97 (2012): 1020–1031.

18. A. J. M. Brown, S. Gandy, R. McCrimmon, J. G. Houston, A. D. Struthers, and C. C. Lang, "A Randomized Controlled Trial of

Dapagliflozin on Left Ventricular Hypertrophy in People With Type Two Diabetes: The DAPA-LVH Trial," *European Heart Journal* 41 (2020): 3421–3432.

19. G. Carreras-Badosa, A. Gómez-Vilarrubla, B. Mas-Parés, et al., "A 24-Month Metformin Treatment Study of Children With Obesity: Changes in Circulating GDF-15 and Associations With Changes in Body Weight and Visceral Fat," *Pediatric Obesity* 17 (2022): e12845.

20. S. Frøssing, M. Nylander, E. Chabanova, et al., "Effect of Liraglutide on Ectopic Fat in Polycystic Ovary Syndrome: A Randomized Clinical Trial," *Diabetes, Obesity & Metabolism* 20 (2018): 215–218.

21. A. Gambineri, L. Patton, A. Vaccina, et al., "Treatment With Flutamide, Metformin, and Their Combination Added to a Hypocaloric Diet in Overweight-Obese Women With Polycystic Ovary Syndrome: A Randomized, 12-Month, Placebo-Controlled Study," *Journal of Clinical Endocrinology and Metabolism* 91 (2006): 3970–3980.

22. H. Ghanim, M. Batra, K. Green, et al., "Liraglutide Treatment in Overweight and Obese Patients With Type 1 Diabetes: A 26-Week Randomized Controlled Trial; Mechanisms of Weight Loss," *Diabetes, Obesity & Metabolism* 22 (2020): 1742–1752.

23. W. Guo, W. Tian, L. Lin, et al., "Liraglutide or Insulin Glargine Treatments Improves Hepatic Fat in Obese Patients With Type 2 Diabetes and Nonalcoholic Fatty Liver Disease in Twenty-Six Weeks: A Randomized Placebo-Controlled Trial," *Diabetes Research and Clinical Practice* 170 (2020): 108487.

24. J. Harreiter, I. Just, M. Leutner, et al., "Combined Exenatide and Dapagliflozin Has No Additive Effects on Reduction of Hepatocellular Lipids Despite Better Glycaemic Control in Patients With Type 2 Diabetes Mellitus Treated With Metformin: EXENDA, a 24-Week, Prospective, Randomized, Placebo-Controlled Pilot Trial," *Diabetes, Obesity & Metabolism* 23 (2021): 1129–1139.

25. M. Jensterle, V. Salamun, T. Kocjan, et al., "Short Term Monotherapy With GLP-1 Receptor Agonist Liraglutide or PDE 4 Inhibitor Roflumilast Is Superior to Metformin in Weight Loss in Obese PCOS Women: A Pilot Randomized Study," *Journal of Ovarian Research* 8 (2015): 32.

26. R. Kohli, A. Shevitz, S. Gorbach, and C. Wanke, "A Randomized Placebo-Controlled Trial of Metformin for the Treatment of HIV Lipodystrophy," *HIV Medicine* 8 (2007): 420–426.

27. M. Koshizaka, K. Ishikawa, R. Ishibashi, et al., "Comparing the Effects of Ipragliflozin Versus Metformin on Visceral Fat Reduction and Metabolic Dysfunction in Japanese Patients With Type 2 Diabetes Treated With Sitagliptin: A Prospective, Multicentre, Open-Label, Blinded-Endpoint, Randomized Controlled Study (PRIME-V Study)," *Diabetes, Obesity & Metabolism* 21 (2019): 1990–1995.

28. A. Latva-Rasku, M. J. Honka, J. Kullberg, et al., "The SGLT2 Inhibitor Dapagliflozin Reduces Liver Fat but Does Not Affect Tissue Insulin Sensitivity: A Randomized, Double-Blind, Placebo-Controlled Study With 8-Week Treatment in Type 2 Diabetes Patients," *Diabetes Care* 42 (2019): 931–937.

29. J. A. Requena-Ibáñez, C. G. Santos-Gallego, A. Rodriguez-Cordero, et al., "Mechanistic Insights of Empagliflozin in Nondiabetic Patients With HFrEF: From the EMPA-TROPISM Study," *JACC Heart Fail* 9 (2021): 578–589.

30. K. Shirai, T. Fujita, M. Tanaka, et al., "Efficacy and Safety of Lipase Inhibitor Orlistat in Japanese With Excessive Visceral Fat Accumulation: 24-Week, Double-Blind, Randomized, Placebo-Controlled Study," *Advances in Therapy* 36 (2019): 86–100.

31. A. Vanderheiden, L. B. Harrison, J. T. Warshauer, et al., "Mechanisms of Action of Liraglutide in Patients With Type 2 Diabetes Treated With High-Dose Insulin," *Journal of Clinical Endocrinology and Metabolism* 101 (2016): 1798–1806.

32. D. Weghuber, A. Forslund, H. Ahlström, et al., "A 6-Month Randomized, Double-Blind, Placebo-Controlled Trial of Weekly Exenatide in Adolescents With Obesity," *Pediatric Obesity* 15 (2020): e12624.

33. C. Hadigan, C. Corcoran, N. Basgoz, B. Davis, P. Sax, and S. Grinspoon, "Metformin in the Treatment of HIV Lipodystrophy Syndrome: A Randomized Controlled Trial," *Journal of the American Medical Association* 284 (2000): 472–477.

34. S. M. Agarwal, R. Panda, K. A. Costa-Dookhan, et al., "Metformin for Early Comorbid Glucose Dysregulation and Schizophrenia Spectrum Disorders: A Pilot Double-Blind Randomized Clinical Trial," *Translational Psychiatry* 11 (2021): 219.

35. F. Baghban, M. Hosseinzadeh, H. Mozaffari-Khosravi, A. Dehghan, and H. Fallahzadeh, "The Effect of L-Carnitine Supplementation on Clinical Symptoms, C-Reactive Protein and Malondialdehyde in Obese Women With Knee Osteoarthritis: A Double Blind Randomized Controlled Trial," *BMC Musculoskeletal Disorders* 22 (2021): 195.

36. A. Bechlioulis, G. Markozannes, I. Chionidi, et al., "The Effect of SGLT2 Inhibitors, GLP1 Agonists, and Their Sequential Combination on Cardiometabolic Parameters: A Randomized, Prospective, Intervention Study," *Journal of Diabetes and Its Complications* 37 (2023): 108436.

37. M. B. Bizino, I. M. Jazet, P. de Heer, et al., "Placebo-Controlled Randomised Trial With Liraglutide on Magnetic Resonance Endpoints in Individuals With Type 2 Diabetes: A Pre-Specified Secondary Study on Ectopic Fat Accumulation," *Diabetologia* 63 (2020): 65–74.

38. M. Cai, X. Shao, F. Xing, et al., "Efficacy of Canagliflozin Versus Metformin in Women With Polycystic Ovary Syndrome: A Randomized, Open-Label, Noninferiority Trial," *Diabetes, Obesity and Metabolism* 24 (2022): 312–320.

39. H. Chehrehgosha, M. R. Sohrabi, F. Ismail-Beigi, et al., "Empagliflozin Improves Liver Steatosis and Fibrosis in Patients With Non-Alcoholic Fatty Liver Disease and Type 2 Diabetes: A Randomized, Double-Blind," *Placebo-Controlled Clinical Trial. Diabetes Therapy* 12 (2021): 843–861.

40. A. Gambineri, C. Pelusi, S. Genghini, et al., "Effect of Flutamide and Metformin Administered Alone or in Combination in Dieting Obese Women With Polycystic Ovary Syndrome," *Clinical Endocrinology* 60 (2004): 241–249.

41. H. He, Z. Zhao, J. Chen, et al., "Metformin-Based Treatment for Obesity-Related Hypertension: A Randomized, Double-Blind, Placebo-Controlled Trial," *Journal of Hypertension* 30 (2012): 1430–1439.

42. M. Koshizaka, K. Ishikawa, R. Ishibashi, et al., "Comparison of Visceral Fat Reduction by Ipragliflozin and Metformin in Elderly Type 2 Diabetes Patients: Sub-Analysis of a Randomized-Controlled Study," *Diabetes Therapy* 12 (2021): 183–196.

43. J. R. Larsen, L. Vedtofte, M. S. L. Jakobsen, et al., "Effect of Liraglutide Treatment on Prediabetes and Overweight or Obesity in Clozapine- or Olanzapine-Treated Patients With Schizophrenia Spectrum Disorder: A Randomized Clinical Trial," *JAMA Psychiatry* 74 (2017): 719–728.

44. N. Matikainen, S. Söderlund, E. Björnson, et al., "Liraglutide Treatment Improves Postprandial Lipid Metabolism and Cardiometabolic Risk Factors in Humans With Adequately Controlled Type 2 Diabetes: A Single-Centre Randomized Controlled Study," *Diabetes, Obesity and Metabolism* 21 (2019): 84–94.

45. R. J. McCrimmon, A. M. Catarig, J. P. Frias, et al., "Effects of Once-Weekly Semaglutide vs Once-Daily Canagliflozin on Body Composition in Type 2 Diabetes: A Substudy of the SUSTAIN 8 Randomised Controlled Clinical Trial," *Diabetologia* 63 (2020): 473–485.

46. I. J. Neeland, S. P. Marso, C. R. Ayers, et al., "Effects of Liraglutide on Visceral and Ectopic Fat in Adults With Overweight and Obesity at High Cardiovascular Risk: A Randomised, Double-Blind, Placebo-Controlled, Clinical Trial," *Lancet Diabetes and Endocrinology* 9 (2021): 595–605.

47. I. Pernicova, S. Kelly, S. Ajodha, et al., "Metformin to Reduce Metabolic Complications and Inflammation in Patients on Systemic Glucocorticoid Therapy: A Randomised, Double-Blind, Placebo-Controlled,

Proof-of-Concept, Phase 2 Trial," *Lancet Diabetes and Endocrinology* 8 (2020): 278–291.

48. M. Tiikkainen, R. Bergholm, A. Rissanen, et al., "Effects of Equal Weight Loss With Orlistat and Placebo on Body Fat and Serum Fatty Acid Composition and Insulin Resistance in Obese Women," *American Journal of Clinical Nutrition* 79 (2004): 22–30.

49. J. Lord, R. Thomas, B. Fox, U. Acharya, and T. Wilkin, "The Effect of Metformin on Fat Distribution and the Metabolic Syndrome in Women With Polycystic Ovary Syndrome—A Randomised, Double-Blind, Placebo-Controlled Trial," *BJOG: An International Journal of Obstetrics and Gynaecology* 113 (2006): 817–824.

50. M. Mohan, S. Al-Talabany, A. McKinnie, et al., "A Randomized Controlled Trial of Metformin on Left Ventricular Hypertrophy in Patients With Coronary Artery Disease Without Diabetes: The MET-REMODEL Trial," *European Heart Journal* 40 (2019): 3409–3417.

51. B. Gaborit, P. Ancel, A. E. Abdullah, et al., "Effect of Empagliflozin on Ectopic Fat Stores and Myocardial Energetics in Type 2 Diabetes: The EMPACEF Study," *Cardiovascular Diabetology* 20 (2021): 57.

52. S. R. Smith, K. Fujioka, A. K. Gupta, et al., "Combination Therapy With Naltrexone and Bupropion for Obesity Reduces Total and Visceral Adiposity," *Diabetes, Obesity & Metabolism* 15 (2013): 863–866.

53. N. Alexopoulos, D. Katritsis, and P. Raggi, "Visceral Adipose Tissue as a Source of Inflammation and Promoter of Atherosclerosis," *Atherosclerosis* 233 (2014): 104–112.

54. T. Karlsson, M. Rask-Andersen, G. Pan, et al., "Contribution of Genetics to Visceral Adiposity and Its Relation to Cardiovascular and Metabolic Disease," *Nature Medicine* 25, no. 9 (2019): 1390–1395.

55. L. I. Shi, J. Zhu, P. Yang, et al., "Comparison of Exenatide and Acarbose on Intra-Abdominal Fat Content in Patients With Obesity and Type-2 Diabetes: A Randomized Controlled Trial," *Obesity Research & Clinical Practice* 11 (2017): 607–615.

56. X. Liu, Y. Chen, T. Liu, et al., "The Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Adipose Tissue in Patients With Type 2 Diabetes: A Meta-Analysis of Randomized Controlled Trials," *Front Endocrinol (Lausanne)* 14 (2023): 1115321.

57. S. P. Rajeev, D. J. Cuthbertson, and J. P. Wilding, "Energy Balance and Metabolic Changes With Sodium-Glucose Co-Transporter 2 Inhibition," *Diabetes, Obesity & Metabolism* 18 (2016): 125–134.

58. Y. Sawada, Y. Izumida, Y. Takeuchi, et al., "Effect of Sodium-Glucose Cotransporter 2 (SGLT2) Inhibition on Weight Loss Is Partly Mediated by Liver-Brain-Adipose Neurocircuitry," *Biochemical and Biophysical Research Communications* 493 (2017): 40–45.

59. K. M. Lauritsen, J. H. Voigt, S. B. Pedersen, et al., "Effects of SGLT2 Inhibition on Lipid Transport in Adipose Tissue in Type 2 Diabetes," *Endocrine Connections* 11, no. 4 (2022): e210558.

60. F. C. Sasso, V. Simeon, R. Galiero, et al., "The Number of Risk Factors Not at Target Is Associated With Cardiovascular Risk in a Type 2 Diabetic Population With Albuminuria in Primary Cardiovascular Prevention. Post-Hoc Anal NID-2 Trial," *Cardiovascular Diabetology* 21 (2022): 235.

61. H. Yan, C. Huang, X. Shen, et al., "GLP-1 RAs and SGLT-2 Inhibitors for Insulin Resistance in Nonalcoholic Fatty Liver Disease: Systematic Review and Network Meta-Analysis," *Front Endocrinol (Lausanne)* 13 (2022): 923606.

62. Q. Shi, Y. Wang, Q. Hao, et al., "Pharmacotherapy for Adults With Overweight and Obesity: A Systematic Review and Network Meta-Analysis of Randomised Controlled Trials," *Lancet* 399, no. 10321 (2022): 259–269.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:**Main characteristics of the included studies. CT, computed tomography; MRI, magnetic resonance imaging; DXA, dual-energy x-ray absorptiometry. **Figure S1:** Risk of bias graph. Review of authors' judgments about each risk of bias presented as percentages across all included studies. **Figure S2:** Quality assessment findings using Cochran risk of bias tool. Review of authors' judgments about each risk of bias for each included study. **Figure S3:** Ranking probabilities of different weight-lowering agents for different outcome indicators (A) VAT, (B) SAT, (C) weight and (D) waist circumference. Higher SUCRA values indicate that a treatment regimen is at the highest level or highly effective, resulting in the optimal intervention for the outcome measure. **Figure S4:** Netleague for network meta-analysis. The columns present the column drug class compared to the row drug class. The rows present the column drug class compared to the column drug class. The standardized mean difference (SMD) with 95% confidence intervals was used to assess the effect of anti-obesity agents on fat distribution including VAT and SAT. The mean difference (MD) with 95% confidence intervals was used to assess the effect of weight and waist circumference. **Figure S5:** Through node-splitting method, there is no evidence of overall network inconsistencies or heterogeneity between direct and indirect evidence, and there were no local inconsistencies. **Figure S6:** After the loop inconsistency analysis, the 95% CI of the closed loop formed by each intervention for VAT, SAT, weight and waist circumference contained 0, suggesting no significant inconsistency between direct and indirect comparisons. **Figure S7:** Multiple sensitivity analyses. **Figure S8:** Comparison-adjusted funnel plot of interventions. It was utilized for assessing included literature. Symmetrical plot represents the absence of publication bias.