Diabetes, Metabolic Syndrome and Obesity

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REVIEW

The Effects of Exercise Combined with Pharmacotherapy on Body Composition and Metabolic Parameters in Overweight/Obese Adults: A Meta-Analysis and Network Pharmacology Study

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Objective: Overweight and obesity are major global health issues. Traditional interventions have limited efficacy, while pharmacological treatments are hindered by side effects and weight rebound. This study evaluates the effects of combined exercise and medication on body composition and metabolic health in overweight/obese adults, using network pharmacology to explore potential synergistic mechanisms.

Methods: A systematic search of PubMed, EMBASE, Scopus, Web of Science, Medline, and Cochrane up to October 2025 identified 18 randomized controlled trials with 5,620 participants. Meta-analysis was performed using RevMan 5.4 and Stata 14. Outcomes included weight, BMI, body fat percentage, and metabolic markers. Network pharmacology was conducted using liraglutide and orlistat to identify shared targets and perform enrichment analysis.

Results: Combined exercise and medication significantly reduced weight (MD = −2.49, 95% CI: −3.83, −1.14), BMI (MD = −0.79, 95% CI: −1.25, −0.34), and body fat percentage (MD = −1.97, 95% CI: −3.76, −0.18) compared to exercise alone. The combined intervention also significantly reduced systolic and diastolic blood pressure and triglycerides. However, compared to medication alone, it showed only reductions in weight and BMI, with no significant improvements in lean body mass, HDL, LDL, or fasting glucose. Network pharmacology revealed 109 obesity-related targets, including IL1B, STAT3, and SIRT1, involved in inflammation, lipid metabolism, and energy regulation. GO/KEGG analysis showed enrichment in fatty acid metabolism and AMPK signaling pathways. These pathways were highly consistent with metabolic adaptations induced by exercise, suggesting potential synergistic effects between exercise and medication in metabolic regulation.

Conclusion: Combined exercise and medication significantly enhance weight loss in overweight/obese adults. Network pharmacology suggests that the IL1B-STAT3 inflammatory axis and SIRT1/CD36 lipid metabolism network may be central to the mechanisms. Future studies should explore the long-term efficacy and mechanistic specificity of different drug-exercise combinations.

Keywords: exercise intervention, medication, obesity, overweight, meta-analysis, network pharmacology analysis

Introduction

The global obesity epidemic has emerged as one of the most pressing public health challenges of the 21st century. According to data from the World Health Organization (WHO), the global adult obesity rate has more than doubled since 1990, while the adolescent obesity rate has increased nearly threefold. As of 2022, approximately 2.5 billion adults worldwide are overweight, with 890 million suffering from obesity.[1–3] Notably, the rise in obesity is particularly

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pronounced in rapidly urbanizing regions.[4] According to WHO criteria, overweight is defined as a body mass index (BMI) ≥25, and obesity is defined as BMI ≥30. Obesity is strongly associated with numerous chronic diseases, including type 2 diabetes, immune system disorders, cardiovascular diseases, hypertension, breast cancer, and colorectal cancer,[5–10] making it a major driver of the global increase in non-communicable diseases (NCDs). This, in turn, leads to significant reductions in quality of life, increased risk of premature death, and a heavy economic burden.[11–13] Therefore, establishing efficient and sustainable weight management strategies is of paramount importance.

Currently, the core interventions for overweight/obese adults primarily consist of lifestyle management (diet and exercise) and pharmacotherapy. Regular exercise serves as the foundation for weight management, offering a wide range of benefits, including increased energy expenditure, improved cardiorespiratory fitness, enhanced insulin sensitivity, maintenance of lean body mass, and improved psychological health.[14] Even without significant weight loss, exercise can notably improve metabolic health.[15,16] Numerous studies have confirmed that aerobic exercise effectively reduces blood pressure, blood lipids, and visceral fat.[17,18] However, relying solely on exercise typically results in moderate weight loss of 2–4 kg, which may be affected by compensatory mechanisms such as increased appetite or reduced non-exercise activity thermogenesis (NEAT), thereby diminishing the extent of weight loss.[19–22] To enhance weight management outcomes, pharmacological interventions are widely used as adjunctive measures. The main mechanisms of pharmacotherapy include: (1) appetite suppression, such as liraglutide and phentermine, which reduce energy intake by modulating neurotransmitters like norepinephrine, serotonin, and dopamine; (2) reduction of fat absorption, such as orlistat, which inhibits gastrointestinal lipase to reduce fat intake; (3) increased energy expenditure, such as sibutramine, which enhances sympathetic nervous system activity to promote lipolysis and thermogenesis.[23–26] Despite the clear advantages of pharmacotherapy for short-term weight loss, its long-term effectiveness is limited due to issues such as cost, side effects, decreased adherence, and weight rebound after discontinuation. Single-drug interventions alone are insufficient for achieving long-term weight maintenance.

Increasing evidence suggests that combined exercise and pharmacological interventions may offer superior weight loss effects and greater metabolic benefits. Previous studies have shown that adding medication to a diet and exercise regimen further enhances weight loss, improves body composition, and can increase patient adherence.[27–30] Exercise helps maintain lean body mass and improves fitness, while medications rapidly establish an energy deficit by reducing energy intake, creating a complementary, synergistic model. However, the existing evidence remains fragmented, making it difficult to determine the overall effect of combined interventions and the optimal combination. A key obstacle to the consistency of results is the significant heterogeneity in existing randomized controlled trials (RCTs). On one hand, there are vast differences in medication types, doses, administration frequencies, and treatment durations, including orlistat, phentermine/topiramate, naltrexone/bupropion, and various GLP-1 receptor agonists.[24,31–35] On the other hand, exercise prescriptions vary significantly in terms of type, intensity, frequency, supervision, and intervention period, all of which affect treatment outcomes.[36–39] This multidimensional heterogeneity in prescriptions has made it difficult to answer critical clinical questions: Is combined intervention generally superior to single interventions? Which medications and exercise modalities exhibit the best synergistic effects? What are the long-term effects? While combination therapies are widely used in clinical practice, there is still a lack of consistent, comprehensive evidence regarding the specific comparative outcomes of exercise and medication treatments.

In recent years, researchers have systematically explored the synergistic effects of different medication and exercise combinations, focusing on three main areas. First, GLP-1 receptor agonists (such as liraglutide) combined with structured exercise (including both aerobic and resistance training) show significant metabolic synergy. A randomized controlled trial by Sandsdal et al confirmed that combining exercise training with liraglutide treatment significantly reduced the severity of metabolic syndrome, visceral fat content, and systemic inflammatory markers, with mechanisms involving improved insulin sensitivity and alleviation of chronic inflammation.[40] Jensen et al further found that the combined regimen of exercise and GLP-1 receptor agonists was more effective in maintaining weight loss for up to one year after medication cessation (with about 6 kg less weight rebound compared to medication alone), underscoring the crucial role of exercise in long-term weight management.[41] Second, orlistat, which promotes weight loss by inhibiting gastrointestinal fat absorption, shows enhanced efficacy when combined with dietary control and regular exercise. A multicenter RCT by Chanoine et al indicated that orlistat combined with lifestyle interventions (including structured exercise)

resulted in statistically significant improvements in weight and body fat percentage in obese adolescents, although long-term effects still require further high-quality evidence.[42] Third, exercise prescription heterogeneity is an important variable influencing the effects of combined interventions. Willis et al found that aerobic training was most effective for fat reduction, while resistance training was crucial for maintaining lean body mass; combining both training types could optimize body composition synergistically.[43] Ho et al's 12-week intervention trial further confirmed that combined training outperformed single exercise modes in weight loss, fat reduction, and improvements in cardiorespiratory function.[44] The HEARTY trial by Sigal's team confirmed this conclusion in obese adolescents, demonstrating that aerobic, resistance, and combined training all effectively reduced overall fat and waist circumference, with the most significant benefits seen in participants with high adherence.[45] A meta-analysis by Liu et al also highlighted the significant advantages of a multimodal exercise regimen, combining aerobic and resistance training, in improving body composition and metabolic parameters in overweight/obese children and adolescents.[46] This literature stratification based on intervention types not only helps clarify the synergistic mechanisms of different drug-exercise combinations but also provides evidence-based support for the optimization of future personalized obesity treatment strategies.

Understanding the molecular basis of the combined effects of exercise and pharmacological treatments is essential for developing precise obesity intervention strategies. Exercise, as a powerful systemic metabolic stimulus, can simultaneously reshape the expression of thousands of genes, involving energy metabolism reprogramming, inflammation modulation, neuro-endocrine regulation, and mitochondrial function enhancement.[47–50] Pharmacological treatments, on the other hand, target specific receptors or metabolic enzymes (eg., GLP-1 receptors, pancreatic lipases, or the norepinephrine system), triggering downstream signals that produce more specific pharmacological effects.[23–25] Their combination may lead to complex interactions, such as pathway cross-talk, signal amplification, or compensatory effects. However, these "drug-exercise interaction networks" have not yet been systematically elucidated.[51,52] Although clinical trials have demonstrated the individual effects of exercise and pharmacological treatments, these studies have primarily focused on outcome measures, without delving into the underlying mechanisms of their combined interventions. The addition of network pharmacology could help bridge this gap, providing a novel perspective to generate mechanistic hypotheses. By integrating drug target databases, exercise-induced molecular changes, GO/KEGG pathway enrichment analyses, and protein-protein interaction (PPI) networks, network pharmacology can identify co-regulated molecular nodes, core targets, and potential synergistic mechanisms, providing a theoretical framework and testable hypotheses for the design of combined intervention strategies.[53–55] Previous systematic reviews have also suggested that multimodal interventions (diet + exercise + drugs) yield better long-term weight loss results compared to single interventions. However, poor adherence, inconsistent prescriptions, and diverse trial designs have led to inconclusive clinical conclusions.[56] Therefore, it is necessary to conduct rigorous and systematic evidence integration assessments based on current evidence.

Methods

Meta-Analysis Methodology

Registration and Guidelines

This systematic review has been prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42024604403.[57] The report of this systematic review and meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for literature search.[58]

Inclusion and Exclusion Criteria

Study Type

Randomized controlled trials (RCTs).

Study Population

Adult participants aged ≥18 years with overweight/obesity (BMI ≥ 25), regardless of nationality, ethnicity, gender, or age, who received both exercise interventions and pharmacological treatment (including exercise training or physical activity promotion combined with pharmacological agents).

Interventions

Intervention groups combined exercise interventions (aerobic exercise, resistance training, high-intensity interval training, etc.) with medication. The control groups received either exercise alone or pharmacotherapy alone.

Outcome Measures

The primary outcomes measured were body weight, BMI, body fat percentage, waist circumference, hip circumference, and lean body mass. The secondary outcomes included systolic blood pressure, diastolic blood pressure, fasting blood glucose, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides (TG).

Exclusion Criteria

Studies were excluded if they involved duplicate publications, trials that only tested pharmacological treatments or exercise alone, or studies without accessible raw data or full text concerning key outcomes. Also excluded were studies that focused on outcomes unrelated to body composition and metabolic measures, such as cognitive function or quality of life, and those combining exercise with other treatments (eg., bariatric surgery).

Literature Search Strategy

A comprehensive computer-based search will be conducted in the following databases: MEDLINE, EMBASE, Cochrane Library, Scopus, Web of Science, and PubMed. The search will cover the period from database inception to October 2025. The search terms will combine both subject headings and free text keywords, adjusted to suit each database's characteristics (as shown in Supplementary Table 1). Additionally, the reference lists of included studies will be examined to supplement relevant data. English search terms include: "Anti-Obesity Agents", "Obesity", "Overweight", "Adults", "Exercise interventions", and others (detailed search strategies are listed in Supplementary Table 2).

Study Selection and Data Extraction

Two independent researchers will screen the literature, extract relevant data, and cross-check results. Discrepancies will be resolved through discussion or consultation with a third researcher. Initial screening will involve reviewing titles to exclude obviously irrelevant studies, followed by abstract and full-text assessments to determine eligibility. If necessary, original authors will be contacted via Email or phone to obtain critical information not provided in the published studies. Data to be extracted include: the first author and publication year, study population characteristics (eg., age, sample size), intervention details (including exercise type and the name/dosage of medications), and primary outcome measures.

Risk of Bias Assessment in Included Studies

The risk of bias in included studies will be independently assessed by two researchers using the Cochrane Risk of Bias 5.1.0 tool. This will evaluate various bias risks, with particular attention to random sequence generation, allocation concealment, blinding, outcome assessment, and selective reporting. Disagreements will be resolved through consensus.

Statistical Analysis

Meta-analysis will be performed using RevMan 5.4 and Stata 14.0 software. The choice between fixed-effects and random-effects models will depend on whether a common true effect across studies is assumed, not solely on the I^2 value. When I^2 <50% (indicating moderate or low heterogeneity), a fixed-effects model will be used, while a random-effects model will be applied for I^2 ≥50% (high heterogeneity), excluding clinical heterogeneity factors (eg., differences in drug types and exercise interventions) to ensure accurate results. The DerSimonian-Laird estimator will be used for the random-effects model to ensure reproducibility and consistency of the analysis. Data processing will standardize median or quartile data to mean and standard deviation when necessary. When outcome measures are identical in measurement and units, the Mean Difference (MD) will be used as the effect size; otherwise, Standardized Mean Difference (SMD) will be employed, with a 95% confidence interval (95% CI) for statistical inference. The I^2 statistic will be used to quantify heterogeneity; if I^2 ≥50%, a random-effects model will be applied; if I^2 <50%, a fixed-effects model will be used.[59] Subgroup analyses will further explore sources of heterogeneity, such as exercise type, intensity, and supervision

levels.[60] The significance level for the meta-analysis will be set at $\alpha = 0.05$. Sensitivity analysis (one-by-one exclusion method) will be performed to assess the robustness of results, and Egger's linear regression test will be used to detect publication bias.

Assessment of the Quality of Evidence for Each Outcome

The quality of evidence for the outcomes was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, and a Summary of Results table was generated for comparison. The system was used to assess the quality of evidence for outcomes in randomised controlled trials. Using this system, randomised controlled trials are initially high level evidence and randomised trial evidence is downgraded to moderate, low or even very low quality evidence depending on the presence of five factors: risk of bias, inconsistency, indirectness, imprecision and publication bias.[61] We have included a summary of results and reported the reasons for our judgements in each of these domains as footnotes in the summary of results table.

Network Pharmacology Analysis Methodology

Databases and Software

This study integrates data from multiple databases to construct a network pharmacology analysis framework for drug-disease-target interactions. Drug-related information is sourced from PubChem (https://pubchem.ncbi.nlm.nih.gov/), which provides compound structure and SMILES data; target predictions are obtained from SwissTargetPrediction (http://www.swisstargetprediction.ch/), SEA (https://sea.bkslab.org/), and ChEMBL (https://www.ebi.ac.uk/chembl/); disease-related targets are retrieved from GeneCards (http://www.genecards.org), OMIM (https://omim.org/), TTD (https://db.idrblab.net/ttd/), and DrugBank (https://go.drugbank.com/). Protein-protein interaction (PPI) analysis is conducted using STRING (https://string-db.org/), and target annotations are standardized via UniProt (http://www.uniprot.org). Functional enrichment analyses are carried out in DAVID (https://david.ncifcrf.gov/). Network visualization is done using Cytoscape 3.9.1, and association analysis is completed via the WeiShengXin platform (http://www.bioinformatics.com.cn/). All databases are queried for their latest versions to ensure up-to-date and authoritative results.

Obtaining Drug Targets

The SMILES expressions of Orlistat and Liraglutide are extracted from the PubChem database and input into SwissTargetPrediction, SEA, and ChEMBL for target prediction. Only potential targets with a prediction probability (Probability) greater than 0 will be selected as candidates. These predicted targets will then be standardized using UniProt (species: Homo sapiens), forming a standardized target set for each drug.

Identification of Potential Targets for Overweight and Obesity

Keywords such as "overweight" and "obesity" are used to search for relevant disease targets from the GeneCards, OMIM, TTD, and DrugBank databases. For GeneCards, the Relevance Score is used as the selection threshold (above the median value) to increase specificity. All relevant genes from the other databases are included. After integration and deduplication, the disease-related target set for overweight/obesity is obtained.

Identification of Common Genes

The drug target predictions and disease targets are uploaded to the MicroLife platform for Venn analysis to obtain the common targets, ie., the "drug-overweight/obesity" intersection targets. Venn diagrams are created online to visually represent target overlap.

Constructing Drug-Target-Disease Network

Using the intersection target data, a drug-target-disease interaction network is built using Cytoscape 3.9.1. This network demonstrates the polypharmacological nature of the drug's action and reveals the topological positions of key targets, highlighting the potential mechanisms of the drug's effect on overweight/obesity.

Building Protein-Protein Interaction (PPI) Network

The common targets are input into the STRING database, with Homo sapiens as the species and a confidence threshold of 0.4 (medium confidence). The PPI data is then downloaded and analyzed in Cytoscape 3.9.1 using network topology analysis tools, calculating Betweenness Centrality (BEC), Closeness Centrality (CLC), and Degree Centrality (DEC). The core hub targets are selected based on the criteria that all three parameters are greater than or equal to the median value, leading to the identification of key targets for the drug's effects.

GO Biological Process Enrichment and KEGG Pathway Analysis

To systematically analyze the potential molecular mechanisms of combined drug and exercise interventions, the intersection targets of the drug and obesity-related differentially expressed genes are imported into the DAVID database for functional annotation analysis. Gene Ontology (GO) analysis is performed in three categories: Biological Process (BP), Cellular Component (CC), and Molecular Function (MF) to identify key biological functions involved in the targets. Furthermore, KEGG pathway enrichment analysis is conducted in DAVID to identify the potential signaling pathways and metabolic networks involved. All enrichment analyses are based on hypergeometric tests, and P-values are corrected using the Benjamini–Hochberg method with an FDR <0.05 threshold for statistical significance. The results are visualized using the MicroLife platform.

Results

Meta-Analysis Results

Literature Screening Process and Results

A total of 912 articles were initially identified, and after a stepwise screening process, 18 RCTs were finally included, comprising 5620 participants.[62–79] The literature screening process and results are shown in Figure 1.

Basic Characteristics and Risk of Bias Assessment of the Included Studies

Table 1 summarizes the basic characteristics of the included studies. These 18 studies, published between 2011 and 2024, originated from multiple countries: five studies from the United States,[67,70,71,73,74] two each from Iran,[62,75] Turkey,[77,78] and Denmark,[65,76] and one each from Austria,[63] Germany,[64] Norway,[66] Mexico,[68] India,[69] Ireland,[72] and Brazil.[79] The total sample size (n = 5620) ranged from 24 to 4008 participants, with the percentage of female participants varying from 0% to 100%. The average age of participants was between 18 and 75 years, and the BMI ranged from 25 to 45 kg/m^2. The predominant exercise intervention type was aerobic exercise, although some studies included combined aerobic and resistance training. Only five studies reported specific exercise intensity, and half of the exercise interventions were supervised. The pharmacological treatments used varied widely, with liraglutide and orlistat being the most frequently studied. The dosage of these medications typically increased over the course of the intervention. The Cochrane Risk of Bias tool was used to assess the risk of bias in the included studies.[61] Among the 18 studies, the randomization quality was deemed adequate for all, with six studies providing information on allocation concealment. Eight studies employed a double-blind design, and 17 described blinding in outcome assessments. The outcome data in all studies were complete, and nine studies did not report selective outcomes. However, five studies were considered to have a high risk of other biases due to funding from pharmaceutical companies.[80] The risk of bias assessment results are shown in Figure 2.

Analysis of Key Indicators

This meta-analysis integrated data from RCTs investigating the combined effects of exercise and pharmacological interventions on overweight/obese adults. The results of body weight, BMI, body fat percentage, lean body mass, waist circumference, hip circumference, and metabolic parameters (blood pressure, blood lipids, and blood glucose) are summarized in Table 2. The forest plots for the primary outcomes are provided in Supplementary Figures 1–15.

Body Weight and BMI

The combination of exercise and pharmacological interventions led to a significant reduction in body weight compared to exercise alone (MD = −2.49, 95% CI: −3.83, −1.14). In subgroup analysis, the combination of exercise with liraglutide or

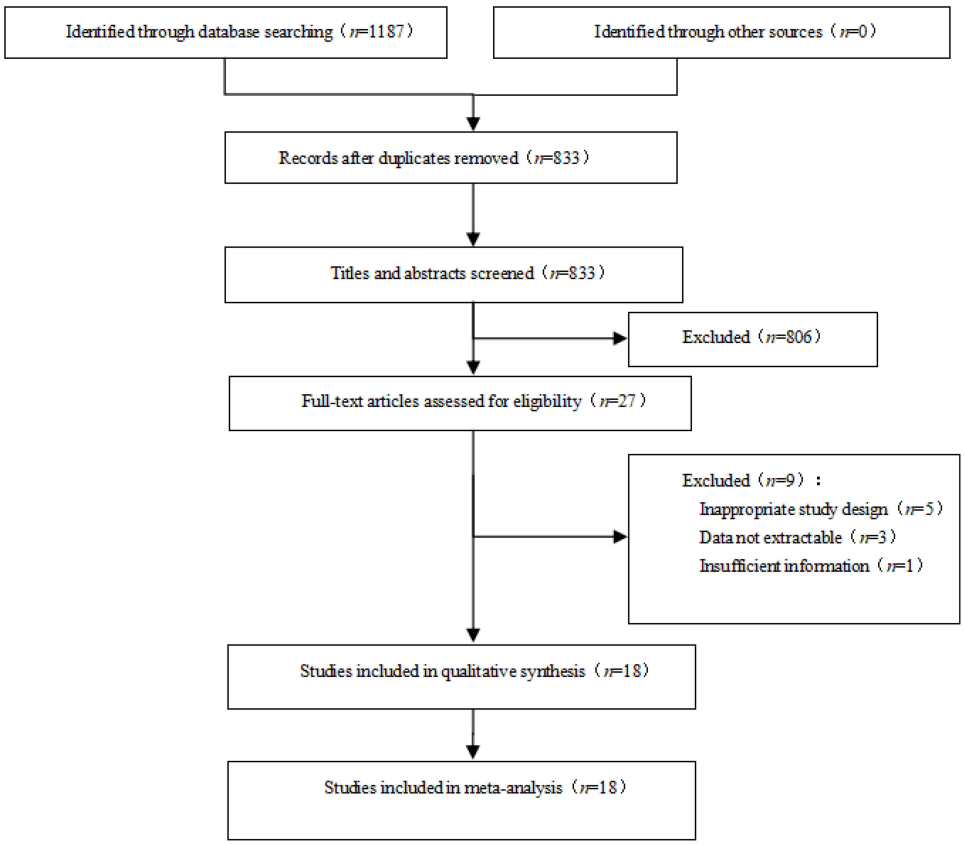

Figure 1 Flowchart of study selection and inclusion. Number of articles retrieved per database: PubMed (n = 151), Web of Science (n = 478), Cochrane Library (n = 158), Scopus (n = 263), EMBASE (n = 10), MEDLINE (n = 127). Excluded studies and reasons are listed in Supplementary Table 3.

orlistat (L+O) resulted in a more pronounced weight loss effect (MD = −4.37, 95% CI: −7.95, −0.79). When compared to pharmacological interventions alone, combined interventions also significantly reduced body weight (MD = −1.80, 95% CI: −3.34, −0.26). BMI also showed a downward trend, with combined interventions significantly reducing BMI compared to exercise alone (MD = −0.79, 95% CI: −1.25, −0.34). After excluding high-heterogeneity studies in a subgroup analysis (≥16 weeks, excluding Birketvedt 2000), this effect was more pronounced (MD = −0.96, 95% CI: −1.21, −0.70). Compared to pharmacological interventions, combined interventions also showed a notable improvement in BMI (MD = −0.93, 95% CI: −1.44, −0.42).

Body Fat Percentage and Lean Body Mass

Combined interventions significantly reduced body fat percentage compared to exercise alone (MD = −1.97, 95% CI: −3.76, −0.18). Subgroup analysis revealed that combined aerobic and resistance training (A+R) significantly reduced body fat percentage (MD = −1.96, 95% CI: −2.59, −1.33). However, there were no significant changes in lean body mass, regardless of whether combined interventions were compared to exercise or pharmacological treatments.

Waist and Hip Circumference

No significant changes were observed in waist circumference or hip circumference when combined interventions were compared to exercise alone.

Blood Pressure Parameters

Combined interventions significantly reduced systolic blood pressure (MD = −0.74, 95% CI: −1.34, −0.14) and diastolic blood pressure (MD = −0.45, 95% CI: −0.87, −0.03) compared to exercise alone, after excluding the Birketvedt 2000 study.

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Table 1 Basic Characteristics of Included Studies

Included Study	Country	Age (Years)	Sample Size (Female)	BMI (kg/m^2)	Exercise Type	Medication	Dose (mg/day)	Intervention Duration	Supervision	Outcomes
Nakhaee 2013[62]	Iran	31 ± 8.8	40(30)	30.1 ± 2.6	Not reported	Acarbose	150-300	5 months	Unsupervised	②
Ofner 2014[63]	Austria	30-60	40(32)	25-45	A+R	Salacia extract	600	4 weeks	Supervised	①②③
Pokhis 2015[64]	Germany	21-75	115(79)	26-45	A	Polyglucosamine	1700	26 weeks	Unsupervised	①②④
Mensberg 2017[65]	Denmark	>18	33(23)	>25	A+R	Liraglutide	0.6–1.8	16 weeks	Supervised	①②③⑦⑧
Birketvedt 2000[66]	Norway	18-59	60(55)	>25	A	Cimetidine	Not reported	42 months	Unsupervised	①②③④⑤
Blackman 2016[67]	America	18-64	359(101)	≥30	Not reported	Liraglutide	0.6–3.0	32 weeks	Unsupervised	①②④⑥⑦⑧⑨
Carlos Poston 2003[68]	Mexico	21-65	108(108)	≥27	A	Orlistat	360	12 months	Unsupervised	①②④⑥⑦⑧⑨⑩⑪⑫
Dixit 2018[69]	India	21-50	140(58)	27-29.9	A	LI85008F	900	16 weeks	Unsupervised	①②③④⑦⑧⑩⑪⑫
DeFina 2011[70]	America	30-60	128(88)	26-40	A	Omega-3	15,000	6 months	Supervised	①②④⑤
Fidler 2011[71]	America	18-65	4008(3194)	27-45	Not reported	Lorcaserin	10/20	52 weeks	Unsupervised	①②③④⑦⑧
Grannell 2021[72]	Ireland	54.4 ± 10.7	78(38)	43 ± 6	A+R	Liraglutide	0.6–3.0	16 weeks	Supervised	①
Grube 2013[73]	America	18-60	125(93)	25-35	A	Litramine IQP G-002AS	1000	12 weeks	Unsupervised	②
Zenk 2005[74]	America	25-45	47(33)	≥27	A	Lean System 7	3910.2	8 weeks	Unsupervised	①②④⑤⑦⑧
Zakavi 2018[75]	Iran	33.63 ± 4.78	40(0)	>30	A	Chavir extract	Not reported	12 weeks	Supervised	①②③
Lundgren 2021[76]	Denmark	18-65	195(124)	32-43	A	Liraglutide	0.6–3.0	12 months	Supervised	①
Colak 2004[77]	Turkey	37.9 ± 8.86	24 (21)	38.0 ± 4.87	A	Orlistat	360	4 weeks	Supervised	①②③⑥
Ozcelik 2015[78]	Turkey	39.6 ± 2.71	28 (28)	39.1 ± 2.5	A	Orlistat	360	12 weeks	Supervised	①②③⑥
Bagherzadeh-Rahmani 2024[79]	Brazil	20-32	52(0)	36.15 ± 1.43	A+R	Tirzepatide	0.36/0.71	6 weeks	Supervised	①②③④

Notes: A, Aerobic exercise; A+R, Combined aerobic and resistance training. The primary outcomes included: ①Body weight; ②BMI; ③Body fat percentage; ④Waist circumference; ⑤Hip circumference; ⑥Lean body mass. The secondary outcomes included: ⑦SBP; ⑧DBP; ⑨Fasting glucose; ⑩HDL; ⑪ LDL; ⑫ TG.

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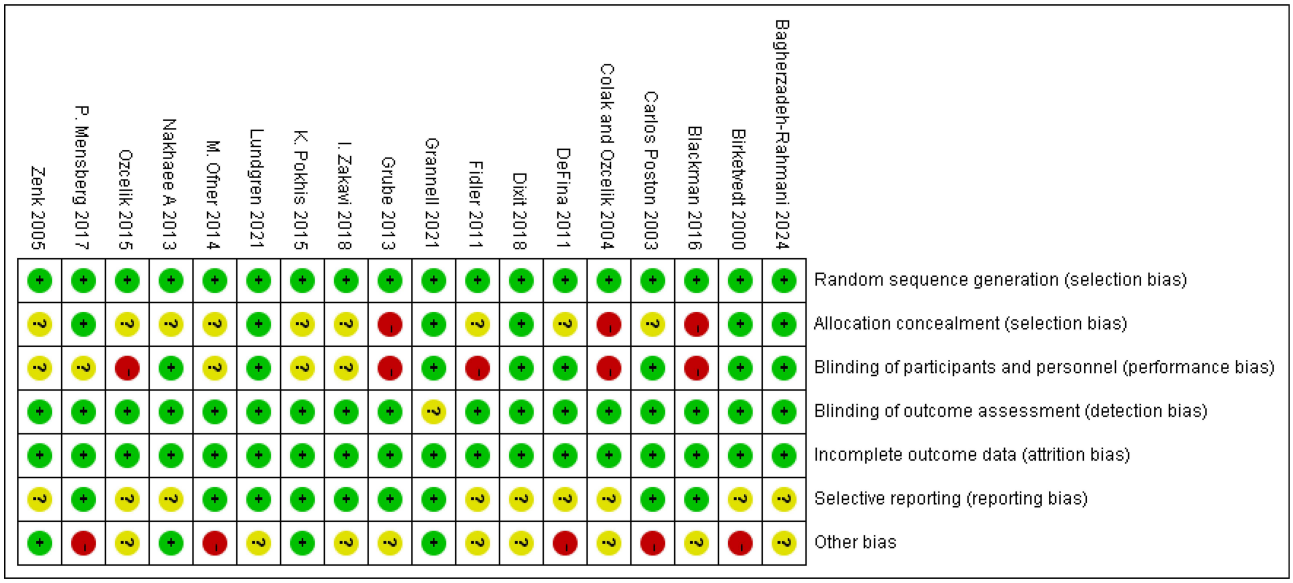

Figure 2 Risk of Bias Assessment of Included Studies. The methodological quality of the included randomized controlled trials was independently evaluated by two reviewers using the Cochrane Collaboration's Risk of Bias tool, covering the following seven domains: ① random sequence generation; ② allocation concealment; ③ blinding of participants and study personnel; ④ blinding of outcome assessment; ⑤ incomplete outcome data; ⑥ selective reporting; and ⑦ other potential sources of bias. Disagreements were resolved through discussion or consultation with a third reviewer.

Blood Glucose and Lipids

No significant effect on fasting blood glucose was observed with combined interventions compared to exercise alone. However, combined interventions significantly reduced TG levels (MD = −7.68, 95% CI: −11.13, −4.23), while no significant effects were seen on HDL or LDL.

Sensitivity Analysis

A sensitivity analysis was conducted by sequentially removing individual studies. The results indicated that the inclusion of the Birketvedt et al (2000) study significantly increased heterogeneity in the effect sizes for BMI, waist circumference, systolic blood pressure, and diastolic blood pressure. Further analysis revealed that this study was an open-label, non-randomized design with a multifactorial intervention (diet + exercise + intermittent drug), and a long follow-up period of 42 months, which might explain the significant differences in participant characteristics, intervention types, and outcome measurement methods compared to other RCTs. Excluding this study markedly reduced heterogeneity, suggesting that it was a major source of inconsistency.

Publication Bias Test

Egger's linear regression method was used to assess publication bias for the primary outcomes. The results indicated no evidence of publication bias ($P > 0.05$) (see Supplementary Figures 16–23).

Overall Evidence Quality

The quality of evidence for the majority of outcomes was downgraded to "low" or "very low", primarily due to high risk of implementation bias, inconsistency (inconsistency between the 95% confidence intervals, I^2 values, or pooled effects), and imprecision (small sample sizes). The overall quality assessment of evidence, including the quality assessment for each outcome, is presented in Supplementary Table 4.

Network Pharmacology Analysis Results

To explore the potential molecular targets of anti-obesity medications (specifically liraglutide and orlistat) in the treatment of obesity, and the potential synergistic mechanisms of combining exercise with these medications,

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Table 2 Meta-Analysis Results of Body Composition and Metabolic Indicators

Outcome	No. of Studies	Heterogeneity		Model	Meta-Analysis Outcomes	
		I^2 (%)	*P* Value		MD (95% CI)	*P* Value
BW (Exercise)	13	54	<0.05	Random	−2.49 (−3.83,-1.14)	<0.05
L+O	4	0	0.55	Fixed	−4.37 (−7.95,-0.79)	<0.05
BW (Drug)	5	0	0.68	Fixed	−1.80 (−3.34,-0.26)	<0.05
BMI (Exercise)	13	78	<0.05	Random	−0.79 (−1.25, −0.34)	<0.05
≥16 (excluding Birketvedt 2000)	8	31	0.17	Fixed	−0.96 (−1.21,-0.70)	<0.05
BMI (Drug)	4	40	0.15	Fixed	−0.93 (−1.44,-0.42)	<0.05
Body Fat Percentage (Exercise)	10	95	<0.05	Random	−1.97 (−3.76, −0.18)	<0.05
A+R	2	0	0.9	Fixed	−1.96 (−2.59, −1.33)	<0.05
Lean Body Mass (Exercise)	2	19	0.27	Fixed	1.17 (−4.62,6.96)	0.69
Lean Body Mass (Drug)	2	0	0.95	Fixed	0.67 (−2.31,3.64)	0.66
Waist Circumference (Exercise)	9	87	<0.05	Random	−1.70 (−3.57,0.16)	0.07
Hip Circumference (Exercise)	3	89	<0.05	Random	−5.71 (−14.64,3.23)	0.21
Systolic Blood Pressure (Exercise)	7	88	<0.05	Random	−3.76 (−6.36, −1.16)	<0.05
Systolic Blood Pressure (Exercise) (excluding Birketvedt 2000[66])	6	1	0.41	Fixed	−0.75 (−1.37, −0.13)	<0.05
Diastolic Blood Pressure (Exercise)	7	82	<0.05	Random	−0.56 (−0.98, −0.15)	<0.05
Diastolic Blood Pressure (Exercise) (excluding Birketvedt 2000[66])	6	0	0	Fixed	−0.45 (−0.87, −0.03)	<0.05
Fasting Glucose (Exercise)	2	0	0.44	Fixed	−0.18 (−0.36, 0.00)	0.05
HDL (Exercise)	3	81	<0.05	Random	−0.44 (−2.70, 1.83)	0.71
LDL (Exercise)	3	32	0.22	Fixed	−0.31 (−1.75, 1.12)	0.67
TG (Exercise)	3	0	0.84	Fixed	−7.68 (−11.13, −4.23)	<0.05

Notes: Exercise, comparator was exercise alone; Drug, comparator was pharmacotherapy alone; ≥16, intervention duration ≥16 weeks; A+R, subgroup receiving combined aerobic + resistance training; L+O, liraglutide + orlistat subgroup.

a comprehensive network pharmacology analysis was performed (Figure 3). Initially, target predictions for orlistat and liraglutide were made using the SwissTargetPrediction, SEA, and ChEMBL databases. A total of 259 standardized drug targets were identified with a probability >0 (Supplementary Table 5). Subsequently, 2563 genes related to overweight/obesity were retrieved from GeneCards, OMIM, TTD, and DrugBank databases (Supplementary Table 6). A Venn diagram was used to select 109 common therapeutic targets shared between anti-obesity drugs and obesity (Figure 3A).

To illustrate the potential therapeutic mechanisms of anti-obesity drugs in treating obesity, a "drug-target-disease" network was constructed using Cytoscape software. The network, depicted in Figure 3B, demonstrates a typical multi-target action mode, where some targets exhibit high connectivity, suggesting their potential key roles in lipid metabolism, energy homeostasis, and inflammation regulation. These 109 common targets were imported into the STRING database, leading to the construction of a protein-protein interaction (PPI) network with 28 nodes and 160 edges (Figure 3C). This network predominantly involves biological processes closely related to obesity pathophysiology, such as inflammation regulation, lipid metabolism, liver function, and neuroendocrine modulation.

Further analysis of the core nodes (Figure 3D) revealed that the protein ALB had the highest degree of connectivity, interacting with 50 proteins, followed by IL1B, ESR1, ACE, MMP9, CYP3A4, STAT3, CD36, SIRT1, and HMGCR, each interacting with 41, 33, 32, 28, 28, 27, 25, 25, and 25 proteins, respectively. Some of these identified hub genes,

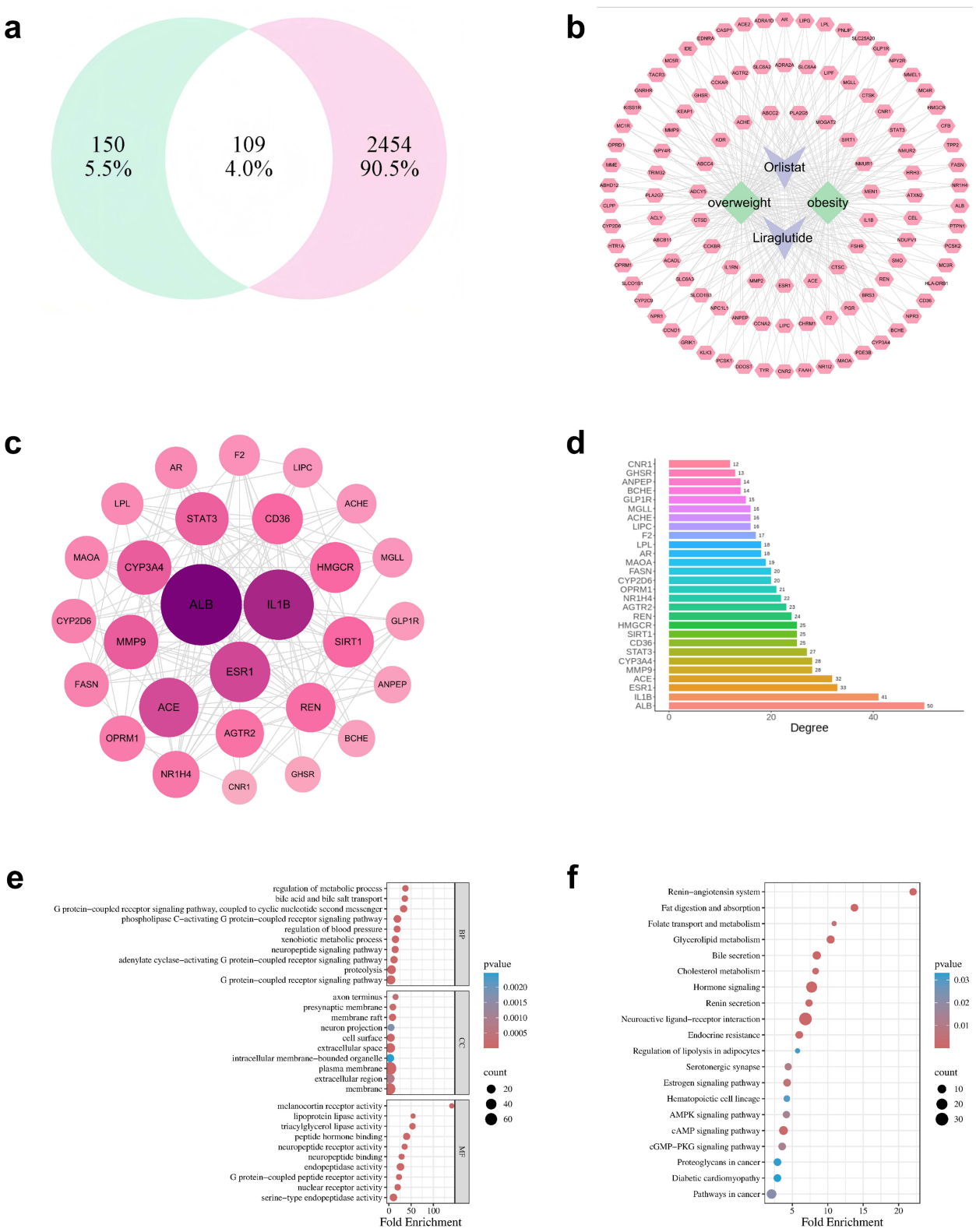

Figure 3 Network pharmacology analysis of anti-obesity drugs and obesity-related targets. (**a**) Venn diagram of 259 drug targets, 2,563 obesity/overweight targets, and 109 shared targets. (**b**) Drug–target–disease network; node connectivity highlights potential key targets. (**c**) PPI network of shared targets; node size reflects centrality, color indicates relevance, core targets located in inner circle. (**d**) Top 10 hub targets by degree. (**e**) GO enrichment analysis; fold enrichment (x-axis) versus term (y-axis), with Biological Process (BP), Cellular Component (CC) and Molecular Function (MF) categories respectively. (**f**) KEGG enrichment analysis; fold enrichment (x-axis) versus term (y-axis).

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such as IL1B, STAT3, and SIRT1, play critical roles in exercise interventions, with IL1B and STAT3 regulating inflammation and lipid metabolism, while SIRT1 is involved in fat oxidation and energy balance.[81–83] Therefore, these genes not only serve as targets for pharmacological interventions but may also represent synergistic targets for exercise, providing preliminary evidence for combined drug-exercise treatments.

To further elucidate the potential mechanisms of anti-obesity drug treatment, Gene Ontology (GO) enrichment analysis was performed on the drug targets using the DAVID database. A total of 262 significant GO terms were enriched, with 163 terms in biological processes (BP), 29 in cellular components (CC), and 70 in molecular functions (MF). The top 10 results for each category are presented as a bubble chart (Figure 3E). The results indicated that the targets of anti-obesity drugs are primarily enriched in biological processes such as fatty acid metabolism regulation, lipoprotein processing, hormone response, inflammation mediator regulation, cell membrane receptor binding, and redox processes, suggesting that these drugs may improve lipid metabolism and energy balance through multiple pathways.

To further explore the potential signaling pathways involved in anti-obesity drug mechanisms, KEGG pathway enrichment analysis was conducted on the targets. A total of 25 significantly enriched pathways were identified, with the top 20 pathways presented as a bubble chart (Figure 3F). These pathways include the renin-angiotensin system (RAS), fat digestion and absorption, triglyceride metabolism, bile secretion and cholesterol metabolism, neuroactive ligand-receptor interaction, AMPK signaling pathway, cAMP/cGMP-PKG metabolic regulation, adipocyte lipolysis regulation, estrogen signaling pathway, and serotoninergic synaptic regulation. These pathways are highly relevant to the pathophysiological characteristics of obesity, including energy metabolism dysfunction, lipid accumulation, enhanced inflammatory responses, and endocrine signal imbalance.

Discussion

This study systematically integrated data from 18 RCTs and combined network pharmacology approaches to evaluate the effects and potential mechanisms of exercise combined with pharmacological interventions in improving body composition and metabolic health in overweight/obese adults. Overall, combined interventions demonstrated a superior trend in weight, BMI, and body fat percentage improvements compared to exercise alone. However, the effects varied across different outcomes and should be interpreted with caution. Pharmacological treatments promote weight loss through mechanisms such as appetite suppression, increased metabolic rate, and reduced fat absorption,[84,85] but their clinical application remains limited due to side effects, decreased adherence, and weight rebound following cessation. Exercise interventions, on the other hand, not only enhance energy expenditure but also improve cardiovascular health, psychological well-being, and insulin sensitivity, making it a crucial foundation for weight management.[85,86] However, the weight reduction effect of exercise alone is often modest, with WHO recommending at least 150 minutes of moderate-intensity exercise per week for maintaining health and weight control.[87] Our meta-analysis revealed that, compared to exercise alone, combined interventions led to significant improvements in weight, BMI, and body fat percentage, but did not show consistent improvements in lean body mass, HDL, LDL, or fasting glucose. The improvement in body fat percentage was particularly pronounced, consistent with previous studies on medication combined with lifestyle interventions.[88,89] Moreover, combined interventions demonstrated weight and BMI reductions when compared to pharmacological treatments alone, possibly due to the number of studies included in the analysis. Further analysis indicated that the combination of aerobic and resistance training was the most effective in reducing body fat, suggesting that the structure of exercise prescriptions plays a significant role in the effectiveness of combined interventions.

In our analytical framework, we hypothesized that pharmacological and exercise interventions act on multiple biological pathways of obesity through their independent mechanisms, thereby inducing a synergistic effect. The network pharmacology analysis, from a systems biology perspective, revealed the molecular basis for this potential synergy, identifying 109 shared drug-obesity targets, with core targets such as IL1B, STAT3, SIRT1, CD36, ESR1, ACE, and MMP9 in the protein-protein interaction (PPI) network. These targets span multiple pathophysiological processes related to obesity, including chronic inflammation, lipid metabolism dysregulation, muscle function decline, endocrine disruption, and cardiovascular activation.[90–96] GO and KEGG enrichment analyses further indicated that anti-obesity drug targets are primarily involved in fatty acid metabolism, redox regulation, AMPK and cAMP/PKG signaling pathways, lipolysis regulation, the renin-angiotensin system (RAS), and neuroactive ligand-receptor interactions—key pathways

also involved in exercise-induced physiological adaptations. These results suggest that pharmacological treatments and exercise share overlapping and synergistic effects at multiple molecular levels.[97–99]

The IL1B–STAT3 inflammatory axis represents the most prominent synergistic pathway. Chronic low-grade inflammation induced by obesity weakens the beneficial effects of exercise on insulin sensitivity and fat oxidation. Our study found that IL1B and STAT3 exhibited high centrality in the drug-obesity target network and were closely linked to inflammation regulation. Previous evidence suggests that exercise can attenuate IL-1β and TNF-α expression through muscle-derived IL-6, while GLP-1 receptor agonists can inhibit the NLRP3/IL-1β signaling pathway and improve hypothalamic STAT3 activity, enhancing satiety signals and energy metabolism.[99–102] On the other hand, the significant improvement in body fat percentage with combined interventions in this study aligns well with the enrichment of metabolic targets. Core targets like SIRT1, CD36, and HMGCR are involved in fatty acid uptake, mitochondrial function, and cholesterol metabolism. SIRT1 is a central regulator of exercise adaptation (eg., promoting PGC-1α activation) and synergizes with GLP-1RA medications; CD36 is a key membrane protein in exercise-induced fat oxidation; HMGCR is associated with cholesterol metabolism, which is consistent with the KEGG pathways related to "bile secretion" and "triglyceride metabolism".[103–108] These findings suggest that pharmacological treatments may amplify the fat metabolism-enhancing effects induced by exercise, thereby explaining the advantage of combined interventions in reducing body fat. In terms of energy intake control, while exercise may temporarily suppress appetite, it is difficult to maintain this effect long-term; GLP-1 drugs, however, reduce energy intake by enhancing satiety and delaying gastric emptying.[109] The network pharmacology analysis revealed that ESR1 is significantly enriched in multiple neuroactive ligand-receptor interaction pathways, indicating that combined interventions may exhibit complementary effects in central appetite regulation and sex hormone-related metabolism, thus explaining the more stable improvements in weight and BMI observed in this study.[110,111]

In cardiovascular risk indicators, combined interventions led to robust improvements in systolic and diastolic blood pressure. Network pharmacology suggested that targets such as ACE and REN are involved in the RAS system and regulate vascular relaxation and oxidative stress in conjunction with the cGMP–PKG pathway, consistent with our findings of improved blood pressure.[112–114] In contrast, combined interventions did not significantly impact HDL, LDL, or fasting glucose, possibly due to insufficient exercise dosage, short intervention periods, or differences in drug effects. It is important to emphasize that, within the context of short-term pharmacological weight loss, exercise plays an irreplaceable role in maintaining lean body mass, improving cardiovascular health, and preventing weight rebound. Our findings are consistent with previous literature. A study by Douketis et al (2005) showed that long-term pharmacological treatments combined with lifestyle interventions significantly reduced weight and BMI, though the effect on cardiovascular function was limited.[115] Another review also confirmed that various FDA-approved anti-obesity medications were effective in reducing weight and BMI with treatments lasting ≥1 year, further supporting the conclusions of this study.[26]

In this study, liraglutide and orlistat were selected as representative drugs for network pharmacology analysis due to their established clinical applications in chronic weight management and complementary pharmacological mechanisms. Liraglutide, a GLP-1 receptor agonist initially used for type 2 diabetes, was later approved for long-term weight management. Its effects on weight loss and metabolic improvements, including delayed gastric emptying, increased satiety, and reduced energy intake, have been demonstrated in numerous clinical trials and systematic reviews, and it is recommended by international guidelines.[116,117] Orlistat, a gastrointestinal lipase inhibitor, reduces energy intake by blocking the absorption of fat, representing a pharmacological mechanism distinct from GLP-1 drugs.[118] Therefore, these two drugs, when combined with exercise, comprehensively represent the primary categories of current pharmacological treatments. It is worth noting that with the expanding drug portfolio for obesity treatment, new-generation drugs such as semaglutide and tirzepatide have demonstrated more significant weight loss effects.[119,120] For example, in the SURMOUNT-1 trial, tirzepatide at various doses resulted in an average weight loss of 15%–20%,[121] and other studies have shown that semaglutide outperforms liraglutide in weight management.[119] The emergence of these new drugs suggests that future combined interventions may yield even more pronounced effects. However, high-quality randomized controlled trials specifically evaluating the combination of these emerging drugs with exercise are still lacking. Hence, liraglutide and orlistat, supported by extensive existing clinical evidence, were selected in this study to control for heterogeneity and ensure the interpretability of the results.

Although this study provides comprehensive evidence by combining RCTs with network pharmacology analysis, it still has limitations, including insufficient quantification of exercise prescriptions, considerable heterogeneity in drug types, insufficient sample sizes for some indicators, and short follow-up periods. Future research should adopt standardized exercise prescriptions, conduct stratified randomized trials focusing on specific drug classes (including emerging drugs), and extend follow-up periods. Additionally, omics techniques and network pharmacology should be integrated to validate key pathways to further elucidate the drug-exercise synergistic mechanisms. Overall, this study demonstrates that exercise combined with pharmacological treatments has an advantage in improving body composition and certain metabolic indicators in overweight/obese adults, although the effects vary by outcome. Network pharmacology analysis provides hypothetical mechanisms for their synergistic effects, offering valuable insights for developing personalized comprehensive intervention strategies in clinical practice.

Conclusion

This study indicates that exercise combined with pharmacological interventions significantly improves weight, BMI, and body fat percentage in overweight/obese adults compared to exercise alone, with some benefits for systolic and diastolic blood pressure and triglycerides. However, no consistent improvements were observed in lean body mass, HDL, LDL, or fasting glucose, suggesting variable effects depending on the outcome. Network pharmacology analysis further identified core targets such as IL1B, STAT3, SIRT1, CD36, HMGCR, ESR1, and ACE, as well as key pathways, including inflammation regulation, fatty acid metabolism, AMPK and cAMP/PKG signaling, the RAS system, and neuroactive ligand-receptor interactions, which may form the molecular basis for the synergistic effects of drugs and exercise. Overall, drugs primarily enhance energy intake control through appetite suppression, reduced fat absorption, and endocrine signaling modulation, while exercise enhances metabolic adaptation by improving fat oxidation, mitochondrial function, and lean body mass. The two interventions complement each other in terms of inflammation alleviation, lipid metabolism optimization, and cardiovascular regulation, providing a mechanistic foundation for the clinical benefits of combined interventions. Given the existing heterogeneity in exercise prescriptions and drug types, future long-term, standardized randomized controlled trials combined with mechanistic validation are needed to identify the optimal drug-exercise combination strategies and promote precision obesity management.

Data Sharing Statement

All datasets presented in this study are included in the article/Supplementary Material.

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Author Contributions

T.P.: Conceptualization; Methodology; Data curation; Formal analysis; Writing – original draft.
W.L.: Data curation; Validation; Writing – review & editing.
J.W.: Data curation; Methodology; Writing – review & editing.
N.D.: Investigation; Formal analysis; Writing – review & editing.
X.T.: Investigation; Validation; Writing – review & editing.
Z.Z.: Conceptualization; Supervision; Formal analysis; Writing – review & editing. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

References

1. Murray CJL, Aravkin AY, Zheng P, et al. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet*. 2020;396(10258):1223–1249. doi:10.1016/S0140-6736(20)30752-2
2. Okunogbe A, Nugent R, Spencer G, Powis J, Ralston J, Wilding J. Economic impacts of overweight and obesity: current and future estimates for 161 countries. *BMJ Glob Health*. 2022;7(9):e009773. doi:10.1136/bmjgh-2022-009773
3. Obesity and overweight. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed October 17, 2024.
4. World Obesity Atlas. World obesity federation. 2022. Available from: https://www.worldobesity.org/resources/resource-library/world-obesity-atlas-2022. Accessed October 17, 2024.
5. Organization WH. Global report on diabetes. World Health Organization. 2016. Available from: https://iris.who.int/handle/10665/204871. Accessed October 17, 2024.
6. Parkin DM, Boyd L. 8. Cancers attributable to overweight and obesity in the UK in 2010. *British J Cancer*. 2011;105(Suppl S2):S34. doi:10.1038/bjc.2011.481
7. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC Public Health*. 2009;9(1):88. doi:10.1186/1471-2458-9-88
8. Obesity as a medical problem | nature. Available from: https://www.nature.com/articles/35007508. Accessed October 17, 2024.
9. Kadhim AS, Al-Karawi AS. Investigating the multifactorial correlation between obesity and rheumatoid arthritis: a study of immunological and biochemical markers. *Obesity Medicine*. 2025;53:100578. doi:10.1016/j.obmed.2024.100578
10. Kadhim HI, Kadhim AS. Exploring the association between obesity, inflammation, and type II Diabetes: insights from body mass index correlation and immune response analysis. *Al-Nahrain J Sci*. 2024;27(3):50–55. doi:10.22401/ANJS.27.3.06
11. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. Available from: https://pubmed.ncbi.nlm.nih.gov/23280227/. Accessed October 17, 2024.
12. Jung RT. Obesity as a disease. doi:10.1093/oxfordjournals.bmb.a011615.
13. Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB. Years of life lost due to obesity. *JAMA*. 2003;289(2):187–193. doi:10.1001/jama.289.2.187
14. Kelley GA, Kelley KS, Pate RR. Exercise and adiposity in overweight and obese children and adolescents: protocol for a systematic review and network meta-analysis of randomised trials. *BMJ Open*. 2017;7(12):e019512. doi:10.1136/bmjopen-2017-019512
15. Oppert J-M, Bellicha A, van Baak MA, et al. Exercise training in the management of overweight and obesity in adults: synthesis of the evidence and recommendations from the European association for the study of obesity physical activity working group. *Obes Rev*. 2021;22(Suppl S4):e13273. doi:10.1111/obr.13273
16. Ross R, Blair S, de Lannoy L, Després J-P, Lavie CJ. Changing the endpoints for determining effective obesity management. *Prog Cardiovasc Dis*. 2015;57(4):330–336. doi:10.1016/j.pcad.2014.10.002
17. Physical activity and public health: updated recommendation for adults from the American college of sports medicine and the American heart. Available from: https://pubmed.ncbi.nlm.nih.gov/17762377/. Accessed October 17, 2024.
18. Physical activity and reduced risk of cardiovascular events: potential mediating mechanisms. Available from: https://pubmed.ncbi.nlm.nih.gov/17967770/. Accessed October 17, 2024.
19. Donnelly JE, Blair SN, Jakicic JM, et al. American college of sports medicine position stand. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. *Med Sci Sports Exerc*. 2009;41(2):459–471. doi:10.1249/MSS.0b013e3181949333
20. Melanson EL, Keadle SK, Donnelly JE, Braun B, King NA. Resistance to exercise-induced weight loss: compensatory behavioral adaptations. *Med Sci Sports Exerc*. 2013;45(8):1600–1609. doi:10.1249/MSS.0b013e31828ba942
21. Boutcher SH, Dunn SL. Factors that may impede the weight loss response to exercise-based interventions. *Obes Rev*. 2009;10(6):671–680. doi:10.1111/j.1467-789X.2009.00621.x
22. Kotz CM, Levine JA. Role of nonexercise activity thermogenesis (NEAT) in obesity. *Minn Med*. 2005;88(9):54–57.
23. Narayanaswami V, Dwoskin LP. Obesity: current and potential pharmacotherapeutics and targets. *Pharmacol Ther*. 2017;170:116–147. doi:10.1016/j.pharmthera.2016.10.015
24. Elizalde-Romero CA, Leyva-López N, Contreras-Angulo LA, et al. Current evidence of natural products against overweight and obesity: molecular targets and mechanisms of action. *Receptors*. 2024;3(3):362–379. doi:10.3390/receptors3030017
25. Secher A, Jelsing J, Baquero AF, et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. *J Clin Invest*. 2014;124(10):4473–4488. doi:10.1172/JCI75276
26. Khera R, Murad MH, Chandar AK, et al. Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. *JAMA*. 2016;315(22):2424–2434. doi:10.1001/jama.2016.7602
27. Swift DL, Johannsen NM, Lavie CJ, Earnest CP, Church TS. The role of exercise and physical activity in weight loss and maintenance. *Prog Cardiovasc Dis*. 2014;56(4):441–447. doi:10.1016/j.pcad.2013.09.012
28. Yanovski S, Yanovski J. Long-term drug treatment for obesity a systematic and clinical review. *JAMA*. 2013;311. doi:10.1001/jama.2013.281361
29. Kang JG, Park C-Y. Anti-obesity drugs: a review about their effects and safety. *Diabetes Metab J*. 2012;36(1):13. doi:10.4093/dmj.2012.36.1.13
30. Lifestyle modification for obesity new developments in diet, physical activity, and behavior therapy | request PDF. ResearchGate. doi:10.1161/CIRCULATIONAHA.111.039453.
31. Yang M, Liu S, Zhang C. The related metabolic diseases and treatments of obesity. *Healthcare*. 2022;10(9):1616. doi:10.3390/healthcare10091616
32. Del Prato S, Gallwitz B, Holst JJ, Meier JJ. The incretin/glucagon system as a target for pharmacotherapy of obesity. *Obes Rev*. 2022;23(2):e13372. doi:10.1111/obr.13372
33. Gudzune KA, Kushner RF. Medications for obesity: a review. *JAMA*. 2024;332(7):571–584. doi:10.1001/jama.2024.10816

34. Pedersen SD, Manjoo P, Dash S, Jain A, Pearce N, Poddar M. Pharmacotherapy for obesity management in adults: 2025 clinical practice guideline update. *CMAJ*. 2025;197(27):E797–E809. doi:10.1503/cmaj.250502
35. Wang -F-F, Wu Y, Zhu Y-H, et al. Pharmacologic therapy to induce weight loss in women who have obesity/overweight with polycystic ovary syndrome: a systematic review and network meta-analysis. *Obes Rev*. 2018;19(10):1424–1445. doi:10.1111/obr.12720
36. Geneen LJ, Moore RA, Clarke C, Martin D, Colvin LA, Smith BH. Physical activity and exercise for chronic pain in adults: an overview of cochrane reviews. *Cochrane Database Syst Rev*. 2017;1(1):CD011279. doi:10.1002/14651858.CD011279.pub2
37. Liang M, Pan Y, Zhong T, Zeng Y, Cheng ASK. Effects of aerobic, resistance, and combined exercise on metabolic syndrome parameters and cardiovascular risk factors: a systematic review and network meta-analysis. *Rev Cardiovasc Med*. 2021;22(4):1523–1533. doi:10.31083/j.rcm2204156
38. Schneider VM, Frank P, Fuchs SC, Ferrari R. Effects of recreational sports and combined training on blood pressure and glycated hemoglobin in middle-aged and older adults: a systematic review with meta-analysis. *Exp Gerontol*. 2021;154:111549. doi:10.1016/j.exger.2021.111549
39. Agarwal M, Alexiuk J, Bohm C, Sikora L, Zimmerman D. Factors influencing recruitment, retention, and adherence rates in exercise interventions in ESKD: a scoping review. *Kidney Med*. 2025;7(1):100933. doi:10.1016/j.xkme.2024.100933
40. Sandsdal RM, Juhl CR, Jensen SBK, et al. Combination of exercise and GLP-1 receptor agonist treatment reduces severity of metabolic syndrome, abdominal obesity, and inflammation: a randomized controlled trial. *Cardiovasc Diabetol*. 2023;22(1):41. doi:10.1186/s12933-023-01765-z
41. Jensen SBK, Blond MB, Sandsdal RM, et al. Healthy weight loss maintenance with exercise, GLP-1 receptor agonist, or both combined followed by one year without treatment: a post-treatment analysis of a randomised placebo-controlled trial. *EClinicalMedicine*. 2024;69:102475. doi:10.1016/j.eclinm.2024.102475
42. Chanoine J-P, Hampl S, Jensen C, Boldrin M, Hauptman J. Effect of orlistat on weight and body composition in obese adolescents: a randomized controlled trial. *JAMA*. 2005;293(23):2873–2883. doi:10.1001/jama.293.23.2873
43. Willis LH, Slentz CA, Bateman LA, et al. Effects of aerobic and/or resistance training on body mass and fat mass in overweight or obese adults. *J Appl Physiol*. 2012;113(12):1831–1837. doi:10.1152/japplphysiol.01370.2011
44. Ho SS, Dhaliwal SS, Hills AP, Pal S. The effect of 12 weeks of aerobic, resistance or combination exercise training on cardiovascular risk factors in the overweight and obese in a randomized trial. *BMC Public Health*. 2012;12(1):704. doi:10.1186/1471-2458-12-704
45. Sigal RJ, Alberga AS, Goldfield GS, et al. Effects of aerobic training, resistance training, or both on percentage body fat and cardiometabolic risk markers in obese adolescents: the healthy eating aerobic and resistance training in youth randomized clinical trial. *JAMA Pediatr*. 2014;168(11):1006–1014. doi:10.1001/jamapediatrics.2014.1392
46. Liu X, Li Q, Lu F, Zhu D. Effects of aerobic exercise combined with resistance training on body composition and metabolic health in children and adolescents with overweight or obesity: systematic review and meta-analysis. *Front Public Health*. 2024;12:1409660. doi:10.3389/fpubh.2024.1409660
47. Plaza-Diaz J, Izquierdo D, Torres-Martos Á, Baig AT, Aguilera CM, Ruiz-Ojeda FJ. Impact of physical activity and exercise on the epigenome in skeletal muscle and effects on systemic metabolism. *Biomedicines*. 2022;10(1):126. doi:10.3390/biomedicines10010126
48. Severinsen MCK, Pedersen BK. Muscle–organ crosstalk: the emerging roles of myokines. doi:10.1210/endrev/bnaa016.
49. Egan B, Zierath JR. Exercise metabolism and the molecular regulation of skeletal muscle adaptation. *Cell Metab*. 2013;17(2):162–184. doi:10.1016/j.cmet.2012.12.012
50. Pillon NJ, Gabriel BM, Dollet L, et al. Transcriptomic profiling of skeletal muscle adaptations to exercise and inactivity. *Nat Commun*. 2020;11(1):470. doi:10.1038/s41467-019-13869-w
51. Jin S, Zhang M, Wang M, Yu L. A deep graph model for the signed interaction prediction in biological network. *arXiv*. 2025. doi:10.48550/arXiv.2407.07357
52. Hopkins AL. Network pharmacology: the next paradigm in drug discovery. *Nat Chem Biol*. 2008;4(11):682–690. doi:10.1038/nchembio.118
53. Wang Y, Yang SH, Zhong K, et al. Network pharmacology-based strategy for the investigation of the anti-obesity effects of an ethanolic extract of zanthoxylum bungeanum maxim. *Front Pharmacol*. 2020;11:572387. doi:10.3389/fphar.2020.572387
54. Qiu S, Cai Y, Yao H, et al. Small molecule metabolites: discovery of biomarkers and therapeutic targets. *Signal Transduct Target Ther*. 2023;8(1):132. doi:10.1038/s41392-023-01399-3
55. Oh KK. Network pharmacology study to reveal underlying mechanisms, targets, and bioactives of Aralia cordata against obesity. *Network Modeling Analysis Health Informat Bioinformat*. 2022;11(1):29. doi:10.1007/s13721-022-00372-4
56. Franz MJ, VanWormer JJ, Crain AL, et al. Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. *J Ame Dietetic Assoc*. 2007;107(10):1755–1767. doi:10.1016/j.jada.2007.07.017
57. Booth A, Clarke M, Ghersi D, Moher D, Petticrew M, Stewart L. An international registry of systematic-review protocols. *Lancet*. 2011;377(9760):108–109. doi:10.1016/S0140-6736(10)60903-8
58. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement | PLOS Medicine. Available from: https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000097. Accessed October 3, 2024.
59. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557–560. doi:10.1136/bmj.327.7414.557
60. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. *Introduction to Meta-Analysis*. John Wiley & Sons; 2021.
61. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. doi:10.1136/bmj.d5928
62. N A, S M. Evaluation of effect of acarbose consumption on weight losing in non-diabetic overweight or obese patients in Kerman. *J Res Med Sci*. 2013;18(5). https://pubmed.ncbi.nlm.nih.gov/24174943/.
63. Ofner M, Tomaschitz A, Wonisch M, Litscher G. Complementary treatment of obesity and overweight with salacia reticulata and vitamin D. *Int J Vitamin Nutrit Res*. 2013;83(4):216–223. doi:10.1024/0300-9831/a000162
64. Efficacy of polyglucosamine for weight loss—confirmed in a randomized double-blind, placebo-controlled clinical investigation | BMC obesity. Available from: https://link.springer.com/article/10.1186/s40608-015-0053-5. Accessed October 21, 2024.
65. Mensberg P, Nyby S, Jørgensen PG, et al. Near-normalization of glycaemic control with glucagon-like peptide-1 receptor agonist treatment combined with exercise in patients with type 2 diabetes. *Diabetes Obesity Metabol*. 2017;19(2):172–180. doi:10.1111/dom.12797

66. Birketvedt GS, Thom E, Bernersen B, Florholmen J. Combination of diet, exercise and intermittent treatment of cimetidine on body weight and maintenance of weight loss. A 42 months follow-up study. *Med Sci Monit*. 2000;6(4):699–703.
67. Blackman A, Foster GD, Zammit G, et al. Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE sleep Apnea randomized clinical trial. *Int J Obes*. 2016;40(8):1310–1319. doi:10.1038/ijo.2016.52
68. Carlos Poston WS, Reeves RS, Haddock CK, et al. Weight loss in obese Mexican Americans treated for 1-year with orlistat and lifestyle modification. *Int J Obes*. 2003;27(12):1486–1493. doi:10.1038/sj.ijo.0802439
69. Dixit K, Kamath DV, Alluri KV, Davis BA. Efficacy of a novel herbal formulation for weight loss demonstrated in a 16-week randomized, double-blind, placebo-controlled clinical trial with healthy overweight adults. *Diabetes Obesity Metabol*. 2018;20(11):2633–2641. doi:10.1111/dom.13443
70. DeFina LF, Marcoux LG, Devers SM, Cleaver JP, Willis BL. Effects of omega-3 supplementation in combination with diet and exercise on weight loss and body composition. *Ame J Clin Nutrit*. 2011;93(2):455–462. doi:10.3945/ajcn.110.002741
71. One-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the blossom trial | the journal of clinical endocrinology & metabolism | oxford academic. Available from: https://academic.oup.com/jcem/article-abstract/96/10/3067/2834879. Accessed October 21, 2024.
72. Grannell A, Martin WP, Dehestani B, Al-Najim W, Murphy JC, le Roux CW. Liraglutide does not adversely impact fat-free mass loss. *Obesity*. 2021;29(3):529–534. doi:10.1002/oby.23098
73. Grube B, Chong P-W, Lau K-Z, Orzechowski H-D. A natural fiber complex reduces body weight in the overweight and obese: a double-blind, randomized, placebo-controlled study. *Obesity*. 2013;21(1):58–64. doi:10.1002/oby.20244
74. Zenk JL, Leikam SA, Kassen LJ, Kuskowski MA. Effect of lean system 7 on metabolic rate and body composition. *Nutrition*. 2005;21(2):179–185. doi:10.1016/j.nut.2004.05.025
75. Zakavi I, Karimian A, Isazadeh R, et al. Effect of aquatic extract of ferulago angulata boiss with aerobic exercises on serum levels of interleukin-10 and C-reactive protein of obese males. *Crescent J Med Biolog Sci*. 2018;5(4).
76. Lundgren JR, Janus C, Jensen SBK, et al. Healthy weight loss maintenance with exercise, liraglutide, or both combined. *N Engl J Med*. 2021;384(18):1719–1730. doi:10.1056/NEJMoa2028198
77. Colak R, Ozcelik O. Effects of short-period exercise training and orlistat therapy on body composition and maximal power production capacity in obese patients. *Physiol Res*. 2004;53(1):53–60. doi:10.33549/physiolres.930279
78. Ozcelik O, Ozkan Y, Algul S, Colak R. Beneficial effects of training at the anaerobic threshold in addition to pharmacotherapy on weight loss, body composition, and exercise performance in women with obesity. *Patient Prefer Adherence*. 2015;9:999–1004. doi:10.2147/PPA.S84297
79. Bagherzadeh-Rahmani B, Marzetti E, Karami E, et al. RETRACTED: tirzepatide and exercise training in obesity. *Clin Hemorheol Microcirc*. 2024;87(4):465–480. doi:10.3233/CH-242134
80. Armstrong R, Waters E, Doyle J. Reviews in public health and health promotion. In: *Cochrane Handbook for Systematic Reviews of Interventions*. John Wiley & Sons, Ltd; 2008:593–606. doi:10.1002/9780470712184.ch21
81. Ding Y, Xu X. Anti-inflammatory effect of exercise training through reducing inflammasome activation-related inflammatory cytokine levels in overweight/obese populations: a systematic review and meta-analysis. *Complement Ther Clin Pract*. 2022;49:101656. doi:10.1016/j.ctcp.2022.101656
82. Hu W, Lv J, Han M, et al. STAT3: the art of multi-tasking of metabolic and immune functions in obesity. *Prog Lipid Res*. 2018;70:17–28. doi:10.1016/j.plipres.2018.04.002
83. Liu H-W, Kao -H-H, Wu C-H. Exercise training upregulates SIRT1 to attenuate inflammation and metabolic dysfunction in kidney and liver of diabetic db/db mice. *Nutr Metab*. 2019;16(1):22. doi:10.1186/s12986-019-0349-4
84. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: an endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100(2):342–362. doi:10.1210/jc.2014-3415
85. de Lannoy L, Cowan T, Fernandez A, Ross R. Physical activity, diet, and weight loss in patients recruited from primary care settings: an update on obesity management interventions. *Obesity Sci Prac*. 2021;7(5):619–628. doi:10.1002/osp4.514
86. Lavie CJ, Johannsen N, Swift D, et al. Exercise is Medicine—the importance of physical activity, exercise training, cardiorespiratory fitness and obesity in the prevention and treatment of type 2 diabetes. *Euro Endocrinol*. 2014;10(1):18–22. doi:10.17925/EE.2014.10.01.18
87. WHO guidelines on physical activity and sedentary behaviour: at a glance. Available from: https://www.who.int/europe/publications/i/item/9789240014886. Accessed October 4, 2024.
88. Ruiz-González D, Cavero-Redondo I, Hernández-Martínez A, et al. Comparative efficacy of exercise, diet and/or pharmacological interventions on BMI, ovulation, and hormonal profile in reproductive-aged women with overweight or obesity: a systematic review and network meta-analysis. *Hum Reprod Update*. 2024;30(4):472–487. doi:10.1093/humupd/dmae008
89. Chu J, Zhang H, Wu Y, et al. Efficacy of lifestyle modification combined with GLP-1 receptor agonists on body weight and cardiometabolic biomarkers in individuals with overweight or obesity: a systematic review and meta-analysis. *EClinicalMedicine*. 2025;88:103464. doi:10.1016/j.eclinm.2025.103464
90. Hardaway AL, Podgorski I. IL-1β, RAGE and FABP4: targeting the dynamic trio in metabolic inflammation and related pathologies. *Future Med Chem*. 2013;5(10):1089–1108. doi:10.4155/fmc.13.90
91. Li Y, Yang H, Zhang X, et al. Integrated proteomic and metabolomic profiling identifies distinct molecular signatures and metabolic pathways associated with obesity and potential targets for anti-obesity therapies. *Front Endocrinol*. 2025;16:1625501. doi:10.3389/fendo.2025.1625501
92. Liao Y, Wang M, Qin F, Liu T, Chen J. Integrating network pharmacology, quantitative transcriptomic analysis, and experimental validation revealed the mechanism of cordycepin in the treatment of obesity. *Front Pharmacol*. 2025;16:1571480. doi:10.3389/fphar.2025.1571480
93. Zhou Q, Gwag T, Wang S. Thrombospondin1 antagonist peptide treatment attenuates obesity-associated chronic inflammation and metabolic disorders in a diet-induced obese mouse model. *Sci Rep*. 2023;13(1):20193. doi:10.1038/s41598-023-47635-2
94. Xia H, Liu J, Yang W, et al. Integrated strategy of network pharmacological prediction and experimental validation elucidate possible mechanism of Bu-Yang herbs in treating postmenopausal osteoporosis via ESR1. *Front Pharmacol*. 2021;12:654714. doi:10.3389/fphar.2021.654714
95. Akopyan AA, Kirillova KI, Strazhesko ID, Samokhodskaya LM, Orlova YA. Association of AGT, ACE, NOS3, TNF, MMP9, CYBA polymorphism with subclinical arterial wall changes. *Kardiologiia*. 2021;61(3):57–65. doi:10.18087/cardio.2021.3.n1212

96. Tian M, Gao H, Jiao H, et al. Mechanisms of the Jian Pi Tiao Gan Yin in the treatment of simple obesity revealed by network pharmacology. *Ann Transl Med*. 2022;10(6):335. doi:10.21037/atm-22-553
97. Jang D, Jeong H, Kim C-E, Leem J. A system-level mechanism of anmyungambi decoction for obesity: a network pharmacological approach. *Biomolecules*. 2021;11(12):1881. doi:10.3390/biom11121881
98. Tyurina YY, Tyurin VA, Anthonymuthu T, et al. Redox lipidomics technology: looking for a needle in a haystack. *Chem Phys Lipids*. 2019;221:93–107. doi:10.1016/j.chemphyslip.2019.03.012
99. Qi QYD, Cox A, McNeil S, Sumithran P. Obesity medications: a narrative review of current and emerging agents. *Osteoarthritis and Cartilage Open*. 2024;6(2):100472. doi:10.1016/j.ocarto.2024.100472
100. Bocarsly ME. Pharmacological interventions for obesity: current and future targets. *Curr Addict Rep*. 2018;5(2):202–211. doi:10.1007/s40429-018-0204-0
101. Guo X, Zhou Z, Lyu X, et al. The antiobesity effect and safety of GLP-1 receptor agonist in overweight/obese patients without diabetes: a systematic review and meta-analysis. *Horm Metab Res*. 2022;54(7):458–471. doi:10.1055/a-1844-1176
102. Patoulias D, Michailidis T, Dimosiari A, Fragakis N, Tse G, Rizzo M. Effect of Glucagon-like peptide-1 receptor agonists on cardio-metabolic risk factors among obese/overweight individuals treated with antipsychotic drug classes: an updated systematic review and meta-analysis of randomized controlled trials. *Biomedicines*. 2023;11(3):669. doi:10.3390/biomedicines11030669
103. Ye X, Li M, Hou T, Gao T, Zhu W-G, Yang Y. Sirtuins in glucose and lipid metabolism. *Oncotarget*. 2017;8(1):1845–1859. doi:10.18632/oncotarget.12157
104. Hirschey MD, Shimazu T, Huang J-Y, Schwer B, Verdin E. SIRT3 regulates mitochondrial protein acetylation and intermediary metabolism. *Cold Spring Harb Symp Quant Biol*. 2011;76:267–277. doi:10.1101/sqb.2011.76.010850
105. Najt CP, Khan SA, Heden TD, et al. Lipid droplet-derived monounsaturated fatty acids traffic via PLIN5 to allosterically activate SIRT1. *Mol Cell*. 2020;77(4):810–824.e8. doi:10.1016/j.molcel.2019.12.003
106. Niu B, He K, Li P, et al. SIRT1 upregulation protects against liver injury induced by a HFD through inhibiting CD36 and the NF-κB pathway in mouse kupffer cells. *Mol Med Rep*. 2018;18(2):1609–1615. doi:10.3892/mmr.2018.9088
107. Liu TF, Vachharajani VT, Yoza BK, McCall CE. NAD+-dependent sirtuin 1 and 6 proteins coordinate a switch from glucose to fatty acid oxidation during the acute inflammatory response. *J Biol Chem*. 2012;287(31):25758–25769. doi:10.1074/jbc.M112.362343
108. Zhao J, Jiang P, Zhang W. Molecular networks for the study of TCM pharmacology. *Brief Bioinform*. 2010;11(4):417–430. doi:10.1093/bib/bbp063
109. Bonfante ILP, Duft RG, Mateus KCDS, et al. Combined training and hormones/enzymes with insulinotropic actions in individuals with overweight and type 2 diabetes mellitus: a randomized controlled trial. *Eur J Sport Sci*. 2024;24(1):97–106. doi:10.1002/ejsc.12057
110. Kaur J, Farooqi H, Chandra K, Panda BP. Predicting the bioactive compounds of Lentinula edodes and elucidating its interaction with genes associated to obesity through network pharmacology and in-vitro cell-based assay. *Heliyon*. 2024;10(5):e27363. doi:10.1016/j.heliyon.2024.e27363
111. Kurtov M, Rubinić I, Likić R. The endocannabinoid system in appetite regulation and treatment of obesity. *Pharmacol Res Perspect*. 2024;12(5):e70009. doi:10.1002/prp2.70009
112. Collier SR, Sandberg K, Moody AM, et al. Reduction of plasma aldosterone and arterial stiffness in obese pre- and stage1 hypertensive subjects after aerobic exercise. *J Hum Hypertens*. 2015;29(1):53–57. doi:10.1038/jhh.2014.33
113. Taquiqui A, Ferrer AM, David JR, Deocaris CC, Alinsug MV. Network-based analysis on pharmacological mechanisms underlying the anti-diabetic property of Coix lacryma-jobi. *bioRxiv*. 2021;464488. doi:10.1101/2021.10.15.464488
114. Physical activity in obesity and metabolic syndrome - Strasser - 2013 - annals of the New York academy of sciences - Wiley online library. Available from: https://nyaspubs.onlinelibrary.wiley.com/doi/full/10.1111/j.1749-6632.2012.06785.x. Accessed December 7, 2025.
115. Rucker D, Padwal R, Li SK, Curioni C, Lau DCW. Long term pharmacotherapy for obesity and overweight: updated meta-analysis. *BMJ*. 2007;335(7631):1194–1199. doi:10.1136/bmj.39385.413113.25
116. Shah MY, Mohammad A, Bashir Ahmed Samejo R, et al. Weight loss that lasts: reviewing the long-term impact of GLP-1 receptor agonists. *Cureus*. 2025;17(7):e88334. doi:10.7759/cureus.88334
117. Zheng Z, Zong Y, Ma Y, et al. Glucagon-like peptide-1 receptor: mechanisms and advances in therapy. *Sig Transduct Target Ther*. 2024;9(1):234. doi:10.1038/s41392-024-01931-z
118. Son JW, Kim S. Comprehensive review of current and upcoming anti-obesity drugs. *Diabetes Metab J*. 2020;44(6):802–818. doi:10.4093/dmj.2020.0258
119. Patel JP, Hardaswani D, Patel J, et al. Comparative effectiveness of semaglutide, liraglutide, orlistat, and phentermine for weight loss in obese individuals: a systematic review. *Cureus*. 2025;17(3):e80321. doi:10.7759/cureus.80321
120. Jensterle M, Rizzo M, Haluzík M, Janež A. Efficacy of GLP-1 RA approved for weight management in patients with or without diabetes: a narrative review. *Adv Ther*. 2022;39(6):2452–2467. doi:10.1007/s12325-022-02153-x
121. Mohr K, Butcher C. Glucagon like peptide −1 receptor agonists for weight loss: a primary care perspective. *Mo Med*. 2024;121(6):489–494. doi:10.1056/NEJMoa2206038