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Systematic Review and Meta-Analysis of Randomized, Controlled Trials on the Effect of Exercise on Serum Leptin and Adiponectin in Overweight and Obese Individuals

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ABSTRACT

Previous reports have shown that exercise improves serum leptin and adiponectin abnormalities in overweight and obese individuals; however, results to date are controversial. Here we performed a systematic review and meta-analysis of the available randomized controlled trials (RCTs) of the possible beneficial action of exercise on serum leptin and adiponectin levels in overweight and obese individuals. We searched PubMed, EMbase, The Cochrane Library, and the Clinicaltrial.gov databases for relevant studies published between January 1980 and September 2015. Two independent reviewers extracted relevant data and assessed study quality and risk of bias. Data were pooled using a random-effects model for leptin and a fixed-effects model for adiponectin. Effect of size was expressed as mean difference (MD) with 95 % confidence interval (CI). Heterogeneity was assessed (Cochran Q-statistic) and quantified (I^2). Twenty-eight RCTs (40 studies) were identified, of which 24 were on the effects of exercise on leptin (n = 1 358) and 31 referred to changes in adiponectin (n = 1 774). Our analysis revealed that exercise significantly reduced serum leptin (MD = − 2.24 ng/ml; 95 % CI, − 3.26, − 1.23; $p < 0.001$) and increased adiponectin (MD = 0.44 µg/ml; 95 % CI, 0.13, 0.75; $p = 0.005$) levels compared to no exercise as well as control (who were also overweight or obese). Exercise, particularly aerobic exercise, had a significant effect on serum leptin and a possible influence on adiponectin levels, suggesting its therapeutic implications.

Introduction

World Health Organization (WHO) has reported that worldwide obesity has more than doubled since 1980 and is responsible for considerable morbidity and mortality rates. Overweight and obese subjects have significantly higher serum leptin and decreased adiponectin levels, which are mainly secreted by adipose tissue, an endocrine organ [1]. Abnormal levels of leptin and/or adiponectin are causally related to an increased risk of developing type 2 diabetes mellitus (T2DM) [2], cardiovascular diseases [3], and some cancers [4, 5].

Serum levels of leptin, adiponectin, and other cytokines can be influenced by lifestyle modifications. Studies have revealed that several lifestyle modifications including increased sleep duration [6], quitting smoking [7], diet control such as calorie restriction or reduced dietary fat intake [8], diets rich in fruits and vegetables can reduce serum leptin and enhance adiponectin levels.

Exercise is defined as a series of physical activities that are planned, structured, and repetitive whose objective is to improve or maintain physical health and fitness [9]. Exercise exerts a number of beneficial actions including decreasing serum leptin and increasing adiponectin levels [10]. Leptin, one of the first adipose signaling molecules discovered, regulates energy balance and is encoded by the obesity gene [11]. Serum leptin levels are proportional to adiposity and reflect energy status [12]. Exercise reduces serum leptin by increasing energy expenditure and decreasing adiposity. Adiponectin, first identified in 1995 and also known as AdipoQ and ACRP30, is secreted mostly by white adipose tissue into the circulation [13]. Adiponectin promotes insulin sensitivity and inhibits inflammation [14, 15]. Weight loss is associated with a sig-

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nificant increase in serum adiponectin levels in obese people [16], which led us to propose that exercise may increase serum adiponectin levels by reducing body weight. In addition, the mRNA expression of adiponectin is reportedly increased after endurance training in rats [17]. However, human clinical trials that evaluated the effect of exercise on serum leptin and adiponectin levels have been controversial. For instance, some studies showed that exercise can significantly alter leptin or adiponectin levels [18–23], while other studies did not support these results [24–29]. Accordingly, here we performed a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate the effect of exercise on serum leptin and adiponectin levels in humans.

Materials and Methods

Literature search

We searched PubMed, EMbase, The Cochrane Library, and the Clinicaltrial.gov databases for relevant studies published between January 1980 and September 2015. The main terms used to search for relevant publications were: exercise, training, physical activity, adipocytokines, adipokines, leptin, and adiponectin in combination with obesity, obese, overweight, fatness, and adiposity. We also scanned the reference lists of the included articles to identify other relevant studies. We specified the methodology of this systematic review in advance and documented it in a protocol that was published in the PROSPERO prospective register of systematic reviews (www.crd.york.ac.uk/PROSPERO; ref CRD42015027691).

Study selection

Studies were included if they satisfied all of the following inclusion criteria: (1) RCT performed in humans; (2) Subjects were all overweight or obese (body mass index [BMI] ≥ 25 kg/m^2 or a BMI ≥ 23 kg/m^2 in Asian populations) without a cognitive impairment; (3) The study included exercise-only and control or comparative groups without other confounding interventions (non-exercise, habitual exercise, stretching exercise, usual care, etc.); (4) The intervention was regular and consisted of continuous exercise for a specified amount of time; (5) The exercise of the intervention group was quantified in terms of intensity, frequency, time, and duration; (6) The mean serum leptin level and standard deviation was reported for the intervention and control groups; and (7) The study had sound methodology and was of high quality. Studies were excluded if the serum leptin or adiponectin levels were not reported, there were no exercise-only groups, the design was a crossover trial(s), or the study was not published in English.

NY and XYG independently screened all of the articles based on the titles and then reviewed the abstracts and full texts to assess if they met the eligibility criteria. Final eligibility was not determined until the 2 reviewers reached agreement. Any disagreement was settled in consultation with YTR. These decisions are summarized in the PRISMA flow chart (**Supplement 1**).

Data extraction

NY and XYG independently extracted the data and then checked and entered it into an electronic data collection form. The following information was abstracted from the eligible articles: first author's last name, publication year, and country of origin; the modality, intensity, frequency, and time of exercise; sample size; subject characteristics including age, sex, BMI, and baseline leptin or adiponectin levels; intervention duration; and treatment results, including adiponectin and leptin levels. If more than one time point for follow-up was reported, we used the data from the longest follow-up time period. For trials containing multiple intervention arms, we extracted the data of the exercise-only groups without any other confounding interventions and the corresponding comparative or control group. If the trial contained multiple exercise interventions and only one control group was available for comparison, the control group was split into an equal number of subgroups (equal to that of the intervention groups; thus, the control and intervention groups had the same number of groups) such that the number of divided controls obtained is equal to the number of intervention groups [30]. Thus, there were 28 RCTS and 40 studies in the final meta-analysis.

Data analyses

The statistical analysis was performed according to the Cochrane Handbook for Statistical Review of Interventions (Version 5.0.2). The differences between the intervention and control arm's change from baseline value were derived from each trial for endpoints of serum levels of leptin and adiponectin. The mean differences (MD) of leptin were pooled using a random-effects model due to the study heterogeneity ($I^2 = 63\%$, $p < 0.001$), while the pooling of MD of adiponectin used a fixed-effects model because of the slight heterogeneity ($I^2 = 19\%$, $p = 0.17$). The meta-analysis was performed using RevMan software (Cochrane Review Manager version 5.2). Statistical tests were 2-sided ($p < 0.05$).

Heterogeneity was tested and measured with a Q-test and I^2 statistics. We generally assumed that there was substantial heterogeneity if the $I^2 > 50$ or $I^2 > 25\%$ with a low p-value ($p < 0.10$). We explored sources of heterogeneity by comparing mean differences of both endpoints (leptin and adiponectin) between subgroups stratified by modality, intensity, and total time per week of exercise, and study period. Care was taken to see that nearly all of the included studies were performed under supervision and properly recorded when the exercise intervention was executed. To test the robustness of the data, sensitivity analyses were performed by removing each individual trial from the meta-analysis and recalculating the effect size with the remaining trials. Sensitivity analyses were also undertaken by excluding studies with a sample size < 20 for each group and/or studies of high heterogeneity from the meta-analysis. The risk of bias was assessed using the Cochrane Risk of Bias Tool. Potential publication bias of this study was assessed quantitatively through Egger's tests performed by STATA 12.0 software, where a p-value < 0.10 was considered evidence of small study effects.

Results

Characteristics of included studies

Of the 513 potentially relevant publications identified in the initial search and reference lists, 28 RCTs satisfied the inclusion criteria and were included in the meta-analysis. Of these 28 RCTs, 9 contained multiple exercise protocols with intervention groups of different modalities or intensities of exercise with only one control

group for comparison [31–39]. As a result, we split the shared control group into 2 or more groups as described above [30], which resulted in 21 studies. These 28 RCTs (that resulted in 40 studies) included 2316 participants (1 469 exercise, 847 control), and all of them were parallel RCTs that were similar in terms of baseline characteristics, indicating highly qualified randomization. Twenty-four studies reported data for leptin (n = 1 358) vs. 31 for adiponectin (n = 1 774). In one RCT, dropout reasons and number of participants were mentioned [34]; while in 2 RCTs, dropout numbers were stated without any specific reason(s) [40, 41].

The characteristics of the included studies are displayed in ▶ **Table 1**, while the pooled risk of bias results using the Cochrane Risk of Bias Assessment Instrument is shown in **Supplement 2**. In the 28 RCTs (n = 40 studies) that were included in the meta-analysis, 3 modalities of exercise were studied: aerobic exercise (AE) (n = 28 studies), resistance exercise (RE) (n = 6 studies), and combined exercise (CE), which included both aerobic and resistance exercise (n = 6 studies). The exercise forms and intensities varied among the studies. According to the American College of Sports Medicine (ACSM) [42], the aerobic exercise intensity was classified as high intensity (HI) [≥ 6 metabolic equivalents (METs), ≥ 70 % HR_{max}, ≥ 60 % heart rate reserve (HRR), or ≥ 60 % maximum oxygen consumption (VO_{2max})], medium intensity (MI) (3–6 METs, 55–70 % HR_{max}, 40–60 % HRR or 40–60 % VO_{2max}) and low intensity (LI) (< 3 METs, < 55 % HR_{max}, < 40 % HRR, or < 40 % VO_{2max}), which was used to classify the exercises of the studies included in the present meta-analysis. The participants of 4 of the included RCTs had Barrett's esophagus [28], knee osteoarthritis [41], breast cancer [26], and T2DM [43]. Interventions that were included in the control groups of the RCTs used in the present meta-analysis varied among non-exercise, education or advice on physical activity, stretching exercise, and routine care. Since we included an exercise-only group without other confounding interventions and the corresponding control or comparative group of the studies, there are unlikely to be any differences in energy or nutrient intake between the intervention and control groups. The duration of the RCTs was 6 weeks to 18 months. The exercise interventions of the included studies were under supervision and reported good compliance.

Leptin

▶ **Fig. 1** shows a forest plot of the pooled effect of exercise on leptin. Twenty-four studies reported changes in serum leptin concentrations. Of the 24 trials, 5 studies reported a significant reduction in leptin after exercise intervention, with mean differences of − 0.10 to − 15.80 ng/ml. Our meta-analysis of the 24 trials indicated a significant reduction in leptin of − 2.24 ng/ml (95 % CI, − 3.26, − 1.23; p < 0.001) compared with control or comparative groups with substantial heterogeneity across the studies (I^2 = 63 %, p < 0.001).

Adiponectin

▶ **Fig. 2** shows a forest plot of the pooled effect of exercise on serum adiponectin concentrations. Thirty-one studies reported changes in serum adiponectin; of them, 4 reported a significant post-exercise increase in adiponectin levels. The mean differences were 0.02–13.70 µg/ml. The pooled mean difference of the 31 studies was 0.38 µg/ml (95 % CI, 0.13, 0.63; p = 0.003) for adiponectin with slight inter-study heterogeneity in the meta-analysis (I^2 = 19 %, p = 0.17).

Meta-analysis of different exercise modalities

The results of analysis of modalities of exercise on changes in serum leptin and adiponectin concentrations are shown separately in ▶ **Fig. 1,2**, respectively. Serum leptin levels were significantly decreased after AE compared to after RE and CE. Similarly, an increase in serum adiponectin levels was seen after AE but not after RE or CE.

Subgroup analysis

The results of subgroup analysis are shown in ▶ **Table 2**. In the subgroup analysis, studies < 12 weeks in length revealed no significant changes in serum leptin and adiponectin levels. On the other hand, studies > 12 weeks in length showed significantly decreased leptin and increased adiponectin levels.

Since most of the included studies used AE and the intensity classifications in RE and CE were inconsistent, the subgroup analysis of exercise intensity mainly focused on AE. However, 2 AE studies did not specify exercise intensity; hence, they were omitted from this subgroup analysis [22, 40]. Subgroup analysis showed that HI AE resulted in a significant reduction of serum leptin levels (MD = − 6.29 ng/ml, p < 0.001), while LI or MI AE had an insignificant effect on serum leptin levels. Furthermore, HI AE led to a slight increase in serum adiponectin levels (MD = 0.74 µg/ml, p = 0.04), whereas LI and MI AE resulted in no increase or an insignificant increase in serum adiponectin levels.

Since almost all of the RCTs included in the present study were performed under supervision and reported good compliance, we determined that there was no need to stratify them into subgroups by presence or lack of supervision. Eight studies from 6 publications measured serum leptin levels [18, 20, 21, 27, 34, 37] and 15 from 8 publications measured serum adiponectin levels [18, 20, 27, 33, 37–40] did not describe the exact exercise duration per week. In other words, the data of these studies were insufficient for inclusion in a subgroup analysis of exercise duration (≥ 150 min/wk vs. < 150 min/wk).

Sensitivity analysis

While analyzing the changes in serum leptin levels, we evaluated whether removing each individual study one by one would impact the final analysis and found that removing 2 trials with high heterogeneity [18, 21] reduced the overall effect to a limited extent (MD = − 1.48 ng/ml, p < 0.001). In addition, the removal of studies with small sample sizes [18, 21, 24, 27, 28, 32, 34, 35, 37, 44] (n < 20 for each group) did not change the pooled effect significantly (MD = − 2.43 ng/ml, p = 0.003).

A similar analysis performed of serum adiponectin level changes revealed insignificant pooled effects after removal of the studies with high heterogeneity [22, 36] (MD = 0.18 µg/ml, p = 0.19) and trials with small sample sizes [18, 20, 22, 24, 27, 28, 33, 35–37, 39, 40, 43, 45].

Publication bias

Egger's regression was conducted to detect potential publication bias. Those findings indicated significant publication bias for leptin and adiponectin with p-values = 0.012 and 0.051, respectively.

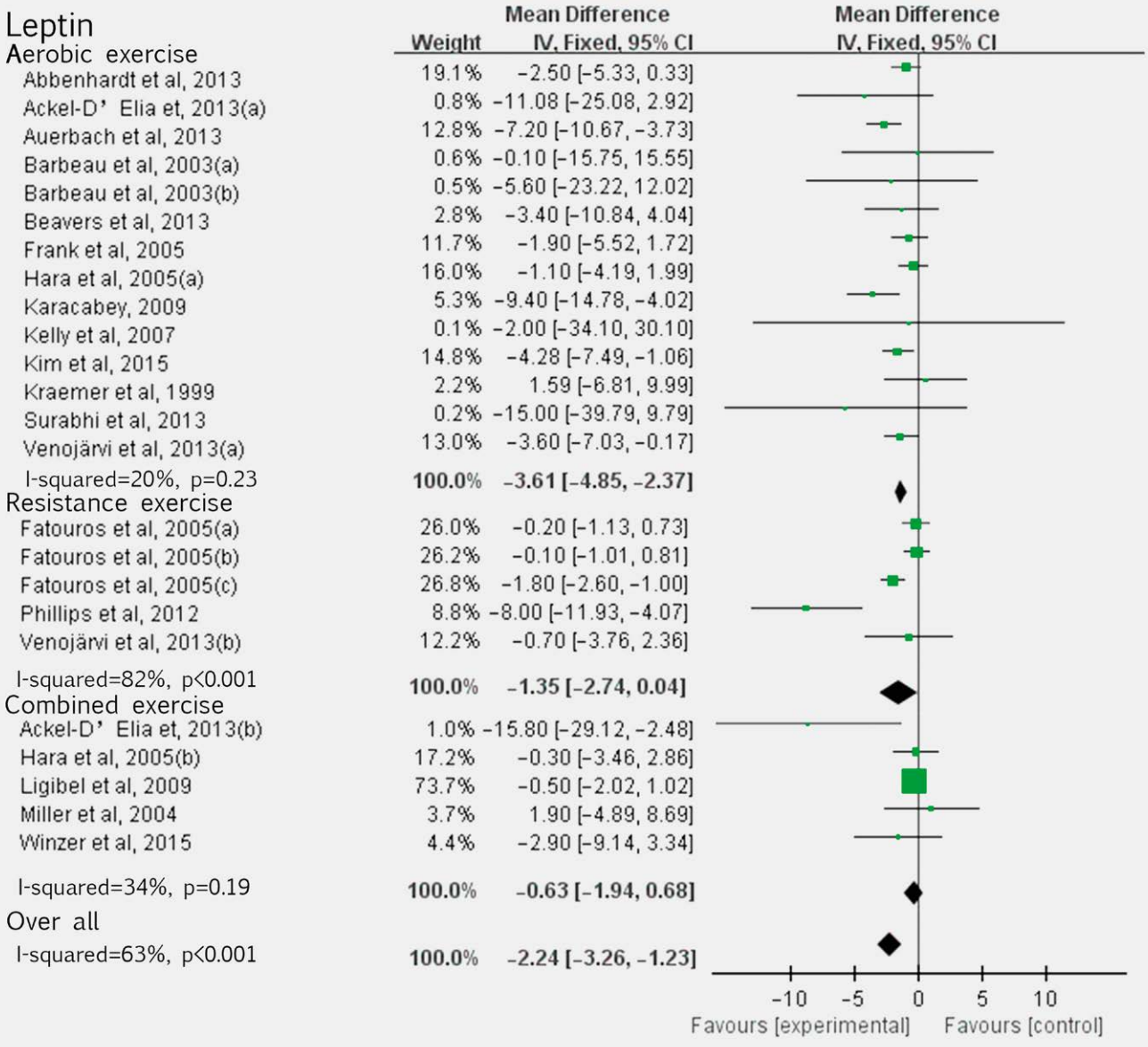
▶ **Table 1** Characteristics of included studies.

Study (Year)	Region	Age(years)	Gender (Male/ Female)	BMI(kg/m²)	No. (Intervention, Control)	Exercise intervention			Duration
						Intensity	Time	Frequency (times/wk)	
Aerobic exercise									
Kelly et al., 2007	USA	EG: 10.8 ± 0.67 CG: 11.0 ± 0.71	NA	EG:32.7 ± 2.6 CG:30.5 ± 2.3	9, 10	HI	30–50 min	4	8-wk
Arsenault et al., 2009	Canada	57.3 ± 6.6	0/100	32.0 ± 5.7	267, 82	MI	4 KKW/wk	3 or 4	6-mo
Abbenhardt et al., 2013	USA	50–75	0/100	≥25.0	117, 87	HI	45 min	5	12-mo
Ackel-D'Elia et al., 2013 (a)	Brazil	15–19	28/72	EG35.06 ± 3.90 CG34.57 ± 3.84	24, 12	HI	60 min	3	6-mo
Murphy et al., 2009	USA	7–12	51/49	EG: 36.9 ± 5.4 CG: 37.3 ± 4.7	23, 12	NA	10–30 min	5	12-wk
Kim et al., 2007	Korea	17 ± 0.11	NA	29.5 ± 2.2	14, 12	HI	40 min	5	6-wk
Racil et al., 2013 (a)	Tunisia	15.9 ± 0.3	0/100	30.8 ± 1.6	11,6	MI	16–20 min	3	12-wk
Racil et al., 2013 (b)	Tunisia	15.9 ± 0.3	0/100	30.8 ± 1.6	11,6	HI	16–20 min	3	12-wk
Lee et al., 2012	Korea	54.50 ± 2.75	0/100	EG25.13 ± 1.63 CG25.19 ± 1.71	8,8	NA	60 min	3	16-wk
Karacabey, 2009	Turkey	10–12	100/0	≥30	20, 20	HI	30–65 min	3	12-wk
Beavers et al., 2013	USA	60–79	NA	>28	97, 93	MI	30 min	5	18-mo
Moghadasi et al., 2012	Iran	35–50	100/0	31.2 ± 4.1	8,8	MI	30 min	4	12-wk
Venojärvi et al., 2013 (a)	Finnland	40–65	100/0	25.1–34.9	39, 20	MI	60 min	3	12-wk
Frank et al., 2005	USA	50–75	0/100	≥25	84, 86	MI	171 ± 88 min/wk	3.7 ± 1.4	12-mo
Pasqualini et al., 2009	Italy	EG:44 ± 6 CG:43 ± 8	75/25	EG:28 ± 3 CG:29 ± 4	24, 24	HI	45 min	4	8-wk
Asad et al., 2012 (a)	Iran	22 ± 0.89	NA	EG29.86 ± 3.94 CG29.26 ± 4.27	12, 3	HI	25–40 min	3	8-wk
Johannsen et al., 2012 (a)	USA	45–75	0/100	25.0–43.0	115, 26	MI	4 KKW	3 or 4	6-mo
Johannsen et al., 2012 (b)	USA	45–75	0/100	25.0–43.0	66, 25	MI	↑1 KKW/wk until 8 KKW	3 or 4	6-mo
Johannsen et al., 2012 (c)	USA	45–75	0/100	25.0–43.0	82, 25	MI	↑1 KKW/wk until 12 KKW	3 or 4	6-mo
Barbeau et al., 2003 (a)	Canada	12–16	NA	NA	20,8	MI	250 kcal	5	8-mo
Barbeau et al., 2003 (b)	Canada	12–16	NA	NA	19,8	HI	250 kcal	5	8-mo
Auerbach et al., 2013	Denmark	20–40	100/0	25–30	12, 12	HI	600 kcal	7	12-wk
Kraemer et al., 1999	USA	EG42.75 ± 1.64 CG40.5 ± 72.80	0/100	EG32.48 ± 1.33 CG34.62 ± 1.78	16, 14	1256 kJ	20 ± 30 min	3 or 4	9-wk

▶ **Table 1** Continued

Study (Year)	Region	Age(years)	Gender (Male/ Female)	BMI(kg/m^2)	No. (Intervention, Control)	Exercise intervention			Duration
						Intensity	Time	Frequency (times/wk)	
Surabhi et al., 2013	USA	25–65	NA	30–39.9	24, 16	HI	25–40 min	3	12-wk
Hara et al., 2005 (a)	Japan	19.2 ± 1.1	100/0	31.1 ± 4.2	7, 4	MI	≥ 30 min	3	8-wk
Marcell et al., 2004 (a)	USA	45.3 ± 8.3	NA	33.7 ± 4.8	20, 7	MI	30 min	5	16-wk
Marcell et al., 20044(b)	USA	45.3 ± 8.3	NA	33.7 ± 4.8	17, 7	HI	30 min	5	16-wk
Kim et al., 2015	Korea	25.31 ± 2.83	100/0	28.41 ± 2.36	29, 10	HI	600 kcal	4	8-wk
Resistance exercise									
Fatouros et al., 2005 (a)	Greece	65–78	100/0	28.7–30.2	14, 3	45–50 % of 1RM	60 min	3	24-wk
Fatouros et al., 2005 (b)	Greece	65–78	100/0	28.7–30.2	12, 3	60–65 % of 1RM	60 min	3	24-wk
Fatouros et al., 2005 (c)	Greece	65–78	100/0	28.7–30.2	14, 4	80–85 % of 1RM	60 min	3	24-wk
Phillips et al., 2012	USA	60–70	0/100	30–40	11, 12	8–12 reps maximum	3 sets	3	12-wk
Venojärvi et al., 2013 (b)	Finnland	40–65	100/0	25.1–34.9	36, 20	50–85 % MAS	60 min	3	12-wk
Asad et al., 2012 (b)	Iran	21 ± 1.57	NA	EG31.48 ± 4.95 CG29.26 ± 4.27	9, 3	1–2wk: 10–15 reps 3–8wk: 22–30reps	3 sets	3	8-wk
Combined exercise									
Winzer et al. 2015	Australia	18–70	100/0	25.0–34.9	15, 15	AT: 60–70 % HRmax RT: 8–15reps	60 min	5	24-wk
Ackel-D'Elia et al., 2013 (b)	Brazil	15–19	33/67	EG35.10 ± 4.67 CG34.57 ± 3.84	24, 12	the ventilatory threshold I (±4 bpm)	60 min	3	6-mo
Miller et al., 2004	USA	≥ 60	NA	≥ 28	79, 76	AT: 50–85 % HRR; RT: 2 sets of 12 reps	60 min	3	18-mo
Ligibel et al., 2009	USA	53	100/0	≥ 25	40, 41	NA	140 min	2	16-wk
Asad et al., 2012 (c)	Iran	21.38 ± 2.6	NA	EG28.64 ± 3.76 CG29.26 ± 4.27	13, 4	the same days with 2 other groups	3	8-wk	
Hara et al., 2005 (b)	Japan	19.2 ± 1.1	100/0	31.1 ± 4.2	7, 3	40.8–54.8 %VO-$_2$max;80 %1RM	≥ 80–90 min	5–6	8-wk

BMI:, Body Mass Index; NA: Not available; EG: Exercise group; CG: Control group; wk: Week; HR: Heart rate; HRR: Heart rate reserve; MAS: VO_2max: Maximal oxygen uptake; reps: Repetitions; HI: High intensity; MI: Moderate intensity; 1RM: Maximal strength; AT: Aerobic training; RT: Resistance training; Y: Yes; N: No

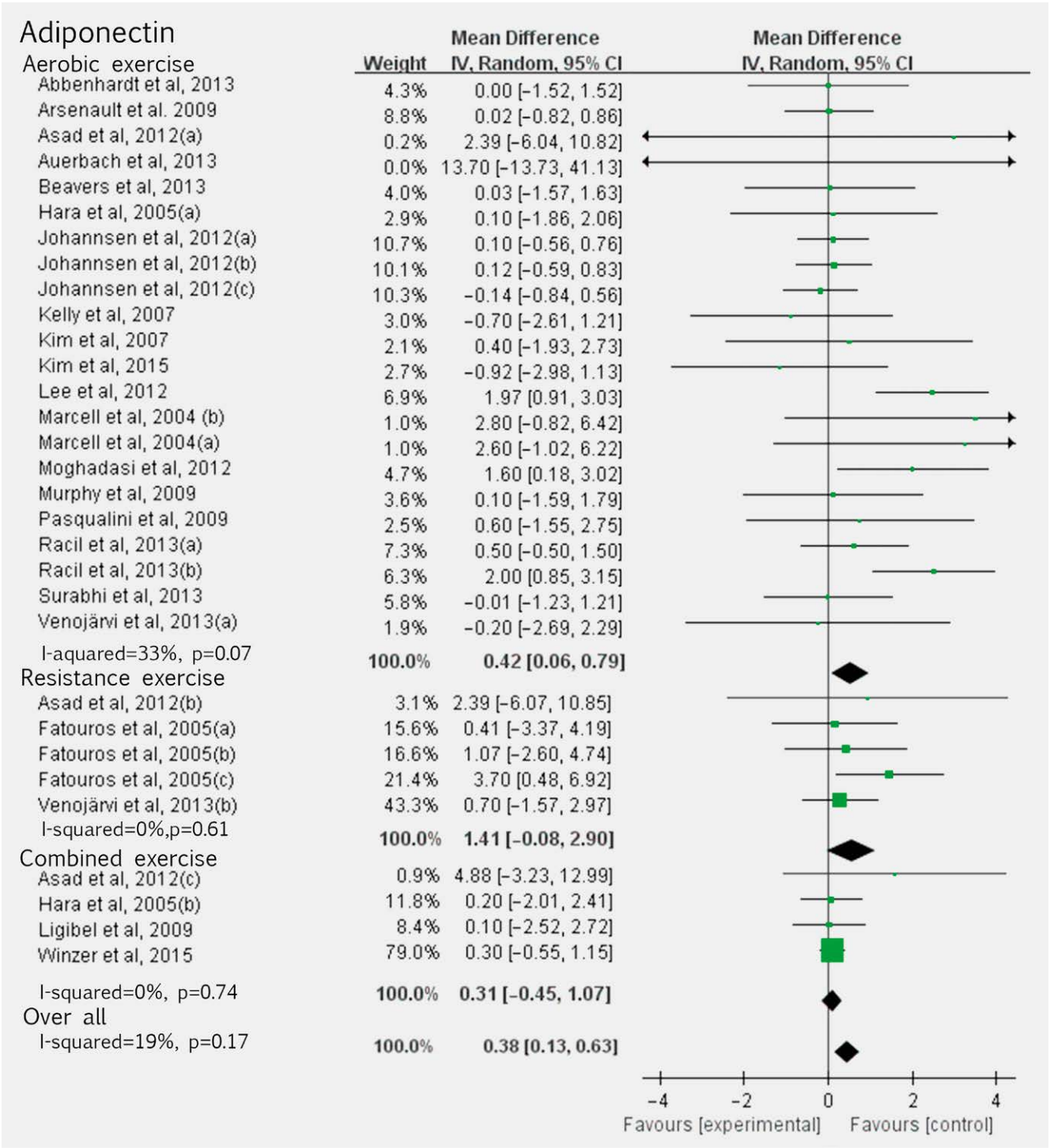


▶ **Fig. 1** Forest plots for changes in leptin: Forest plot of randomized controlled trials comparing the effects of exercise of different modalities and overall effects on serum leptin with control/comparator. Weighted mean differences (95 % CIs) for leptin levels are shown. Pooled estimates (diamonds) calculated by the random effects method. IV: Inverse variance.

Discussion

To the best of our knowledge, this is the first study to systematically analyze the effect of exercise on serum leptin and adiponectin levels in overweight and obese subjects. Leptin, a 167 amino acid peptide hormone, is encoded by the obesity gene and mainly secreted by white adipose tissue [11]. Leptin is not only an "adipostat" that can repress food intake and promote energy expenditure but also has a role in inflammation [3]. Adiponectin, also secreted mainly by the white adipose tissue, is a 30-kDa protein and has anti-inflammatory, antidiabetic and anti-atherogenic properties [46]. Overweight and obese subjects are known to have increased serum leptin and decreased adiponectin levels [47]. Previous studies suggested that increased serum leptin and/or decreased serum adiponectin levels are causally related to various chronic diseases such as T2DM [2], cardiovascular diseases [3], and some cancers [4, 5].

Here we found that exercise significantly reduced serum leptin levels by 2.24 ng/ml and increased adiponectin levels by 0.38 µg/ml, which suggests that these changes may provide considerable health benefits. Although an association between exercise and serum leptin and/or adiponectin levels in overweight and obese subjects has been investigated in a number of studies, the evidence has not been conclusive. The mechanisms responsible for the effects of physical activity impacting serum leptin and adiponectin levels have not been fully deciphered. It is likely that serum leptin and adiponectin levels are strongly related to certain anthropometric changes, including body composition, weight loss, BMI, and body fat distribution [48].



▶ **Fig. 2** Forest plots for changes in adiponectin: Forest plots of randomized controlled trials comparing the effects of exercise of different modalities and overall effects on serum adiponectin with control/comparator. Weighted mean differences (95 % CIs) for adiponectin levels are shown. Pooled estimates (diamonds) calculated by the fixed effects method. IV: Inverse variance.

It is known that interleukin-6 (IL-6) promotes the expression of leptin mRNA and inhibits adiponectin mRNA expression, and physical activity may be impacting serum leptin and adiponectin levels by decreasing IL-6 [49, 50]. Furthermore, catecholamines's response to exercise may also be an important factor in the exercise-induced changes in serum leptin and adiponectin levels [33, 48].

There is substantial inter-study heterogeneity in the overall effect on serum leptin levels. The findings of the present meta-analysis indicated that exercise modality could explain the heterogeneity to some degree. Serum leptin and adiponectin levels presented significant changes in response to AE but not RE or CE. Since serum leptin and adiponectin levels are strongly related to body

▶ **Table 2 Result of subgroup analysis of included randomized, controlled trials in meta-analysis.**

Groups	Leptin (ng/ml)					Adiponectin (μg/ml)				
	n	WMD (95 %CI)	p	I^2 (%)	$P_{heterogeneity}$	n	WMD (95 %CI)	p	I^2 (%)	$P_{heterogeneity}$
Duration										
<12 wk	5	−1.70 (−3.48, 0.08)	0.06	0	0.41	9	0.00 (−0.84, 0.84)	1.00	0	0.88
≥12 wk	19	−2.44 (−3.60, −1.27)	<0.01	69	<0.01	22	0.53 (0.17, 0.90)	<0.01	36	0.05
Intensity of Aerobic exercise										
LI or MI	5	−1.16 (−2.98, 0.66)	0.21	0	0.94	12	0.46 (0.02, 0.90)	0.04	42	0.06
HI	5	−6.29 (−8.43, −4.16)	<0.01	0	0.47	7	0.74 (0.05, 1.44)	0.04	38	0.14

Data are meta-analyzed by using a random-effects model or fixed-effects model as appropriate and are presented as WMD. Statistical heterogeneity was assessed by using the chi-square test and quantified by using the I^2 statistic. WMD: Weight mean difference

composition, weight loss, and body fat distribution [48], the results of the present study support those of a recent network meta-analysis [51], which also showed that AE is more effective at reducing body weight, fat mass, and waist circumference. Thus, it can be suggested that AE is an effective modality to alter body mass that is more likely to affect serum leptin and adiponectin levels than RE. It may be worthwhile to note that including studies of CE in the present meta-analysis with AE weakened the effect of AE, which may account for the lack of effect of CE. After all, in most studies, the total time or amount is approximately equal (AE vs. CE) and RE occupies some AE time or amount in the CE intervention. The subgroup analysis indicated that HI AE can significantly reduce serum leptin levels, whereas LI and MI AE had no significant effects. In addition, HI AE resulted in a slightly increased serum adiponectin level, while LI and MI AE had no effects. The findings of this analysis are consistent with the results of previous studies [52, 53], which suggested that physical activity has a dose-dependent effect on serum leptin and adiponectin levels and that HI exercise is more effective than MI exercise. Since HI results in higher energy expenditure, it will induce a greater reduction in weight or fat mass. Klimcakova and his colleagues [54] concluded that a small weight reduction of even 1 % significantly decreases serum leptin levels. It is possible that LI and MI AE did not result in sufficient weight loss and, therefore, could not significantly reduce serum leptin levels as noted in the present analysis. Moreover, a previous study revealed that a weight loss of at least 10 % is needed to increase serum adiponectin levels [16]. It is possible that HI, MI, and LI AE in the present study resulted in weight loss that can augment serum adiponectin levels. A recent study in experimental animals [17] indicated that intense exercise that contributed to weight loss including a fat mass reduction may have triggered adiponectin secretion. Short-term exercise (<12 weeks) and long-term exercise (≥12 weeks) showed contrasting results regarding changes in serum leptin and adiponectin levels. Our study indicated that short-term exercise had insignificant effects on serum leptin and adiponectin levels, whereas long-term exercise produced significantly decreased serum leptin and increased serum adiponectin levels, which supports previous results [55]. Although the exact mechanism is not clear, we propose that long-term exercise may result in significant weight loss and an adipose tissue decrease that contribute to significant changes in serum leptin and adiponectin levels.

The sensitivity analysis of leptin indicated that these conclusions are robust. However, caution is needed with regard to interpreting the changes in serum adiponectin levels since the removal of studies with high heterogeneity or a small sample size resulted in insignificant pooled effects. We believe that the increase in serum adiponectin is unreliable due to the inclusion of studies with high heterogeneity and small trials with extreme effects. Therefore, our study is consistent with a previous meta-analysis of patients with T2DM [56], which indicated that exercise may not be associated with significant changes in serum adiponectin levels.

Our study has several limitations. First, few of the included RCTs reported concealed allocation, and almost all of them did not have blinded outcome assessments. However, we found no correlation between study quality and the noted outcomes. Second, significant publication bias of the 2 indices was observed in this meta-analysis. This is probably due to gray literature, unreported negative results, or our inclusion of only those articles published in English. Third, some RCTs had fewer than 20 participants for each group, which tend to lead to extreme effects. Hence, further studies with large sample sizes are required to confirm these results.

In conclusion, our meta-analysis revealed that exercise, particularly aerobic exercise, had a significant effect on serum leptin and a possible influence on adiponectin levels. However, caution is needed with regard to the conclusions of the effect of exercise on serum adiponectin because some of the studies with high heterogeneity or a small sample size were included in the present analysis. In summary, exercise promises to be a reasonable therapeutic option to improve serum leptin and adiponectin levels in overweight and obese individuals, which may prevent complications of overweight and obesity.

Author Contributions

N. Yu, Y-T. Ruan, and J. Sun conceived and designed the experiments; N. Yu and X-Y. Gao performed the experiments, Y-T. Ruan and N. Yu analyzed the data; and N. Yu, Y-T. Ruan, and J. Sun wrote the paper. All authors reviewed the final manuscript.

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Declaration of interest

The authors declare that there are no conflicts of interest.

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