Review

The impact of exercise and dietary interventions on circulating leptin and adiponectin in individuals who are overweight and those with obesity: A systematic review and meta-analysis

Mousa Khalafi [1,*], Mohammad Hossein Sakhaei [2], Shokoufeh Kheradmand [3], Michael E. Symonds [4], Sara K. Rosenkranz [5]

[1] Department of Physical Education and Sport Sciences, Faculty of Humanities, University of Kashan, Kashan, Iran; [2] Department of Exercise Physiology, Faculty of Sport Sciences, University of Guilan, Guilan, Iran; [3] Department of Exercise Physiology, Faculty of Sport Sciences, University of Mazandaran, Babolsar, Iran; [4] Centre for Perinatal Research, Academic Unit of Population and Lifespan Sciences, School of Medicine, University of Nottingham, Nottingham, United Kingdom; [5] Department of Kinesiology and Nutrition Sciences, University of Nevada, Las Vegas, NV, USA

ABSTRACT

The effects of exercise training (Ex), dietary interventions (DIs), and a combination of Ex and DI (Ex + DI) on leptin and adiponectin have been established. However, less is known regarding the comparisons of Ex with DI and of Ex + DI with either Ex or DI alone. The aim of the present meta-analysis is to compare the effects of Ex with those of DI and those of Ex + DI with those of either Ex or DI alone on circulating leptin and adiponectin in individuals who are overweight and those with obesity. PubMed, Web of Science, and MEDLINE were searched to identify original articles, published through June 2022, that compared the effects of Ex with those of DI and/or the effects of Ex + DI with those of Ex and/or DI on leptin and adiponectin in individuals with BMIs (in kg/m^2) of $\geq$25 and aged 7–70 y. Standardized mean differences (SMDs), weighted mean differences, and 95% CIs were calculated using random-effect models for outcomes. Forty-seven studies, comprising 3872 participants who were overweight and those with obesity, were included in the current meta-analysis. DI reduced the concentration of leptin (SMD: -0.30; $P = 0.001$) and increased the concentration of adiponectin (SMD: 0.23; $P = 0.001$) compared with Ex, as did Ex + DI (leptin: SMD: -0.34; $P = 0.001$; adiponectin: SMD: 0.37; $P = 0.004$) compared with Ex alone. However, Ex + DI did not affect the concentration of adiponectin (SMD: 0.10; $P = 0.11$) and led to inconsistent and nonsignificant changes in the concentration of leptin (SMD: -0.13; $P = 0.06$) compared with DI alone. Subgroup analyses showed that age, BMI, duration of intervention, type of supervision, quality of the study, and magnitude of energy restriction are sources of heterogeneity. Our results suggest that Ex alone was not as effective as DI or Ex + DI for decreasing leptin and increasing adiponectin in individuals with overweight and obesity. However, Ex + DI was not more effective than DI alone, suggesting that diet plays a critical role in beneficially altering the concentrations of leptin and adiponectin. This review was registered at PROSPERO as CRD42021283532.

Keywords: exercise training, dietary intervention, lifestyle intervention, adipokine, obesity

Statement of significance

Previous systematic reviews and meta-analyses have suggested that exercise training (Ex) and dietary interventions (DIs) are effective in decreasing the concentration of leptin and increasing the concentration of adiponectin. However, to our knowledge, this is the first systematic review and meta-analysis to investigate the comparison of Ex with DI as well as that of Ex + DI with either Ex or DI alone in individuals who are overweight and those with obesity.

Introduction

Obesity is a major global health problem, with the prevalence of obesity-related diseases continuing to increase [1,2]. The accumulation of fat in adipose tissue is strongly associated with risk factors for noncommunicable chronic diseases and health conditions such as insulin resistance, hypertension, and chronic low-grade inflammation [3–5]. It is well established that excess visceral or central adiposity contributes to the development of chronic diseases such as CVD, type 2 diabetes, and some cancers [6]. In addition, obesity is linked to poor outcomes associated with coronavirus disease 2019 (COVID-19) [6], which have potentially exacerbated the spread of COVID-19 and certainly worsened the societal impact of COVID-19 [7].

Adipose tissue is a metabolic and endocrine organ that secretes a number of adipokines that contribute to the etiology of obesity-related metabolic complications [8–10]. A well-established adipokine that is known to change with the accumulation or loss of fat tissue is leptin, which regulates several physiologic processes, including energy balance [11,12] as well as inflammatory and immune responses [13–15]. Similarly, adiponectin has multiple effects, including anti-inflammatory, antiatherogenic, and insulin-sensitizing effects [16–18]. High concentrations of circulating leptin, leptin resistance, and hypoadiponectinemia occur with obesity and related pathologic risk factors for CVD [19–23], suggesting a critical role of these adipokines in the onset of the disease [19].

Lifestyle interventions, characterized by promotion of negative energy balance, are usually a first-line approach for the treatment of obesity. Exercise training (Ex) and dietary interventions (DIs) that promote negative energy balance and subsequent weight loss are associated with improvements in cardiometabolic risk factors [24–31]. A combination of both Ex and DI (Ex + DI) would be expected to have an additive effect, with the potential for better health outcomes following intervention [32–36]. Recent meta-analyses have suggested that a combination of Ex and caloric restriction (CR) is more effective than CR alone in reducing the concentration of proinflammatory cytokines in individuals who are overweight and those with obesity [32,33]. However, these results are not always consistent. For example, 1 meta-analysis did not suggest further reductions in the concentration of inflammatory markers with Ex + DI compared with those with DI [37]. Several meta-analyses have suggested that Ex is effective in decreasing the concentration of leptin and increasing the concentration of adiponectin [38–42], as is DI alone [43–45]. However, the effectiveness of Ex compared with that of DI and the effectiveness of Ex + DI compared with that of either Ex or DI alone were not elucidated in previous meta-analyses. Therefore, the aim of the current systematic review and meta-analysis was to determine the comparative effectiveness of these interventions in individuals who are overweight and those with obesity.

Methods

The current systematic review was conducted in accordance with the PRISMA statement and the Cochrane Handbook of Systematic Reviews of Interventions. The review was registered in the PROSPERO database (ID: CRD42021283532).

Search strategy

PubMed, Web of Science, and MEDLINE were the primary databases searched to identify original research articles, published until October 2021, using a combination of Ex, DI, and outcome terms, as summarized in Supplementary Table 1. In addition, the search was updated through June 2022. The reference lists of all retrieved studies and previous relevant meta-analyses [32,33,37] were manually screened. The search and screening were performed by 2 independent reviewers (MHS and SK), and any disagreements were resolved by discussion with another reviewer (MK).

Study selection and inclusion or exclusion criteria

All retrieved articles were exported to Endnote (version 20.2.1), and duplicate articles were removed. Two independent reviewers (MHS and SK) screened the articles based on titles, abstracts, and key words. Then, all remaining articles were assessed independently, with any disagreements resolved by discussion with another reviewer (MK). The inclusion criteria were as follows: 1) peer reviewed; 2) English language; 3) human participants; 4) results that included serum or plasma leptin and/or adiponectin; 5) duration of intervention $\geq$ 2 wk; and 6) randomized trials that compared Ex with DI and/or Ex + DI with either Ex and/or DI. For the Ex modality, any type of Ex, such as aerobic, resistance, combined (aerobic and resistance training), and interval training, was included. There were no limitations on time, intensity, or the duration of Ex. For the DI modality, any DI with the aim of loss of body weight, such as CR, hypocaloric diets, very-low–calorie diets, or alternate daily fasting, was included. In addition, energy restriction was categorized into 2 subgroups: 1) mild energy restriction and 2) severe energy restriction. Mild energy restriction was defined as a total energy intake of $\geq$1200 kcal/d, an energy restriction of $\leq$500 kcal/d, an energy restriction of $\leq$25% of daily energy intake, or an average weight loss of <0.5 kg/wk. Severe energy restriction was defined as a daily energy intake of <1200 kcal/d, an energy restriction of >500 kcal/d, an energy restriction of >25% of daily energy intake, or an average weight loss of $\geq$0.5 kg/wk. For the study, individuals who were overweight or those with obesity (BMI [in kg/m^2] $\geq$ 25 or mean BMI $\geq$ 27) were included. In the case of pediatric participants, obesity was defined as a BMI of $\geq$95th percentile. There were no limitations regarding the age, sex, or health status of the participants. In order to increase the external generalizability of the results, participants who were overweight and those with obesity, ranging from healthy to diagnosed with a disease, were included. The exclusion criteria were as follows: 1) nonprimary studies, 2) non-English languages, 3) not peer reviewed, 4) animal studies, and 5) studies involving only Ex, only DI, or only Ex + DI.

Data extraction and synthesis

Two reviewers (MK and MHS) independently extracted data, and any disagreements were resolved by discussion with another reviewer (MES). Data from the final list of eligible studies were extracted as follows: 1) study characteristics, including study design and sample size; 2) participant characteristics, including sex, age, BMI, and comorbidities; 3) Ex characteristics, including mode, intensity, duration, and fre-

quency; 4) DI characteristics, including type and duration; 5) outcome variables; 6) preintervention and postintervention means and SDs or mean changes and their SDs. When required, SEs, medians, ranges, and/or IQRs were used to calculate the means and SDs [46–48]. In addition, when the geometric mean and CIs were reported, the methods reported by Higgins et al. [49] were used to calculate the arithmetic means and SDs. When required, the SE values were converted to SDs by using the following formula: $SD = SE \times \sqrt{N}$. When required, the Getdata Graph Digitizer software was used to extract data from figures. If the studies had multiple Ex, DI, or Ex + DI interventions, the groups were combined to create a single pair-wise comparison as suggested by the Cochrane Handbook for Systematic Reviews of Interventions. However, when a subgroup analysis was only based on the type of exercise, all comparisons were included and the sample size of the repeated intervention was divided by the number of comparisons to avoid double counting. In addition, for studies that were published within the last 5 y, when required data were not available in the published article or were not able to be extracted from figures, the corresponding author of the relevant article was contacted. For the current study, 1 author provided missing data.

Quality assessment and sensitivity analyses

To assess the quality of all included studies, we used the PEDro Scale, a valid measure of the methodologic quality of clinical trials [50]. The 11-item tool was modified by excluding 2 items, including blinding of participants and blinding of intervention provider because of the inability to blind participants and interventions across the included studies. Finally, the quality of each study was assessed based on the following criteria by 1 reviewer (MHS) and verified by another (MK): eligibility criteria, random allocation of participants, allocation concealment, group similarity at baseline, blinding of participants, blinding of intervention providers, blinding of assessors, outcomes measures assessed in 85% of participants, intention-to-treat analysis, reporting of between-group statistical comparisons and point measures, and measures of variability reported for main effects. In addition, sensitivity analyses were performed by omitting individual studies and studies involving participants aged <18 y.

Statistical analysis

All analyses were performed using version 2.0 of the Comprehensive Meta-Analysis software (Biostat Inc). Three separate analyses were performed to calculate the standardized mean differences (SMDs), weighted mean differences (WMD), and 95% CIs using random-effect models using the DerSimonian and Laird approach for comparing the effects of the following 1) Ex with DI, 2) Ex + DI with Ex, and 3) Ex + DI with DI on the main outcomes (leptin and adiponectin) and secondary outcome (body weight). The results were pooled using random-effects models based on the assumption that heterogeneity was likely from a clinical or methodologic perspective and may have affected the results [51]. Several subgroup analyses were performed based on the participants' BMIs (overweight: <30; obesity: ≥30), duration of intervention (short term: ≤12 wk; medium term: >12 wk and ≤24 wk; long term: >24 wk), age of the participants (<18 y, ≤18 y to <50 y, or ≥50 y), type of exercise (aerobic, resistance, or combined), type of exercise

supervision (supervised, nonsupervised, or both), PEDro Scale score (score: <5 or ≥5), and magnitude of energy restriction (mild or severe). In pediatric studies, all participants had obesity and were categorized by obesity subgroup. The interpretation of effect sizes was conducted using the Cochrane guidelines, with 0.20–0.49, 0.50–0.79, and ≥0.8 indicating small, medium, and large effect sizes, respectively. Heterogeneity was assessed using the I^2 statistic, which interprets I^2 according to the Cochrane guidelines as follows: 25%, 50%, and 75% indicates low, moderate, and high heterogeneity, respectively. Visual interpretation of funnel plots and Egger tests were used for the detection of publication biases, wherein the Egger test was used as a secondary determinant if P was <0.10. The trim-and-fill correction method was used to address the potential effects of publication biases where relevant [52].

Results

Included studies

The initial search of the databases resulted in 1085 records from PubMed, 1911 records from Web of Science, and 838 records from MEDLINE. A total of 116 articles were identified for full-text review based on our inclusion and exclusion criteria. Of these, 78 articles were excluded because of the reasons presented in Fig. 1. In addition, 1 study was included after updating the search [53]. Finally, 47 randomized trials (parallel-arm trials) were included in the meta-analysis, of which 6 included Ex and DI [54–59], 22 included Ex + DI and DI [60–81], 2 included Ex + DI and Ex [82,83], and 17 included Ex + DI, Ex, and DI [53, 84–99].

Participant characteristics

A total of 3872 participants who were overweight or had obesity were included (Table 1); their mean age and BMI ranged from 7.7 [55] to 70.0 y [87] and 21.1 [55] to 44.0 [62], respectively. The sample size ranged from 16 [70] to 352 [84] participants. Five studies included only male participants [54,56, 57,89,94], whereas 16 studies included only female participants [59,60,66–68,71,73,77,78,80,83,84,86,90–92]. The remaining 26 studies included both male and female participants [53,55, 58,61–65,69,70,72,74–76,79,81,82,85,87,88,93,95–99]. All the participants were overweight or had obesity, with a wide range of health and chronic diseases, including metabolic syndrome, type 2 diabetes, nonalcoholic fatty liver disease, chronic kidney disease, and asthma (Table 1).

Intervention characteristics and quality assessment

The Ex and DI characteristics are summarized in Table 2, and the duration of intervention ranged from ~2 wk [66,75] to 18 mo [82,93], whereas the frequency of Ex sessions ranged from 2 [64,67] to 7 sessions [54,57,58,99]. Most studies used aerobic training modalities such as running, walking, or cycling. Other interventions included resistance [67,73,83,90], combined training [56,60,64,68,87,93,95–97], and yoga [79,80]. Two studies used >1 Ex protocol as separate interventions [72,77]. The studies included supervised exercise, unsupervised exercise, and exercise protocols that included both. For DIs, in most of the studies, the energy intake was reduced by a range of 250–750 kcal/d but included a total energy intake that widely ranged
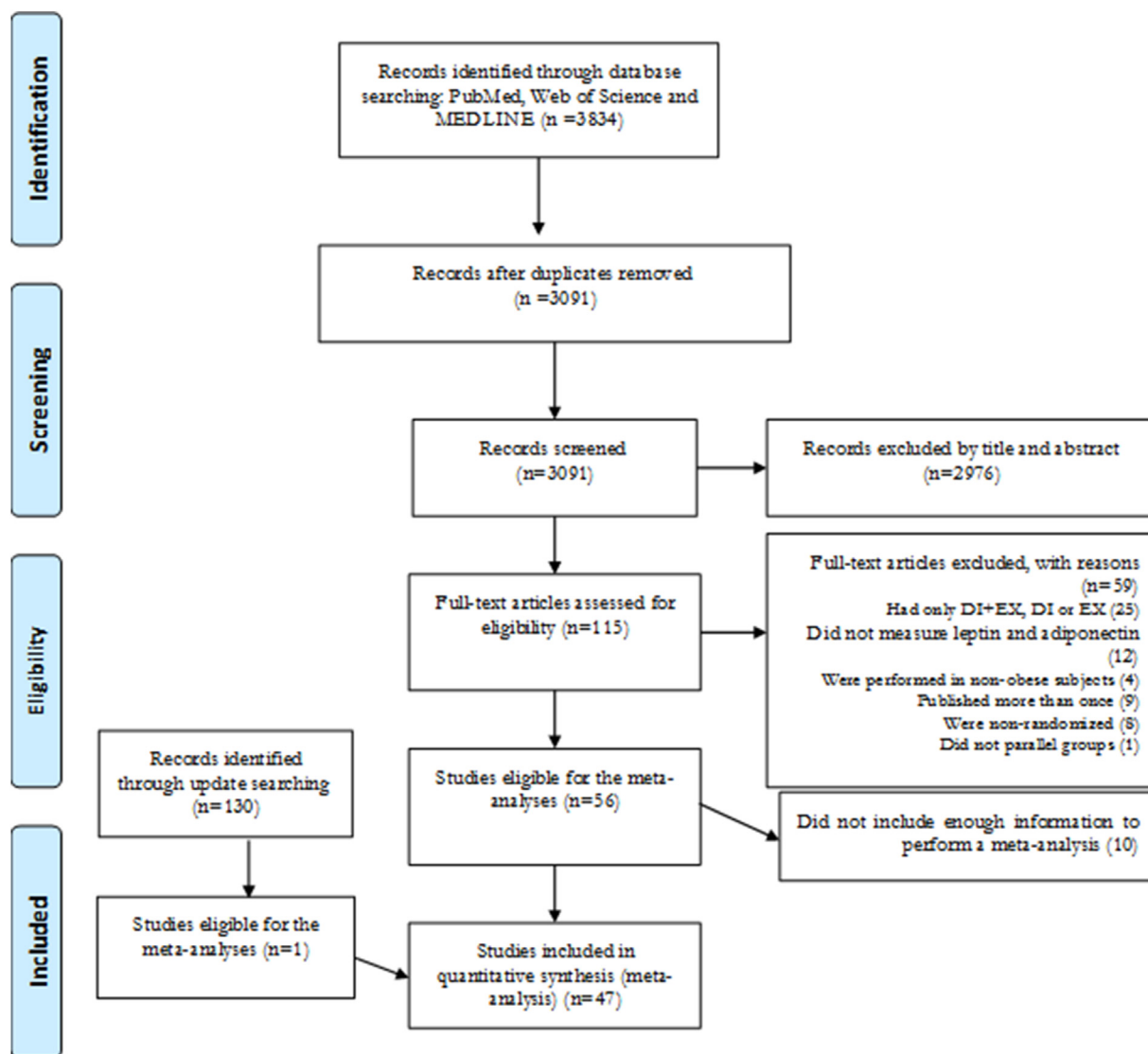
Fig. 1. Flow diagram of systematic literature search. DI, dietary intervention; EX, exercise training.

from 800 to 2100 kcal/d. The overall quality of the studies ranged from 3 to 9 out of a maximum of 9 (Supplementary Table 2).

Meta-analysis

Ex compared with DI

Leptin. Based on 18 intervention arms (18 studies), DI reduced the concentration of leptin (SMD: −0.30; 95% CI: −0.45, −0.14; $P = 0.001$) compared with Ex (Fig. 2). There was significant heterogeneity among the included studies ($I^2 = 38.16\%$; $P = 0.05$). The results of the visual interpretation of funnel plots and Egger test ($P = 0.81$) did not reveal publication biases. The sensitivity analysis conducted by omitting an individual study showed that the significance did not change. In addition, the sensitivity analysis conducted by omitting studies involving participants aged <18 y indicated that DI reduced the concentration of leptin (SMD: −0.26; $P = 0.003$) compared with Ex.

Adiponectin. Based on 17 intervention arms (17 studies), DI increased the concentration of adiponectin (SMD: 0.23; 95% CI: 0.10, 0.36; $P = 0.001$) compared with Ex (Fig. 3). There was no significant heterogeneity among the studies ($I^2 = 0.00\%$;

$P = 0.68$). The results of the visual interpretation of funnel plots and Egger test did not reveal publication biases ($P = 0.90$). The sensitivity analysis conducted by omitting individual studies showed that 1 study was a source of heterogeneity and influenced our results. Therefore, the main analyses were repeated after excluding that study [56]. In addition, the sensitivity analysis conducted by omitting studies involving participants aged <18 y indicated that DI increased the concentration of adiponectin (SMD: 0.18; $P = 0.01$) compared with Ex.

Ex + DI compared with Ex

Leptin. Based on 15 intervention arms (15 studies), Ex + DI reduced the concentration of leptin (SMD: −0.34; 95% CI: −0.47, −0.20; $P = 0.001$) compared with Ex (Fig. 4). There was no significant heterogeneity among the studies ($I^2 = 21.18\%$; $P = 0.218$). The results of the visual interpretation of funnel plots and Egger test did not reveal publication biases ($P = 0.67$). The sensitivity analysis conducted by omitting individual studies showed that the significance and direction of changes were unaffected for leptin outcomes. In addition, the sensitivity analysis conducted by omitting studies involving participants aged <18 y

Table 1
Study and participant characteristics.[1]

Reference, (author(s) [year])	Sample size (n/groups)	Sex (%)	Outcome measured	Age,[4] (y)	BMI[4] (kg/m²)	Weight status[2]	Health status
Abbenhardt et al. (2013) [84]	352 (EX + DI: 117; DI: 118; EX: 117)	F (100%)	Leptin, adiponectin	EX + DI: 58.00 ± 4.40 DI: 58.10 ± 5.90 EX: 58.10 ± 5.00	EX + DI: 31.00 ± 4.30 DI: 31.00 ± 3.90 EX: 30.70 ± 3.70	Obese	Healthy postmenopausal
Auerbach et al. (2013) [54]	32 (DI: 16; EX: 16)	M (100%)	Leptin, adiponectin	DI: 32.00 ± 6.93 EX: 28.00 ± 3.46	DI: 28.00 ± 1.39 EX: 28.30 ± 1.04	Overweight	Healthy
Aydemir et al. (2020) [85]	85 (EX + DI: 30; DI: 28; EX: 27)	F (42%)/M (58%)	Leptin, adiponectin	EX + DI: 52.90 ± 8.60 DI: 55.60 ± 12.60 EX: 54.50 ± 11.70	EX + DI: 34.00 ± 6.70 DI: 33.50 ± 7.30 EX: 32.50 ± 5.80	Obese	Chronic kidney disease
Beavers et al. (2013) [82]	195 (EX + DI: 98; EX: 97)	F (67%)/M (33%)	Leptin, adiponectin	EX + DI: 67.00 ± 4.80 EX: 67.00 ± 4.80	EX + DI: 33.10 ± 4.10 EX: 32.80 ± 3.90	Obese	Cardiovascular or cardiometabolic dysfunction
Ben Ounis et al. (2008) [86]	18 (EX + DI: 6; DI: 6; EX: 6)	F (100%)	Adiponectin	EX + DI: 13.00 ± 4.00 DI: 13.40 ± 2.00 EX: 13.10 ± 1.00	EX + DI: 30.00 ± 2.20 DI: 30.50 ± 2.20 EX: 30.60 ± 2.30	Obese[3]	Healthy
Bouchonville et al. (2014) [87]	80 (EX + DI: 28; DI: 26; EX: 26)	F (61%)/M (39%)	Adiponectin	EX + DI: 70.00 ± 4.00 DI: 70.00 ± 4.00 EX: 70.00 ± 4.00	EX + DI: 37.20 ± 5.40 DI: 37.20 ± 4.50 EX: 36.90 ± 5.40	Obese	Healthy
Christensen et al. (1998) [60]	100 (EX + DI: 49; DI: 51)	F (100%)	Leptin	EX + DI: 49–58 DI: 49–58	EX + DI: 25–42 DI: 25–42	Obese and overweight	Healthy
Christiansen et al. (2010) [88]	79 (EX + DI: 25; DI: 29; EX: 25)	F (48%)/M (52%)	Adiponectin	EX + DI: 37.50 ± 8.00 DI: 35.60 ± 7.00 EX: 37.20 ± 7.00	EX + DI: 34.20 ± 3.00 DI: 35.30 ± 4.00 EX: 33.40 ± 4.00	Obese	Healthy
Civitarese et al. (2007) [61]	24 (EX + DI: 12; DI: 12)	F (54%)/M (46%)	Adiponectin	EX + DI: 34.90 ± 5.54 DI: 38.90 ± 5.54	EX + DI: 27.80 ± 4.20 DI: 27.80 ± 4.20	Overweight	Healthy
Cooper et al. (2012) [62]	90 (EX + DI: 45; DI: 45)	F (91%)/M (11%)	Leptin, adiponectin	EX + DI: 46.80 ± 6.50 DI: 47.50 ± 6.20	EX + DI: 43.80 ± 4.80 DI: 44.00 ± 6.60	Obese	Healthy
de Sousa et al. (2019) [63]	51 (EX + DI: 22; DI: 29)	F (57%)/M (43%)	Leptin	EX + DI: 61.10 ± 6.40 DI: 61.10 ± 6.40	EX + DI: 33.00 ± 3.92 DI: 32.70 ± 4.69	Obese	Type 2 diabetes
Elloumi et al. (2009) [89]	21 (EX + DI: 7; DI: 7; EX: 7)	M (100%)	Leptin, adiponectin	EX + DI: 13.20 ± 0.90 DI: 13.10 ± 0.50 EX: 13.10 ± 0.70	EX + DI: 31.60 ± 3.30 DI: 30.70 ± 2.30 EX: 30.30 ± 3.20	Obese[3]	Healthy
Figueroa et al. (2013) [90]	45 (EX + DI: 15; DI: 15; EX: 15)	F (100%)	Leptin, adiponectin	EX + DI: 54.00 ± 3.74 DI: 54.00 ± 3.61 EX: 54.00 ± 3.74	EX + DI: 32.7 ± 4.11 DI: 34.80 ± 4.33 EX: 32.60 ± 3.74	Obese	Healthy postmenopausal
Freitas et al. (2017) [64]	55 (EX + DI: 28; DI: 27)	F (98%)/M (2%)	Leptin, adiponectin	EX + DI: 45.90 ± 7.70 DI: 48.50 ± 9.60	EX + DI: 38.10 ± 2.80 DI: 37.20 ± 2.10	Obese	Asthma
Galbreath et al. (2018) [83]	72 (EX + DI$_1$: 24; EX + DI$_2$: 24; EX: 24)	F (100%)	leptin, adiponectin	EX + DI$_1$ 63.30 ± 4.80 EX + DI$_2$: 65.50 ± 5.20 EX: 66.00 ± 4.30	EX + DI$_1$ 30.30 ± 4.00 EX + DI$_2$: 31.30 ± 4.20 EX: 29.90 ± 4.10	Obese	Healthy postmenopausal
Georgoulis et al. (2021) [65]	122 (EX + DI: 60; DI: 62)	F (25%)/M (75%)	Adiponectin	EX + DI: 48.00 ± 10.00 DI: 50.00 ± 9.10	EX + DI: 35.80 ± 6.00 DI: 34.90 ± 6.50	Obese	Obstructive sleep apnea
Giannopoulou et al. (2005) [91]	33 (EX + DI: 11; DI: 11; EX: 11)	F (100%)	Leptin, adiponectin	EX + DI: 57.40 ± 5.64 DI: 58.50 ± 5.64 EX: 55.50 ± 5.64	EX + DI: 33.70 ± 6.30 DI: 34.30 ± 6.30 EX: 35.90 ± 6.30	Obese	Type 2 diabetes
Gilbertson et al. (2019) [66]	24 (EX + DI: 12; DI: 12)	F (100%)	Leptin, adiponectin	EX + DI: 50.80 ± 11.43 DI: 45.70 ± 12.12	EX + DI: 37.80 ± 7.27 DI: 37.80 ± 5.54	Obese	Healthy postmenopausal
Ibanez et al. (2010) [67]	25 (EX + DI: 13; DI: 12)	F (100%)	Leptin, adiponectin	DI: 51.40 ± 5.50 EX: 48.60 ± 6.40	DI: 34.60 ± 3.40 EX: 35.00 ± 3.10	Obese	Healthy

(continued on next page)

Table 1 (*continued*)

Reference, (author(s) [year])	Sample size (n/ groups)	Sex (%)	Outcome measured	Age,[4] (y)	BMI[4] (kg/m²)	Weight status[2]	Health status
Kelishadi et al. (2008) [55]	100 (DI: 50; EX: 50)	F/M (not described)	Leptin	DI: 7.70 ± 1.20 EX: 7.70 ± 1.20	DI: 21.10 ± 2.50 EX: 21.10 ± 2.50	Obese[3]	Healthy
Khanna et al. (2017) [68]	86 (EX + DI: 59; DI: 27)	F (100%)	Leptin	EX + DI: 43.50 ± 11.20 DI: 49.40 ± 10.70	EX + DI: 34.90 ± 6.40 DI: 34.70 ± 4.60	Obese	Healthy
Khoo et al. (2015) [56]	80 (DI: 40; EX: 40)	M (100%)	Leptin, adiponectin	DI: 41.80 ± 7.20 EX: 43.30 ± 9.00	DI: 32.10 ± 3.00 EX: 32.10 ± 2.60	Obese	Healthy
König et al. (2015) [69]	50 (EX + DI: 25; DI: 25)	F (57%)/M (43%)	Leptin	EX + DI: 49.00 ± 8.00 DI: 49.00 ± 8.00	EX + DI: 32.50 ± 2.65 DI: 32.90 ± 1.88	Obese	Type 2 diabetes
Lakhdar et al. (2019) [92]	30 (EX + DI: 10; DI: 10; EX: 10)	F (100%)	Adiponectin	EX + DI: 38.90 ± 4.37 DI: 38.90 ± 3.94 EX: 36.20 ± 5.00	EX + DI: 32.98 ± 2.17 DI: 33.02 ± 1.89 EX: 33.52 ± 3.75	Obese	Healthy
Lam et al. (2016) [70]	16 (EX + DI: 8; DI: 8)	F (50%)/M (50%)	Leptin, adiponectin	EX + DI: 37.90 ± 5.09 DI: 39.00 ± 5.94	EX + DI: 27.90 ± 1.70 DI: 27.70 ± 1.41	Overweight	Healthy
Liu et al. (2018) [71]	50 (EX + DI: 30; DI: 20)	F (100%)	Leptin, adiponectin	EX + DI: 14.60 ± 0.70 DI: 14.70 ± 0.80	EX + DI: 33.90 ± 3.10 DI: 34.60 ± 4.90	Obese	Healthy
Loria-kohen et al. (2013) [72]	119 (EX₁ + DI: 30; EX₂ + DI: 30; EX₂ + DI: 30; DI: 29)	F (61%)/M (39%)	Leptin	EX₁ + DI: 35.69 ± 8.07 EX₂ + DI: 36.46 ± 8.9 EX₃ + DI: 36.71 ± 6.99 DI: 36.77 ± 9.24	EX₁ + DI: 28.91 ± 1.78 EX₂ + DI: 29.51 ± 2.00 EX₃ + DI: 28.32 ± 1.54 DI: 28.50 ± 1.29	Overweight	Healthy
McNeil et al. (2015) [73]	93 (EX + DI: 28; DI: 65)	F (100%)	Leptin	EX + DI: 58.10 ± 4.80 DI: 58.10 ± 4.80	EX + DI: 32.10 ± 4.30 DI: 32.10 ± 4.30	Obese	Healthy
Miller et al. (2004) [93]	233 (EX + DI: 74; DI: 80; EX: 79)	F (74%)/M (26%)	Leptin	EX + DI: 68.70 ± 6.70 DI: 67.80 ± 5.50 EX: 69.10 ± 6.50	EX + DI: 34.20 ± 5.60 DI: 34.50 ± 4.90 EX: 34.20 ± 4.80	Obese	Symptomatic knee osteoarthritis
Murakami et al. (2007) [74]	50 (EX + DI: 25; DI: 25)	F (50%)/M (50%)	Leptin	EX + DI: 51.00 ± 10.29 DI: 48.20 ± 8.06	EX + DI: 27.10 ± 1.47 DI: 27.80 ± 2.12	Overweight	Healthy
Rokling-andersen et al. (2007) [94]	176 (EX + DI: 67; DI: 55; EX: 54)	M (100%)	Leptin, adiponectin	EX + DI: 45.10 ± 2.51 DI: 45.10 ± 2.51 EX: 45.10 ± 2.51	EX + DI: 28.40 ± 3.40 DI: 29.20 ± 3.80 EX: 28.50 ± 3.30	Overweight	Cardiovascular and diabetes risk factors
Sartor et al. (2010) [75]	21 (EX + DI: 11; DI: 10)	F (74%)/M (26%)	Leptin	EX + DI: 37.00 ± 10.00 DI: 41.00 ± 14.00	EX + DI: 32.00 ± 4.00 DI: 32.00 ± 3.00	Obese	Healthy
Scott et al. (2013) [95]	46 (EX + DI: 14; DI: 18; EX: 14)	F (52%)/M (48%)	Leptin, adiponectin	EX + DI: 33.90 ± 11.50 DI: 44.70 ± 14.70 EX: 42.20 ± 11.50	EX + DI: 32.70 ± 3.40 DI: 34.70 ± 4.00 EX: 32.80 ± 2.50	Obese	Asthma
Shah et al. (2011) [96]	80 (EX + DI: 28; DI: 26; EX: 26)	F (61%)/M (39%)	Leptin	EX + DI: 70.00 ± 4.00 DI: 70.00 ± 4.00 EX: 70.00 ± 4.00	EX + DI: 37.20 ± 5.40 DI: 37.20 ± 4.50 EX: 36.90 ± 5.40	Obese	Healthy
Shalitin et al. (2009) [97]	174 (EX + DI: 58; DI: 58; EX: 58)	F (50%)/M (50%)	Leptin, adiponectin	EX + DI: 8.20 ± 11.57 DI: 8.51 ± 11.27 EX: 8.21 ± 12.84	EX + DI: 25.9 ± 3.78 DI: 26.50 ± 3.78 EX: 25.50 ± 3.75	Obese[3]	Healthy
Straznicky et al. (2010) [76]	40 (EX + DI: 20, DI: 20)	F (40%)/M (60%)	Leptin	EX + DI: 54.00 ± 4.47 DI: 55.00 ± 4.47	EX + DI: 31.80 ± 3.57 DI: 32.20 ± 4.02	Obese	≥2 metabolic syndrome parameters
Sun et al. (2021) [77]	50 (EX₁ + DI: 17; EX₂ + DI: 17; DI: 16)	F (100%)	Leptin	EX₁ + DI: 21.40 ± 2.90 EX₂ + DI: 21.80 ± 3.10 DI: 21.60 ± 4.30	EX₁ + DI: 24.80 ± 2.00 EX₂ + DI: 24.80 ± 1.90 DI: 24.80 ± 3.30	Overweight	Healthy
Thong et al. (2000) [57]	30 (DI: 14; EX: 16)	M (100%)	Leptin	DI: 42.60 ± 9.73 EX: 45.00 ± 7.60	DI: 30.70 ± 1.87 EX: 32.30 ± 2.00	Obese	Healthy

Table 1 (*continued*)

Reference, (author(s) [year])	Sample size (n/groups)	Sex (%)	Outcome measured	Age,[4] (y)	BMI[4] (kg/m^2)	Weight status[2]	Health status
Volpe et al. (2008) [98]	90 (EX + DI: 28; DI: 28; EX: 34)	F (51%)/M (49%)	Leptin	EX + DI$_f$: 46.51 ± 4.80 EX + DI$_m$: 44.90 ± 9.80 DI$_f$: 44.00 ± 6.50 DI$_m$: 43.90 ± 6.50 EX$_f$: 42.40 ± 7.30 EX$_m$: 44.60 ± 8.10	EX + DI$_f$: 30.40 ± 2.50 EX + DI$_m$: 30.50 ± 3.20 DI$_f$: 30.80 ± 2.80 DI$_m$: 31.10 ± 3.30 EX$_f$: 30.50 ± 3.00 EX$_m$: 30.50 ± 3.60	Obese	Healthy
Wang et al. (2015) [78]	70 (EX + DI: 48; DI: 22)	F (100%)	Adiponectin	EX + DI: 58.40 ± 5.20 DI: 58.50 ± 6.10	EX + DI: 32.90 ± 3.70 DI: 33.50 ± 3.80	Obese	Healthy
Weiss et al. (2006) [58]	45 (DI: 21; EX: 24)	F (60%)/M (40%)	Adiponectin	DI: 55.60 ± 3.60 EX: 58.80 ± 2.80	DI: 27.10 ± 2.50 EX: 27.10 ± 1.90	Overweight	Healthy
Weiss et al. (2017) [99]	69 (EX + DI: 13; DI: 13; EX: 13)	F (75%)/M (25%)	Leptin, adiponectin	EX + DI: 57.00 ± 7.00 DI: 57.00 ± 5.00 EX: 56.00 ± 6.00	EX + DI: 28.30 ± 1.80 DI: 27.70 ± 1.70 EX: 27.00 ± 1.50	Overweight	Healthy
Wiklund et al. (2014) [59]	90 (DI: 45; EX: 45)	F (100%)	Leptin, adiponectin	DI: 42.20 ± 7.50 EX: 41.90 ± 7.30	DI: 31.30 ± 3.10 EX: 28.40 ± 2.10	Overweight	Healthy
Yadav et al. (2019) [79]	260 (EX + DI: 130; DI: 130)	F (68%)/M (32%)	Leptin, adiponectin	EX + DI: 37.70 ± 6.30 DI: 37.60 ± 6.40	EX + DI: 32.30 ± 5.03 DI: 31.40 ± 5.20	Obese	Metabolic syndrome
Yazdanparast et al. (2020) [80]	44 (EX + DI: 22; DI: 22)	F (100%)	Leptin, adiponectin	EX + DI: 40.00 ± 5.90 DI: 40.00 ± 5.90	EX + DI: 30.15 ± 3.15 DI: 31.67 ± 4.64	Obese	Healthy
Yoshimura et al. (2014) [81]	89 (EX + DI: 44; DI: 45)	F (76%)/M (24%)	Leptin	EX + DI: 61.00 ± 7.75 DI: 52.00 ± 8.49	EX + DI: 27.30 ± 4.26 DI: 28.40 ± 4.24	Overweight	Healthy
Cipryan et al. (2022) [53]	88 (EX + DI: 30; DI: 30; EX: 28)	F (71%)/M (29%)	Leptin, adiponectin	EX + DI: 42.00 ± 14.94 DI: 43.17 ± 12.97 EX: 46.03 ± 11.49	EX + DI: 31.10 ± 6.21 DI: 30.67 ± 4.17 EX: 28.83 ± 3.17	Obese	Healthy

DI, diet intervention; EX, exercise training.

[1] n = 47 studies.

[2] Categories for weight status based on BMI (in kg/m^2): overweight BMI, 25.0–29.9; obese BMI, ≥30.0.

[3] Categories for weight status based on BMI percentile for age and sex: obese BMI, values >95th percentile.

[4] Data presented as mean and SD, if not available, were presented as range.

Table 2

Characteristics of diet and exercise interventions[1]

Reference (author(s) [y])	Exercise characteristics			Diet characteristics		Intervention durations
	Type	Exercise protocol description	Supervised or nonsupervised[2]	Dietary intervention	Energy restriction rate[3]	
Abbenhardt et al. (2013) [84]	Aerobic	45 min at 70%–85% $HR_{max/peak}$, 5 d/wk	Supervised and nonsupervised	Total energy intake: 1200–2000 kcal/d	Mild	12 mo
Auerbach et al. (2013) [54]	Aerobic + HIT	Jogging, cycling, rowing, cross training at 65% HRR + 5–6 sets for 3–4 min at 85% HRR, 5 d/wk	Supervised	Reduced energy intake by 600 kcal/d	Severe	12 wk
Aydemir et al. (2020) [85]	Aerobic	30–45-min use of a treadmill, elliptical cross-trainer, Nu-Step cross-trainer, and cycle at 60%–80% $VO_{2max/peak}$, 3 d/wk	Supervised	Reduced energy intake by 10%–15% daily	Mild	4 mo
Beavers et al. (2013) [82]	Aerobic	30-min walking at a rating of 13 on the BRPE, 5 d/wk	Supervised and nonsupervised	Reduced weight: 0.3 kg/wk	Mild	18 mo
Ben Ounis et al. (2008) [86]	Aerobic	90-min running, jumping, and playing with a ball at maximal fat oxidation point, 4 d/wk	Supervised	Reduced energy intake by 500 kcal/d	Mild	2 mo
Bouchonville et al. (2014) [87]	Combined	Resistance: whole-body exercises; 1–2 sets with 8–12 repetitions at 65%–85% 1RM Aerobic: 30 min at 65%–85% $HR_{max/peak}$, 3 d/wk	Supervised	Reduced energy intake by 500–750 kcal/d	Severe	12 months
Christensen et al. (1998) [60]	Combined	Resistance: whole-body exercises; 2–3 sets with 7–15 repetitions at 65% 1RM Aerobic: cycling and walking at 70% $VO_{2max/peak}$, 3 d/wk	Supervised	Total energy intake: 4.2 MJ/d	Severe	12 wk
Christiansen et al. (2010) [88]	Aerobic	60–75 min until 500–600 kcal, 3 d/wk	Supervised	EX + DI: total energy intake of 800 kcal/d DI: total energy intake of 600 kcal/d	Severe	12 wk
Civitarese et al. (2007) [61]	Aerobic	Walking, running, and stationary cycling until 12.5% of daily energy expenditure, 5 d/wk	Supervised and nonsupervised	EX + DI: reduced energy intake by 12.5% daily DI: reduced energy intake by 25% daily	Mild	6 mo
Cooper et al. (2012) [62]	Aerobic	60-min brisk walking at moderate intensity, 5 d/wk	Nonsupervised	Total energy intake of 1200–2100 kcal/d	Mild	6 mo
de Sousa et al. (2019) [63]	HIT	2 sets of 12-min soccer playing and 3-min rest, 3 d/wk	Supervised	Reduced energy intake by 500–1000 kcal/d	Severe	12 wk
Elloumi et al. (2009) [89]	Aerobic	90-min running, jumping, and playing with a ball at maximal fat oxidation point, 4 d/wk	Supervised	Reduced energy intake by 500 kcal/d	Mild	2 mo
Figueroa et al. (2013) [90]	Resistance	Lower-body exercises; 2–3 sets with 18–22 repetitions at low intensity, 3 d/wk	Supervised	Total energy intake: 1250 kcal/d, including portion-controlled foods	Mild	12 wk
Freitas et al. (2017) [64]	Combined	Resistance: exercise for major muscle groups Aerobic: at 50%–75% $VO_{2max/peak}$, 2 d/wk	Supervised	Reduced energy intake by a nutritionist	Mild	3 mo

Table 2 (*continued*)

Reference (author(s) [y])	Exercise characteristics			Diet characteristics		Intervention durations
	Type	Exercise protocol description	Supervised or nonsupervised[2]	Dietary intervention	Energy restriction rate[3]	
Galbreath et al. (2018) [83]	Resistance	Whole-body circuit exercises; with 30 s at 61%–82% 1RM, 3 d/wk	Supervised	EX + DI_1: total energy intake of 1200–2100 kcal/d, with high carbohydrate EX + DI_2: total energy intake of 1200–2100 kcal/d, with high protein	Mild	14 wk
Georgoulis et al. (2021) [65]	Aerobic	≥150 min/wk outdoor and convivial activities	Nonsupervised	DI: reduced 5%–10% of body weight with Mediterranean diet	ND	6 mo
Giannopoulou et al. (2005) [91]	Aerobic	60-min walking at 65%–70% $VO_{2max/peak}$, 3–4 d/wk	Supervised	EX +DI: reduced energy intake by 1460 kJ/d DI: reduced energy intake by 2510 kJ/d	EX + DI: mild DI: severe	14 wk
Gilbertson et al. (2019) [66]	HIT	5–10 sets of 90% $HR_{max/peak}$ by 3-min recovery at 50% $HR_{max/peak}$, 6 d/wk	Supervised	Total energy intake of 1000–1200 kcal/d	Severe	13 d
Ibanez et al. (2010) [67]	Resistance	45–60-min whole-body exercises at 50%–80% 1RM, 2 d/wk	Supervised	Reduced energy intake by 500 kcal/d	Mild	16 wk
Kelishadi et al. (2008) [55]	Aerobic	Physical training included 20 min of fitness-orientated activities and 20 min of playing games and running, 5 d/wk	Nonsupervised	A balanced diet and nutrition consultation	Mild	6 mo
Khanna et al. (2017) [68]	Combined	Resistance: whole-body exercises; with 30 s at 60%–80% 1RM Aerobic: 30-min walking at 60–80% $HR_{max/peak}$, 4 d/wk	Supervised	Total energy intake: 1200–1500 kcal/d	Mild	12 wk
Khoo et al. (2015) [56]	Combined	90–300-min weekly aerobic or resistance training according recommended by the American College of Sports Medicine, 3–7 d/wk	Supervised and nonsupervised	Reduced energy intake by 500 kcal/d	Mild	24 wk
König et al. (2015) [69]	Aerobic	At 55%–75% of $VO_{2max/peak}$, 3 d/wk	Supervised and nonsupervised	EX + DI: total energy intake of 1200–1800 kcal/d DI: total energy intake 1000–1700 kcal/d	Mild	6 mo
Lakhdar et al. (2019) [92]	Aerobic	30–45-min walking and running at 55%–80% $HR_{max/peak}$, 3 d/wk	Nonsupervised	Reduced energy intake by 2093 kJ/d	Mild	24 wk
Lam et al. (2016) [70]	Aerobic	Until 12.5% of total daily energy expenditure	Nonsupervised	EX + DI: reduced energy intake by 12.5% of total daily energy expenditure DI: reduced energy intake by 25% of total daily energy expenditure	Mild	6 mo
Liu et al. (2018) [71]	Aerobic	120-min brisk walking, swimming, jogging, table tennis, and badminton at 100–140 beats of HR, 12 times/wk	Supervised	Total energy intake: 1400–1600 kcal/d	Mild	4 wk
Loria-kohen et al. (2013) [72]	EX_1: aerobic EX_2: resistance EX_3: combined	EX_1: cycling and jogging at 50%–60% HRR, 3 d/wk EX_2: whole-body exercises; with 15 repetitions at 50%–60% 15RM, 3 d/wk EX_3: combined EX_1 and EX_2, 3 d/wk	Supervised	Total energy intake 5028–12,570 kJ/d	Mild	22 wk

(*continued on next page*)

Table 2 (*continued*)

Reference (author(s) [y])	Exercise characteristics			Diet characteristics		Intervention durations
	Type	Exercise protocol description	Supervised or nonsupervised[2]	Dietary intervention	Energy restriction rate[3]	
McNeil et al. (2015) [73]	Resistance	Whole-body exercises; 2–4 sets with 8–15 repetitions at 65%–75% 1RM, 3 d/wk	Supervised	Total energy intake of 1000–1790 kcal/d	Mild	6 mo
Miller et al. (2004) [93]	Combined	Resistance: lower-body exercises; 2 sets with 12 repetitions using ankle cuff weights and a weighted vest aerobic: 30-min walking at 50%–85% HRR, 3 d/wk	Supervised and nonsupervised	Reduced energy intake by 250–500 kcal/d	Mild	18 mo
Murakami et al. (2007) [74]	Aerobic	60 min at anaerobic threshold, 3 d/wk	Supervised	Total energy intake: 1200–1680 kcal/d	Mild	12 wk
Rokling-andersen et al. (2007) [94]	Aerobic	60-min circuit training and fast walking or jogging an average of 1.8 h/wk throughout the year, 3 d/wk	Supervised	Reduced weight: 0.5–2 kg/mo	Mild	12 mo
Sartor et al. (2010) [75]	HIT	10 sets of 4 min at 90% $VO_{2max/peak}$ by 2–3-min recovery, 3 d/wk	Supervised	Total energy intake to 75% of daily energy expenditure	Mild	14 d
Scott et al. (2013) [95]	Combined	Aerobic target of 10,000 steps per day and resistance training at the gymnasium, 3 d/wk	Supervised and nonsupervised	Total energy intake of 885–1170 kcal/d	Severe	12 wk
Shah et al. (2011) [96]	Combined	Resistance: whole-body exercises; 1–3 sets with 6–12 repetitions at 65%–80% 1RM Aerobic: 30 min at 65%–85% $HR_{max/peak}$, 3 d/wk	Supervised	Reduced energy intake by 500–750 kcal/d	Severe	12 mo
Shalitin et al. (2009) [97]	Combined	Aerobic: 45-min team sports and running games Resistance: 45-min sit-ups, hand-lifting of small weights, and ball exercise, 3 d/wk	Supervised	Total energy intake of 1200 kcal/d	Mild	12 wk
Straznicky et al. (2010) [76]	Aerobic	40-min cycling at 65% $HR_{max/peak}$, 3 d/wk	Supervised and nonsupervised	Modified DASH, reduced energy intake by 600 kcal/d	Severe	12 wk
Sun et al. (2021) [77]	EX_1: HIT EX_2: aerobic	EX_1: 10 sets of 6-s cycling at peak workload by 9-s recovery, 5 d/wk EX_2: 30-min cycling at 50%–60% $VO_{2max/peak}$, 5 d/wk	Supervised	Reduced daily carbohydrate intake; approximately 65%, 25%, and 10% of their daily energy intakes were obtained from fats, proteins, and carbohydrates	Mild	4 wk
Thong et al. (2000) [57]	Aerobic	Brisk walking and jogging until 700 kcal at 80% $HR_{max/peak}$, 7 d/wk	Supervised	Reduced energy intake by 700 kcal/d	Severe	12 wk
Volpe et al. (2008) [98]	Aerobic	30-min indoor skiing, 3–5 d/wk	Supervised	Reduced weight: 0.5–1 kg/wk	Severe	6 mo
Wang et al. (2015) [78]	Aerobic	Walking until 700 kcal/wk at 45%–75% HRR, 3 d/wk	Supervised	EX + DI: reduced energy intake by 2100 kcal/wk DI: reduced energy intake by 2800 kcal/wk	Mild	20 wk
Weiss et al. (2006) [58]	Aerobic	Until 16%–20% of total daily energy expenditure, 7 d/wk	Supervised	Reduced energy intake by 16%–20% of total daily energy expenditure	Mild	12 mo
Weiss et al. (2017) [99]	Aerobic	Cardiovascular exercise and functional physical activities until 20% of total daily energy expenditure, 7 d/wk	Supervised and nonsupervised	Reduced energy intake by 20% of total daily energy expenditure	Mild	3–6 mo

Table 2 (*continued*)

Reference (author(s) [y])	Exercise characteristics			Diet characteristics		Intervention durations
	Type	Exercise protocol description	Supervised or nonsupervised[2]	Dietary intervention	Energy restriction rate[3]	
Wiklund et al. (2014) [59]	Aerobic	30–60-min Nordic walking at 60%–75% $HR_{max/peak}$, 3–4 d/wk	Supervised and nonsupervised	Reduced weight of 0.5 kg/wk	Severe	6 wk
Yadav et al. (2019) [79]	Yoga	120-min yoga training, 6 d/wk	Supervised and nonsupervised	Recommended diet included 50%–60% carbohydrate, <30% total fat, <10% saturated fat, 10%–15% monounsaturated fat, 5%–8% polyunsaturated fat, cholesterol <200–300 mg/d, and protein 10%–15%	ND	12 wk
Yazdanparast et al. (2020) [80]	Yoga	60-min yoga training (200 kcal/d), 5 d/wk	Supervised	EX + DI: reduced energy intake by 300 kcal/d DI: reduced energy intake by 500 kcal/d	Mild	8 wk
Yoshimura et al. (2014) [81]	Aerobic	60-min running, walking, and cycling at lactate threshold, 5 d/wk	Supervised and nonsupervised	Total energy intake of 25 kcal/kg of ideal body weight	Mild	12 wk
Cipryan et al. (2022) [53]	HIT	4–8 sets of 3 min at a rating of 18–19 BRPE by 3-min recovery at a rating of 9–11 BRPE, 3 d/wk	Nonsupervised	Very-low-carbohydrate high-fat, maximum 50 g of carbohydrates per day	Mild	12 wk

DI, diet intervention; EX, exercise; HIT, high-intensity interval training; $HR_{max/peak}$, maximal or peak heart rate; HRR, heart rate reverse; 1RM, one-repetition maximum; BRPE, Borg rating of perceived exertion; ND, not described.

[1] n = 47 studies.

[2] Categories for control of training: supervised, whole training sessions controlled; nonsupervised, whole training sessions not controlled; and supervised and nonsupervised, some training sessions controlled.

[3] Categories for energy restriction. Mild energy restriction is defined as a total energy intake of ≥1200 kcal/d, energy restriction of ≤500 kcal/d, energy restriction of ≤25% of daily energy intake or average weight loss of <0.5 kg/wk. Severe energy restriction is defined as a daily energy intake of <1200 kcal/d, energy restriction of >500 kcal/d, energy restriction of >25% of daily energy intake or average weight loss of ≥ 0.5 kg/wk.
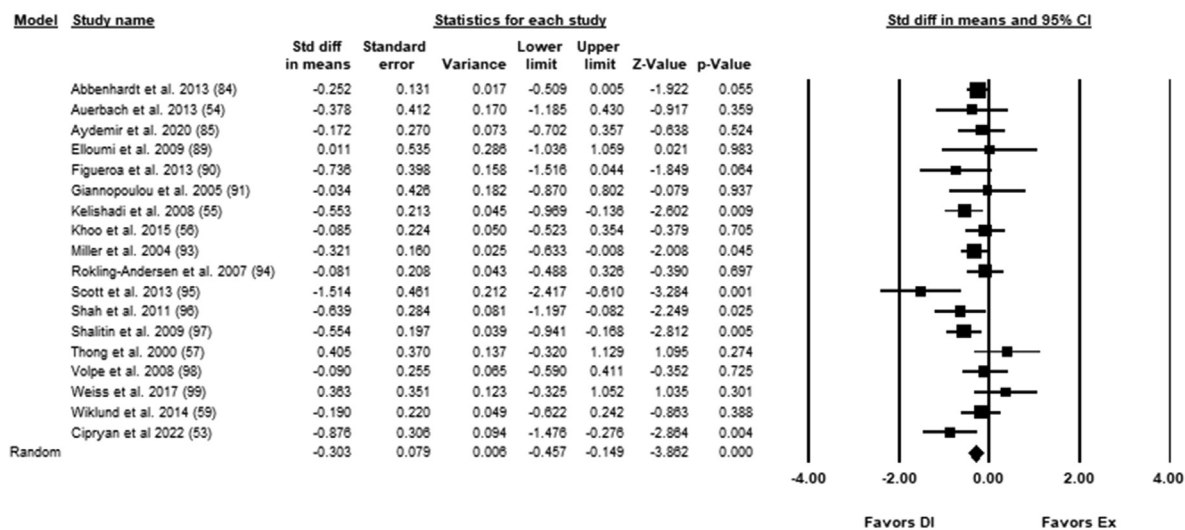
Fig. 2. Forest plot of the effects of exercise training compared with those of dietary intervention on leptin in individuals who were overweight and those with obesity and aged 7–70 y. Data are reported as standardized mean difference and 95% CIs (95% lower and upper limits). DI, dietary intervention; Ex, exercise training.
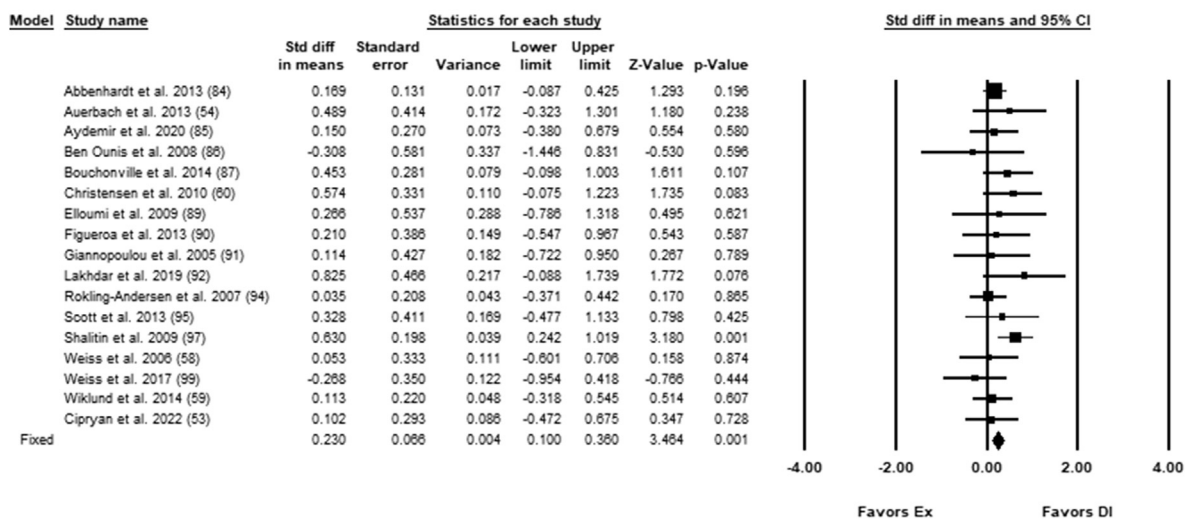

Fig. 3. Forest plot of the effects of exercise training compared with those of dietary intervention on adiponectin in individuals who are overweight and those with obesity and aged 7–70 y. Data are reported as standardized mean difference and 95% CIs (95% lower and upper limits). DI, dietary intervention; Ex, exercise training.

indicated that Ex + DI decreased the concentration of leptin (SMD: −0.31; $P = 0.001$) compared with Ex.

Adiponectin. Based on 16 intervention arms (16 studies), Ex + DI increased the concentration of adiponectin (SMD: 0.37; 95% CI: 0.12, 0.63; $P = 0.004$) compared with Ex (Fig. 5). There was significant heterogeneity among the studies ($I^2 = 70.28\%$; $P = 0.001$). The visual interpretation of funnel plots suggested publication biases; however, the results of the Egger test did not ($P = 0.10$). The trim-and-fill method identified 2 missing studies from the right side of the plot. When these missing studies were accounted for, the overall change was 0.49 (95% CI: 0.23, 0.76),

confirming an increase in SMD. The sensitivity analysis showed that the significance and direction of adiponectin outcomes were unaffected. In addition, the sensitivity analysis conducted by omitting studies involving participants aged <18 y indicated that for adults aged ≥18 y, Ex + DI increased the concentration of adiponectin (SMD: 0.27; $P = 0.03$) compared with Ex.

Ex + DI compared with DI

Leptin. Based on 32 intervention arms (32 studies), Ex + DI did not significantly reduce the concentration of leptin (SMD: −0.13; 95% CI: −0.26, −0.006; $P = 0.06$) compared with DI
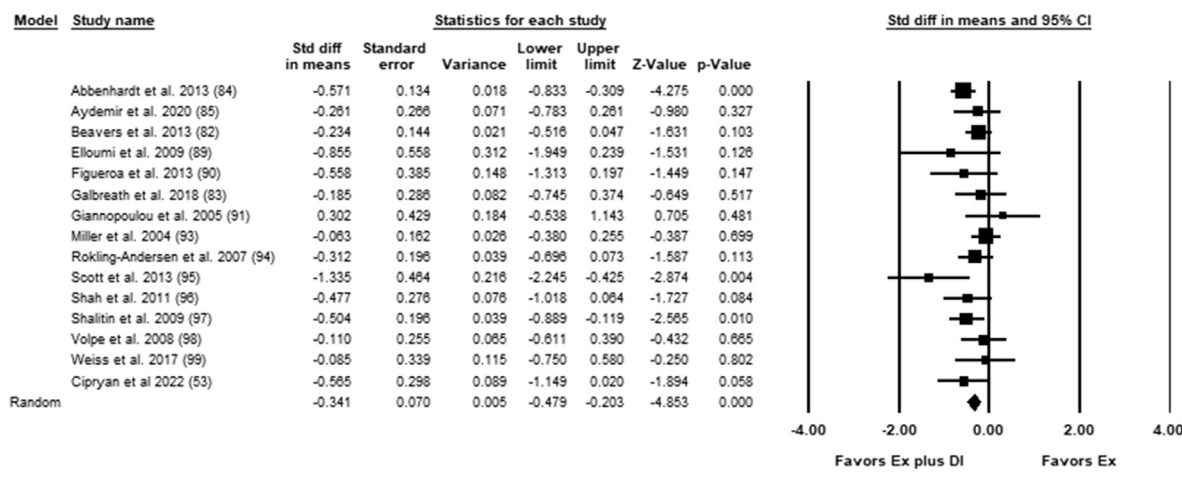
Fig. 4. Forest plot of the effects of exercise training + dietary intervention compared with those of exercise training on leptin in individuals who were overweight and those with obesity and aged ranging from 7 to 70 years of age. Data are reported as standardized mean difference and 95% CIs (95% lower and upper limits). Ex, exercise training; DI, dietary intervention.
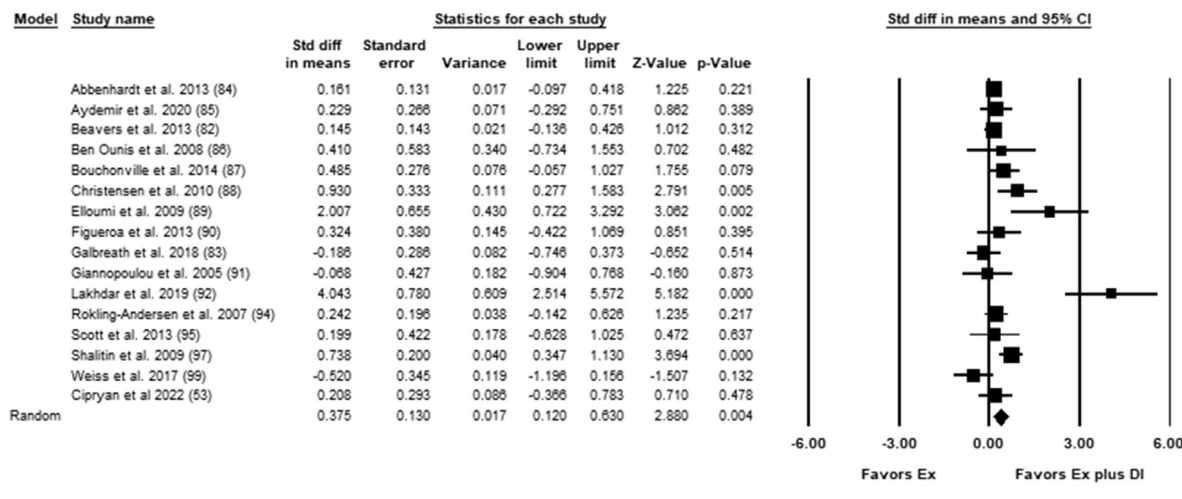

Fig. 5. Forest plot of the effects of exercise training + dietary intervention compared with those of exercise training on adiponectin in individuals who were overweight and those with obesity and aged 7–70 y. Data are reported as standardized mean difference and 95% CIs (95% lower and upper limits). Ex, exercise training; DI, dietary intervention.

(Fig. 6). There was significant heterogeneity among the included studies ($I^2 = 48.19\%$; $P = 0.001$). The visual interpretation of funnel plots suggested publication biases; however, the results of the Egger test did not ($P = 0.61$). The trim-and-fill method identified 6 missing studies from the left side of the plot. When theses missing studies were accounted for, the overall change was −0.23 (95% CI: −0.37, −0.09), confirming an increase in SMD. The sensitivity analysis conducted by omitting individual studies showed a change in significance. Furthermore, the sensitivity analysis conducted by omitting studies involving participants aged < 18 y indicated that Ex + DI did not decrease the concentration of leptin (SMD: −0.09; $P = 0.10$) compared with DI.

Adiponectin. Based on 25 intervention arms (25 studies), Ex + DI did not increase the concentration of adiponectin (SMD: 0.10; 95% CI: −0.02, 0.22; $P = 0.11$) compared with DI (Fig. 7). There was no significant heterogeneity among the studies ($I^2 = 20.72\%$; $P = 0.17$). The visual interpretation of funnel plots suggested publication biases; however, the results of the Egger test did not ($P = 0.51$). The trim-and-fill method identified 1 missing study from the right side of the plot. When this missing study was accounted for, the overall change was 0.11 (95% CI: −0.01, 0.24), confirming no change in SMD. The sensitivity analysis conducted by omitting individual studies showed no effect. In addition, the sensitivity analysis conducted by omitting participants aged <18 y indicated that Ex + DI did not change
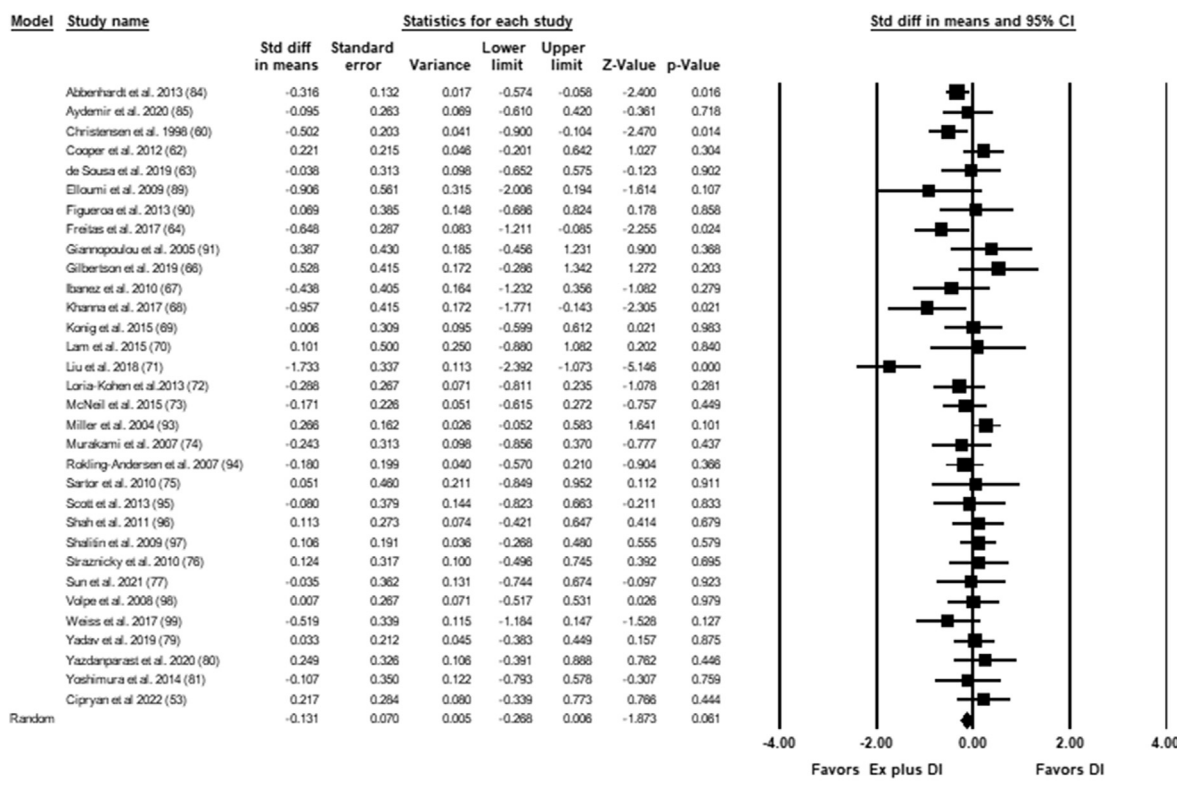
Fig. 6. Forest plot of the effects of exercise training + dietary intervention compared with those of dietary intervention on leptin in individuals who were overweight and those with obesity and aged 7–70 y. Data are reported as standardized mean difference and 95% CIs (95% lower and upper limits). DI, dietary intervention; Ex, exercise training.
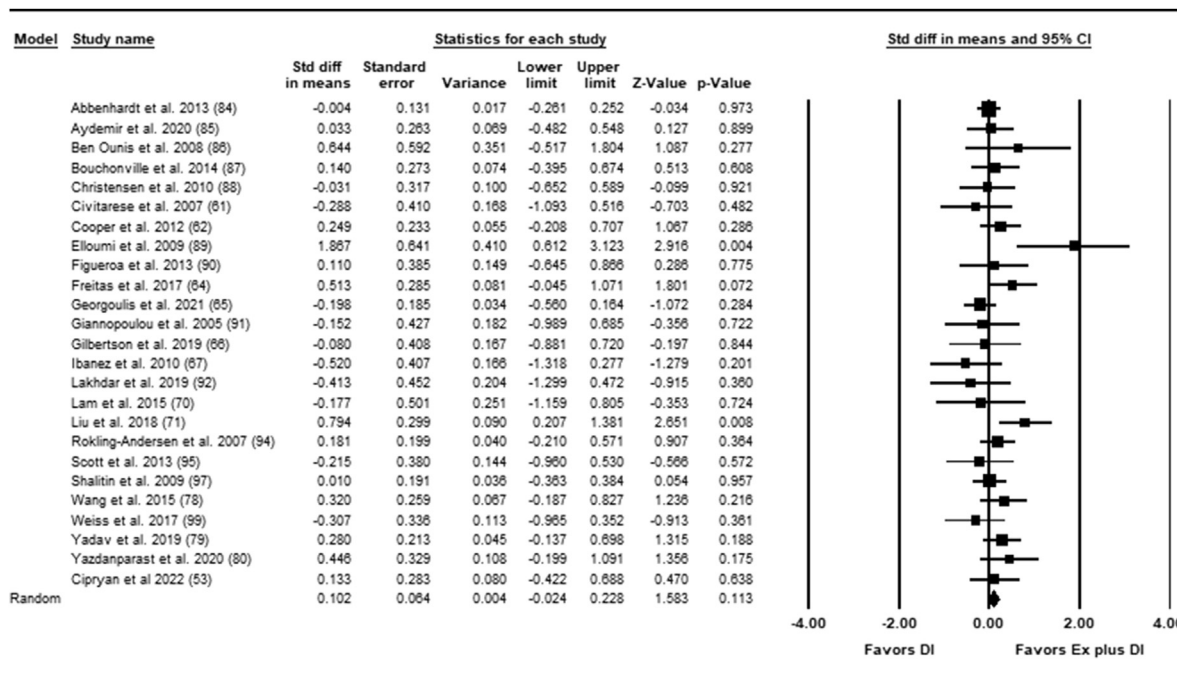

Fig. 7. Forest plot of the effects of exercise training + dietary intervention compared with those of dietary intervention on adiponectin in individuals who were overweight and those with obesity and aged 7–70 y. Data are reported as standardized mean difference and 95% CIs (95% lower and upper limits). DI, dietary intervention; Ex, exercise training.

the adiponectin outcomes (SMD: 0.05; $P = 0.38$) compared with DI.

Body weight

Based on 15 intervention arms, DI decreased the body weight (WMD: −3.12 kg; 95% CI: −5.06, −1.19; $P = 0.002$) compared with Ex (Supplementary Figure 1). There was significant heterogeneity among the studies ($I^2 = 83.42\%$; $P = 0.001$). Based on 11 intervention arms, Ex + DI decreased the body weight (WMD: −5.59 kg; 95% CI: −7.26, −3.93; $P = 0.001$) compared with Ex (Supplementary Figure 2). There was significant heterogeneity ($I^2 = 26.62\%$; $P = 0.19$). Based on 29 intervention arms, Ex + DI decreased the body weight (WMD: −1.78 kg; 95% CI: −2.55, −1.00; $P = 0.001$) compared with DI (Supplementary Figure 3). There was no significant heterogeneity ($I^2 = 0.00\%$; $P = 0.94$).

Subgroup analyses

Comparison of the effect of DI with that of Ex on leptin

The subgroup analyses revealed significant reductions in the concentration of leptin with obesity (SMD: −0.33; $P = 0.001$), age ≥50 y (SMD: −0.27; $P = 0.004$), age <18 y (SMD: −0.51; $P = 0.001$), short-term interventions (SMD: −0.46; $P = 0.007$), long-term interventions (SMD: −0.27; $P = 0.001$), combined training (SMD: −0.49; $P = 0.002$), supervised exercise (SMD: −0.26; $P = 0.01$), nonsupervised exercise (SMD: −0.65; $P = 0.001$), a PEDro score of ≥5 (SMD: −0.31; $P = 0.001$), and mild energy restriction (SMD: −0.30; $P = 0.001$) (Supplementary Table 3).

Comparison of the effect of DI with that of Ex on adiponectin

The subgroup analyses revealed a significant increase in the concentration of adiponectin with obesity (SMD: 0.31; $P = 0.001$), age of 18–50 y (SMD: 0.22; $P = 0.04$), short-term interventions (SMD: 0.38; $P = 0.001$), combined training (SMD: 0.53; $P = 0.001$), supervised exercise (SMD: 0.30; $P = 0.001$), a PEDro score of <5 (SMD: 0.40; $P = 0.04$), a PEDro score of ≥5 (SMD: 0.20; $P = 0.003$), mild energy restriction (SMD: 0.20; $P = 0.01$), and severe energy restriction (SMD: 0.31; $P = 0.01$) (Supplementary Table 3).

Comparison of the effect of Ex + DI with that of Ex on leptin

The subgroup analyses revealed a significant reduction in the concentration of leptin with obesity (SMD: −0.34; $P = 0.001$), overweight (SMD: −0.33; $P = 0.02$), age ≥50 y (SMD: −0.28; $P = 0.001$), age of 18–50 y (SMD: −0.45; $P = 0.02$), age <18 y (SMD: −0.54; $P = 0.003$), short-term interventions (SMD: −0.54; $P = 0.001$), long-term interventions (SMD: −0.32; $P = 0.001$), aerobic training (SMD: −0.31; $P = 0.001$), combined training (SMD: −0.46; $P = 0.02$), supervised exercise (SMD: −0.32; $P = 0.001$), combined supervised and nonsupervised exercise (SMD: −0.35; $P = 0.02$), a PEDro score of ≥5 (SMD: −0.35; $P = 0.001$), and mild energy restriction (SMD: −0.32; $P = 0.001$) (Supplementary Table 4).

Comparison of the effect of Ex + DI with that of Ex on adiponectin

The subgroup analyses revealed a significant increase in the concentration of adiponectin with obesity (SMD: 0.48; $P = 0.002$), age of 18–50 y (SMD: 0.85; $P = 0.02$), age <18 y

(SMD: 0.92; $P = 0.01$), short-term interventions (SMD: 0.60; $P = 0.001$), long-term interventions (SMD: 0.19; $P = 0.01$), aerobic training (SMD: 0.45; $P = 0.01$), combined training (SMD: −0.59; $P = 0.001$), supervised exercise (SMD: 0.42; $P = 0.003$), a PEDro score of ≥5 (SMD: 0.38; $P = 0.004$), mild energy restriction (SMD: 0.34; $P = 0.02$), and severe energy restriction (SMD: 0.57; $P = 0.003$) (Supplementary Table 4).

Comparison of the effect of Ex + DI with that of DI on leptin

The subgroup analyses revealed a significant reduction in concentration of leptin with being overweight (SMD: −0.22; $P = 0.01$), aerobic training (SMD: −0.23; $P = 0.03$), and supervised exercise (SMD: −0.21; $P = 0.02$) (Supplementary Table 5).

Comparison of the effect of Ex + DI with that of DI on adiponectin

The subgroup analysis by the type of exercise supervision revealed a significant increase in the concentration of adiponectin with short-term interventions (SMD: 0.27; $P = 0.01$) and supervised exercise (SMD: 0.21; $P = 0.02$) (Supplementary Table 5).

Discussion

The current systematic review and meta-analysis is the first to compare the effect of Ex with that of DI and the effect of Ex + DI with that of either Ex or DI alone on circulating leptin and adiponectin in individuals who are overweight and those with obesity. Thus, DI appears to be more effective than Ex in decreasing the concentration of leptin and increasing the concentration of adiponectin, as is a combination of Ex and DI. However, Ex + DI was not more effective than DI alone. Our results indicated significant heterogeneity, which may be explained by age, BMI, the duration of intervention, the type of supervision, the quality of the study, and the magnitude of energy restriction.

In general, lifestyle interventions, including Ex and DI, are effective for weight management in individuals with obesity in whom the benefits extend beyond weight loss and include immune and metabolic adaptations [32,33,100–105]. Previous meta-analyses have demonstrated that either Ex or DI is effective in decreasing the concentration of leptin and increasing the concentration of adiponectin [38–45]; however, the effect of DI has not been compared with that of Ex. The current results indicate that DI confers greater benefits compared with Ex with regard to changes in the concentrations of leptin and adiponectin, which appear to be related to weight loss. In the case of leptin, the loss of body weight and fat as well as improved leptin sensitivity are potential mechanisms for decreasing leptin concentration [38]. Increased adiponectin concentration is likely to be a consequence of weight loss as well as beneficial alterations in inflammatory cytokines, including IL-6 and TNF-α, and androgen metabolism as well as improved insulin sensitivity [106,107]. Furthermore, weight loss in response to both Ex and DI has been linked to reduced inflammation [108], which also improves the homeostasis of leptin and adiponectin. Nevertheless, Abbenhardt et al. [84] suggested that reduced leptin concentration and increased adiponectin concentration with weight loss occur in a dose-dependent manner, regardless of the

intervention. Ex can improve body composition and fitness-related outcomes, thereby impacting leptin and adiponectin [109], with Ex having a greater impact on leptin [109]. The current results indicated that DI resulted in a greater loss of body weight than Ex, of up to 3 kg. Although the effect sizes in the current systematic review and meta-analysis were small, they may still be clinically significant because hyperleptinemia and hypoadiponectinemia are both important risk factors for CVD.

There is a substantive body of evidence from meta-analyses suggesting that a combination of Ex and DI is more effective than DI alone in improving the concentrations of inflammatory markers [32,33] and long-term weight loss [35]. It is not known whether the combination of Ex and DI has a superior effect on leptin and adiponectin compared with Ex or DI alone [35]. The current results suggest that a combination of Ex and DI is more effective than Ex alone but not compared with DI alone. From a clinical and practical stand point, these results highlight that DI needs to be added to lifestyle interventions to achieve a more effective treatment approach in populations that are overweight and those with obesity. It is likely that weight loss is necessary for beneficial changes in leptin and adiponectin. In the current study, weight loss through the combination of Ex and DI resulted in an ~1.7 and 6 kg greater weight loss compared with DI or Ex alone. The magnitude of weight loss is an important predictor of improved inflammation [108], with experimental studies showing greater effectiveness of Ex + DI and DI in improving the concentrations of leptin and adiponectin [84,110].

The current study showed that DI compared with Ex and Ex + DI compared with Ex alone effectively decreased the concentration of leptin and increased the concentration of adiponectin. However, these results were heterogeneous, except for the comparison of the effect of DI with that of Ex on adiponectin. Significant heterogeneity may be explained by the participants' BMI and age, demonstrating the notion that an individual's age and BMI play a role in the effect of lifestyle interventions on the response of leptin and adiponectin. Additionally, the duration of intervention, rate of energy restriction, type of training, type of supervision, and quality of studies explain the heterogeneity in the results. However, it should be noted that small numbers of studies in some categories of analysis should be considered while interpreting the results.

Limitations

There was significant heterogeneity in the results reported in the included studies; however, we performed the necessary subgroup analyses to assess the sources of potential differences in the results. We recognize that these differences in the results may also have been introduced by different approaches to study methodologies, exercise protocols, and participant characteristics as well as the quality of the studies. There was a significant publication bias for several of the included analyses. In order to address this publication bias, we used the trim-and-fill correction method to determine the role that missing studies might have played. Overall, the results of these additional analyses suggested the results of the meta-analysis were not affected by the apparent publication bias. However, there were limitations of the random-effects model in the presence of heterogeneity that lead to more relative weight being given to smaller studies

and in the presence funnel plot asymmetry, which skewed the results toward the findings of smaller studies. We did not include any limitations regarding the age of the participants in the present meta-analysis. However, we performed subanalyses by omitting participants aged <18 y. Therefore, in future studies, the age of participants should be considered and appropriate subgroup analyses should be conducted. Finally, because of the exploratory nature of the current meta-analysis, multiple comparisons for multiple outcomes were performed without correction for the alpha level, increasing the risk for type I error.

In conclusion, the results of the current systematic review and meta-analysis suggest that DI alone or combined with Ex is more effective than Ex alone in decreasing the concentration of leptin and increasing the concentration of adiponectin in individuals who are overweight or those with obesity, suggesting that diet plays a critical role in improving the concentrations of leptin and adiponectin. These adaptations are influenced by weight loss, regardless of the type of intervention.

Funding

Disclosures

The authors report no conflicts of interest

Author Responsibilities

The authors' responsibilities were as follows – MK, MHS, SK, MES, and SKR: conceived and designed the study; MK, MHS, and SK: analyzed the data and completed the initial draft of the results; MK: drafted the original manuscript; MES and SKR: revised the manuscript; and all authors read and approve the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https ://doi.org/10.1016/j.advnut.2022.10.001.

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