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SYSTEMATIC REVIEW

# The Effect of Chronic Exercise Training on Leptin: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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**Abstract**

*Background* Leptin is a hormone associated with satiety, lipid oxidation, energy expenditure, and energy homeostasis. To date, the current body of research examining the effect of chronic exercise training on leptin has yielded inconsistent results.

*Objective* The purpose of this meta-analysis was to provide a quantitative estimate of the magnitude of change in leptin levels following participation in exercise interventions lasting ≥ 2 weeks.

*Methods* All studies included were peer-reviewed and published in English. To be included, studies randomized human participants to an exercise training group or non-exercise comparison group for an exercise training intervention. Leptin levels were measured at baseline, during, and/or after completion of the exercise training program. Random-effects models were used to aggregate a mean effect size (ES) and 95% confidence intervals (CIs), and identify potential moderators.

*Results* Seventy-two randomized controlled trials met the inclusion criteria and resulted in 107 effects ($n = 3826$). The mean ES of 0.24 (95% CI 0.16–0.32, $p < 0.0001$) indicated a decrease in leptin following an exercise training program. A decrease in %Fat ($\beta = -0.07$, $p < 0.01$) was associated with a decrease in leptin after accounting for the type of control group ($\beta = -0.38$, $p < 0.0001$) used in each study.

*Conclusion* These results suggest that engaging in chronic exercise training (≥ 2 weeks) is associated with a decrease in leptin levels for individuals regardless of age and sex. However, a greater decrease in leptin occurred with a decreased percentage of body fat.

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s40279-018-0897-1) contains supplementary material, which is available to authorized users.

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**Key Points**

Research indicates that leptin plays a key role in the regulation of body weight, however the research regarding the effect of chronic exercise training on leptin has yielded inconsistent results.

Our results indicate that a small decrease in leptin occurs following chronic exercise training.

Observed decreases in leptin were associated with a decrease in adiposity or weight loss following chronic exercise training, after accounting for differences in study design.

## 1 Introduction

The prevalence of obesity has increased over recent decades, posing a significant public health problem as a number of unfavorable health consequences are associated with increased adiposity [1–4]. Identifying more effective weight loss intervention strategies to alleviate this financial and public health burden is paramount. Exercise training is used by 90% of individuals who attempt weight loss [5], however structured exercise training programs typically lead to only modest reductions in body weight [6]. A portion of the variation in weight loss following a structured exercise training intervention may be explained by hormonal control of energy intake and energy expenditure [7].

Leptin is one of the major hormones responsible for controlling energy balance and body weight by altering energy intake and energy expenditure [8, 9]. It is released in response to acute energy availability during periods of intermittent fasting, caloric restriction, and overfeeding [9–11]. Experimental studies have also indicated that the decrease in leptin observed during periods of caloric restriction is associated with increased feelings of hunger, greater desire to eat, and larger prospective food consumption [12, 13]. Furthermore, exogenous leptin administration appears to increase energy expenditure in obese and non-obese participants following weight loss [14, 15]. Longer-term clinical trials utilizing leptin administration produced a dose–response effect on weight- and fat-loss, such that greater doses of leptin yielded a greater decrease in weight and fat mass [16]. Taken together, decreased leptin levels appear to signal the body to restore energy balance by increasing appetite and decreasing energy expenditure, whereas increased leptin levels suppress appetite and increase energy expenditure [17]. However, obesity may also be associated with leptin resistance, where individuals exhibit increased energy intake and lower levels of physical activity despite higher circulating leptin levels [18].

While it stands to reason than exercise and physical activity could potentially disrupt energy balance and impact circulating leptin levels, the chronic effects of exercise training on leptin levels are somewhat inconsistent [19]. Higher- and lower-intensity aerobic exercise decreased leptin during a 12-week intervention in obese women [20]. In addition, lower-, moderate-, and higher-intensity resistance exercise decreased leptin during a 12-month intervention in older adults [21]. In contrast, 12 weeks of aerobic exercise [22], 12 weeks of resistance training [23], or a shorter 3-week combined aerobic and resistance training yielded no change in leptin levels [24]. Finally, chronic exercise training programs have shown little effect on plasma leptin concentrations in the absence of weight loss or decreased adiposity [25–27].

Leptin has been shown to decrease following a single acute bout of aerobic exercise [28, 29] and following a single acute bout of resistance training [30]. Non-controlled experimental studies have also indicated that exercise can lower leptin in the absence of changes in body composition [31]. The acute decrease in leptin following a single bout of exercise may signal the body to increase energy intake to keep energy balance within a narrow physiological range. This compensatory increase in energy intake could potentially erase the energy deficit caused by exercise and provides a mechanism that explains why weight loss is ineffective for many individuals. However, if chronic exercise training can alter one of the key hormones regulating energy intake and energy expenditure by decreasing leptin and improve leptin resistance, perhaps specific exercise prescription can be used to target this hormone and improve the effectiveness of exercise as a treatment for obesity. Furthermore, the independent effect of chronic exercise training on leptin is still incompletely characterized, and may be influenced by a number of potential moderating factors, including study length, duration, and intensity of the exercise bout, the mode of exercise prescribed, and sex-related differences, in addition to changes in adiposity [25, 27]. As such, the primary aims of this study are to quantify the effect of chronic exercise training ($\geq$ 2 weeks) on plasma leptin values, and identify potential moderators to determine the source of heterogeneity among effects.

## 2 Methods

### 2.1 Search Strategy

The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-

analyses (PRISMA) statement guidelines [32]. Articles published before 14 April 2016 were located by conducting searches of the Physical Education Index ($n$ = 149), PubMed ($n$ = 355), Scopus ($n$ = 225), SPORTDiscus ($n$ = 54), and Web of Science ($n$ = 314) online databases using combinations of the terms 'exercise', 'training', 'exercise training', 'leptin', 'randomized', 'randomized controlled study', and 'randomized controlled trial'. Duplicate publications were removed and preliminary screening of the title and abstract was performed by one of the authors (MVF) for eligibility.

### 2.2 Study Selection

The current analysis was limited to (1) peer-reviewed publications; (2) available in English; (3) involving human subjects; (4) randomized to an exercise training or non-exercise comparison; (5) providing measures of leptin at baseline, during, and/or after completion of the exercise training program; and (6) with the length of the exercise training intervention $\geq$ 2 weeks. Excluded records (1) were non-peer reviewed; (2) provided a review, meta-analysis, position statement, or proposed study design; (3) utilized a cross-sectional or prospective study design; (4) included exercise as part of a multicomponent treatment (e.g. exercise plus dietary intervention), from which an effect size (ES) for exercise alone could not be calculated; or (5) compared exercise only with an active treatment (e.g. nutritional intervention or another mode of exercise). As age was to be explored as a potential moderator, no age limit was used in the current study, and retrieved articles included children/adolescents and adults. In addition, the search was not restricted to a specific range of publication dates. Potential full-text manuscripts were reviewed by three authors (MVF, EDH, CLW-R) during the data extraction process to ensure eligibility based on the criteria provided above, and resolved by consensus. A total of 133 full-text records were identified during the initial electronic database search and evaluated for inclusion in the current analysis. A flowchart of the study selection process is provided in Fig. 1. Two authors (MVF, TDW) manually reviewed reference lists from retrieved articles for additional publications not retrieved using the database search.

Manual searches revealed two additional publications [22, 33]. A request for missing data was sent to nine corresponding authors [34–42], three of whom provided the missing information or an additional publication with the requested data [35, 36, 43].

### 2.3 Effect Size (ES) Calculation

ESs were calculated by subtracting the mean change in the comparison condition from the mean change in the exercise condition and dividing the difference by the pooled standard deviation (SD) of the baseline scores, and adjusted for small sample bias [44]. The inverse variance weight was used to calculate the overall mean ES. When group mean values were presented without a measure of variability [45, 46], the SD from the largest study available with similar demographic characteristics was used to estimate the ES [47]. The sample size for the intervention and control groups, mean leptin values at baseline, and during the intervention, as well as baseline measures of variability, participant age, sex, baseline body mass index (BMI), baseline %Fat, baseline fitness level, exercise mode, exercise session duration, exercise session intensity, exercise session frequency, exercise program length, year of publication, and outcome measure were independently extracted by the authors (MVF, EDH, CLW-R), with discrepancies resolved prior to aggregating effects. A decrease in leptin levels following exercise training resulted in a positive ES.

### 2.4 Bias Assessment

The Jadad scale was used to assess study quality and was coded by two independent reviewers (CLW-R and EDH). Discrepancies were resolved by consensus with a third reviewer (MVF) if needed. Randomization methods, binding, and description of withdrawals were evaluated by reviewers, and scored out of 5 total points. Higher scores indicate a greater number of key criteria having been reported, and trials with scores $\geq$ 3 were considered of high methodological quality. In addition, bias was assessed using a funnel plot and sensitivity analysis, fail-safe N, and Egger's test [48, 49].

### 2.5 Statistical Analysis

Random-effects models were used to aggregate a mean ES and 95% confidence intervals (CIs) for leptin, and to test variation in effects according to moderator variables using macros (MeanES, MetaF, and MetaReg) in IBM SPSS 23.0 (IBM Corporation, Armonk, NY, USA). Initial comparisons were made using MetaF and MetaReg based on a number of independent variables chosen a priori due to their influence on leptin levels. The definition of subgroups and moderator variables can be found in electronic supplementary Table 1.

Two-way (effects $\times$ raters) intraclass correlation coefficients for absolute agreement were calculated to examine interrater reliability for calculated effects. The initial intraclass correlation coefficients were $>$ 0.87. Intraclass correlation increased to 100% after adjusting for discrepancies between reviewers.

Missing values not obtained from the literature were imputed using the mean of the available values. Multilevel

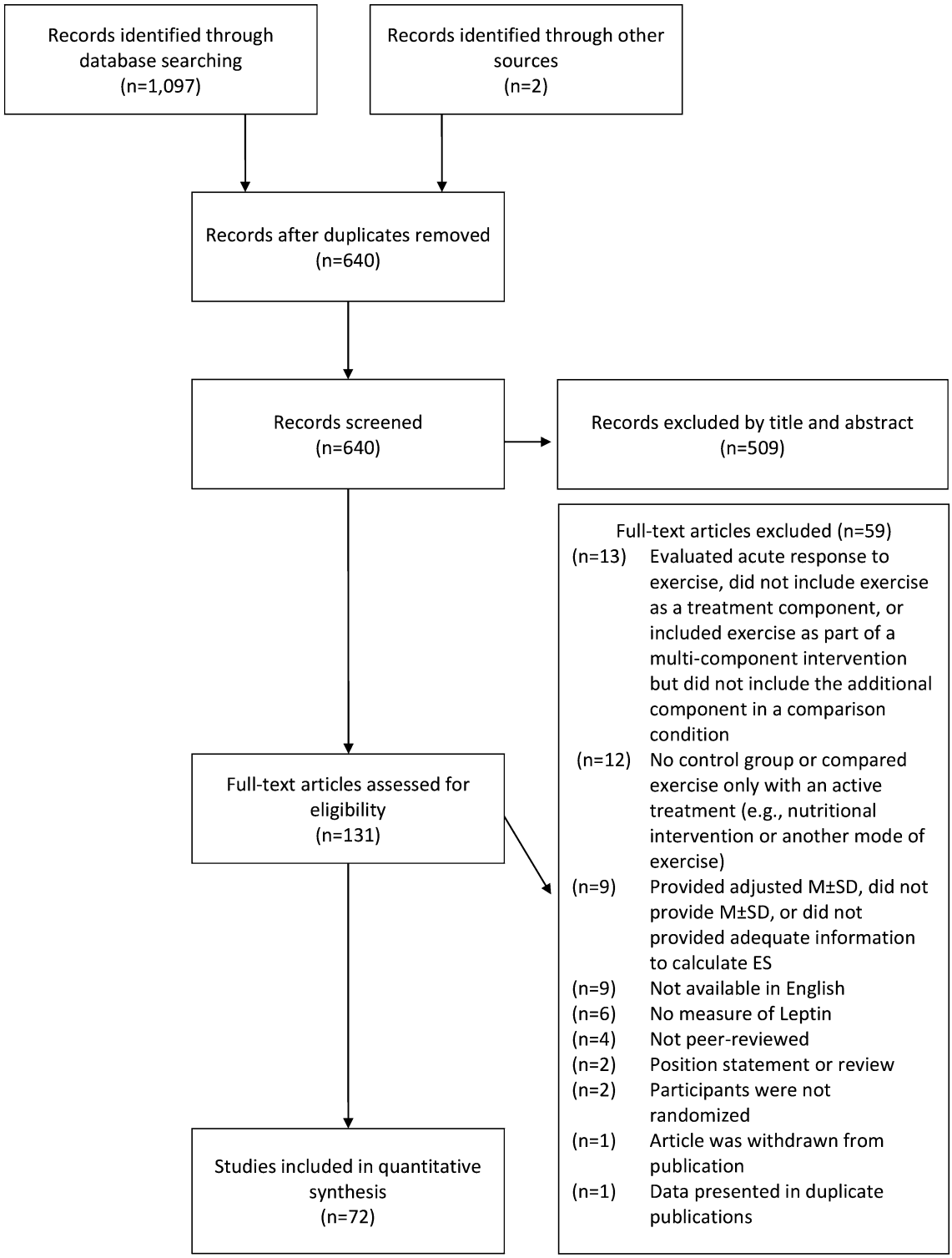


**Fig. 1** Study selection process. *ES* effect size, *n* number of studies, *m* mean, *SD* standard deviation

linear regression with maximum likelihood estimation was used according to standard procedures to adjust for between-study variance and the correlation between effects nested within studies [50, 51]. This was required as multiple effects were gathered from studies with multiple intervention groups or reporting subgroup comparisons in addition to the mean change. The data analysis for the multilevel model was performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Data available for study

**Table 1** Summary of subgroup analysis

| Effect moderator | Effects (*k*) | Mean ES | 95% CI | *p* value | Between-group comparison *p* value |
|---|---|---|---|---|---|
| Age group, years | | | | | |
| < 20 | 6 | − 0.1743 | − 0.5098, 0.1611 | 0.3083 | |
| 20–55 | 63 | 0.2889 | 0.1844, 0.3935 | < 0.0001 | |
| > 55 | 38 | 0.2293 | 0.1140, 0.3446 | 0.0001 | 0.0344 |
| Sex | | | | | |
| Female | 49 | 0.2846 | 0.1824, 0.3869 | < 0.0001 | |
| Male | 38 | 0.3253 | 0.1947, 0.4559 | < 0.0001 | |
| Mixed | 20 | −0.0288 | −0.1933, 0.1357 | 0.7315 | 0.0018 |
| Baseline weight status | | | | | |
| Normal weight | 23 | 0.2528 | 0.0692, 0.4365 | 0.0070 | |
| Overweight | 39 | 0.2647 | 0.1312, 0.3983 | 0.0001 | |
| Obese | 45 | 0.2242 | 0.1085, 0.3400 | 0.0001 | 0.8988 |
| Exercise mode | | | | | |
| Aerobic | 55 | 0.2589 | 0.1568, 0.3610 | < 0.0001 | |
| Resistance | 21 | 0.3446 | 0.1413, 0.5480 | 0.0009 | |
| Combined | 31 | 0.1541 | 0.0071, 0.3011 | 0.0399 | 0.2927 |
| Exercise intensity | | | | | |
| Low | 38 | 0.1714 | 0.0383, 0.3045 | 0.0116 | |
| Moderate | 25 | 0.3120 | 0.1454, 0.4786 | 0.0002 | |
| Vigorous | 44 | 0.2637 | 0.1460, 0.3814 | < 0.0001 | 0.3887 |
| Clinical diagnosis | | | | | |
| Healthy participants | 19 | 0.3595 | 0.1630, 0.5560 | 0.0003 | |
| Type 1 diabetes mellitus | 1 | 0.2692 | − 0.7715, 1.3099 | 0.6122 | |
| Type 2 diabetes mellitus | 13 | 0.0839 | − 0.1046, 0.2724 | 0.3830 | |
| Overweight/obese | 58 | 0.2817 | 0.1959, 0.3674 | < 0.0001 | |
| Chronic kidney disease | 1 | 1.0781 | 0.2253, 1.9309 | 0.0132 | |
| Polycystic ovarian syndrome | 2 | 0.8035 | − 0.6260, 0.7931 | 0.8175 | |
| Pregnancy | 1 | − 0.7979 | − 1.3445, −0.2513 | 0.0052 | |
| Cardiovascular disease | 1 | 0.3000 | − 0.2844, 0.8844 | 0.3144 | |
| Breast cancer | 1 | 0.1155 | − 0.3872, 0.6182 | 0.6614 | |
| Colorectal cancer | 1 | 0.0887 | − 0.7712, 0.9486 | 0.8398 | |
| Esophageal cancer | 1 | 0.3352 | − 0.4313, 1.1017 | 0.3914 | |
| Knee osteoarthritis | 1 | − 0.2560 | − 0.7026, 0.1906 | 0.2612 | |
| Metabolic syndrome | 6 | 0.1375 | − 0.0916, 0.3666 | 0.2394 | |
| Spinal cord injury | 1 | 0.7601 | − 0.2748, 1.7950 | 0.1500 | 0.0055 |

*CI* confidence interval, *ES* effect size

and participant characteristics are presented as mean ± SD unless otherwise indicated.

## 3 Results

### 3.1 Mean ES

Effects analyzed included data collected from 3826 participants following exercise training. These individuals received some form of exercise training in an intervention setting that ranged from 4 to 166 participants (29.8 ± 31.7) per effect. The age of participants ranged from 8.2 to 71.2 years (47.4 ± 15.4 years), and participants were predominantly female (67.6 ± 42.5%), with 18.7% of effects obtained from samples of mixed sex. Eighty-seven effects were obtained from sex-specific samples (35.5% male only, 45.8% female only). Average BMI and %Fat across all effects were 30.0 ± 3.0 kg/m$^2$ and 38.0 ± 8.4%Fat, respectively.

Training interventions varied in design but utilized aerobic training only (51.4%), resistance training only (19.6%), or a combination of training modes (29.0%). Exercise interventions were 3 weeks up to 24 months in length (7.5 ± 4.8 months) and trained participants from 2 to 7 days (4.0 ± 1.0 days), reaching 24–90 min (52.3 ± 13.7 min) of exercise per session at the conclusion of the study. Studies included in the current analysis are presented in electronic supplementary Table 2.

The cumulative results from 107 effects extracted from 72 articles, published between 1998 and 2016, indicate that chronic exercise training can effectively reduce leptin levels (ES 0.2430, 95% CI 0.1647–0.3212, $p < 0.0001$) (Fig. 2). The estimate of the effect increased slightly after accounting for the nesting of multiple effects within a single study (ES 0.2437, 95% CI 0.1390–0.3483, $p < 0.0001$).

### 3.2 Homogeneity of Results

The significant decrease in leptin following chronic exercise training presented moderate heterogeneity ($Q_{106} = 194.8$, $p < 0.001$, $I^2 = 45.6\%$), with sampling error accounting for 71.7% of the observed variance [44, 52]. Based on a significant $Q$ statistic and an $I^2$ near 50% indicating moderate heterogeneity, the variability in leptin following chronic exercise training is greater than would have occurred naturally based on study sample error. The null hypothesis for homogenous distribution was rejected, and subgroup and moderator analyses were performed to determine the source of variability among effects.

### 3.3 Subgroup and Moderator Analysis

Subgroup comparisons indicated that the change in leptin among older adults (> 55 years) was no different ($k = 38$, ES 0.23, 95% CI 0.11–0.34, $p < 0.001$) than the change in younger adults (20–55 years) ($k = 63$, ES 0.29, 95% CI 0.18–0.39, $p < 0.001$), however both appeared to be greater than children/adolescents (< 20 years) ($k = 6$, ES − 0.17, 95% CI − 0.51 to 0.16, $p = 0.3083$) as significant differences were noted between groups ($p = 0.0344$). The effect of chronic exercise training on leptin was significant for both men ($k = 38$, ES 0.31, 95% CI 0.20–0.42, $p < 0.0001$) and women ($k = 49$, ES 0.27, 95% CI 0.19–0.35, $p < 0.001$), with no sex differences observed ($p = 0.5606$). Finally, exercise training interventions that utilized a no-treatment control group ($k = 78$, ES 0.33, 95% CI 0.24–0.42, $p < 0.001$) yielded larger effects compared with training interventions that used an 'active' control group (i.e. diet vs. diet + exercise) ($k = 29$, ES 0.05, 95% CI − 0.08 to 0.19, $p = 0.4653$), with significant differences observed between conditions ($p = 0.0008$). Additional subgroup comparisons are presented in Table 1.

The independent effects of each potential moderating variable were examined using univariate meta-regression and are presented in Table 2. In the multivariate model, control group comparison ($\beta = -0.38$, standard error [SE] 0.0901, $p < 0.001$) and change in %Fat ($\beta = -0.0684$, SE 0.03, $p = 0.0078$) were associated with the effect of exercise on leptin, collectively accounting for 14.4% of the variation in effects. These data indicate that a greater decrease in leptin was observed in individuals who experienced a reduction in %Fat, after accounting for the type of control group. Both parameters, control group comparison ($\beta = -0.33$, SE 0.09, $p = 0.0012$) and change in %Fat ($\beta = -0.08$, SE 0.03, $p = 0.0092$) remained

**Table 2** Summary of univariate moderator analysis

| Effect moderator | Unstandardized $\beta$ | 95% CI | $R^2$ (%) | $p$ value |
|---|---|---|---|---|
| Age | − 0.0016 | − 0.0064, 0.0032 | 0.36 | 0.5228 |
| Percentage female | − 0.0873 | − 0.2653, 0.0907 | 0.80 | 0.3366 |
| Baseline BMI | − 0.0098 | − 0.0333, 0.0137 | 0.57 | 0.4148 |
| Change BMI ES | 0.1197 | − 0.0092, 0.2303 | 3.82 | 0.0338 |
| Baseline %Fat | − 0.0042 | − 0.0134, 0.0049 | 0.71 | 0.3673 |
| Change %Fat ES | − 0.0178 | − 0.0657, 0.0302 | 0.45 | 0.4685 |
| Exercise session duration | − 0.0037 | − 0.0094, 0.0019 | 1.41 | 0.1976 |
| Exercise program length | − 0.0093 | − 0.0257, 0.0072 | 1.06 | 0.2685 |
| Exercise frequency | − 0.0182 | − 0.0588, 0.0952 | 0.19 | 0.6433 |
| Exercise intensity | 0.0436 | − 0.0454, 0.1325 | 0.79 | 0.3373 |
| Comparison condition | − 0.2791 | − 0.4430, − 0.1153 | 9.20 | 0.0008 |

*BMI* body mass index, *CI* confidence interval, *ES* effect size, *%Fat* relative adiposity

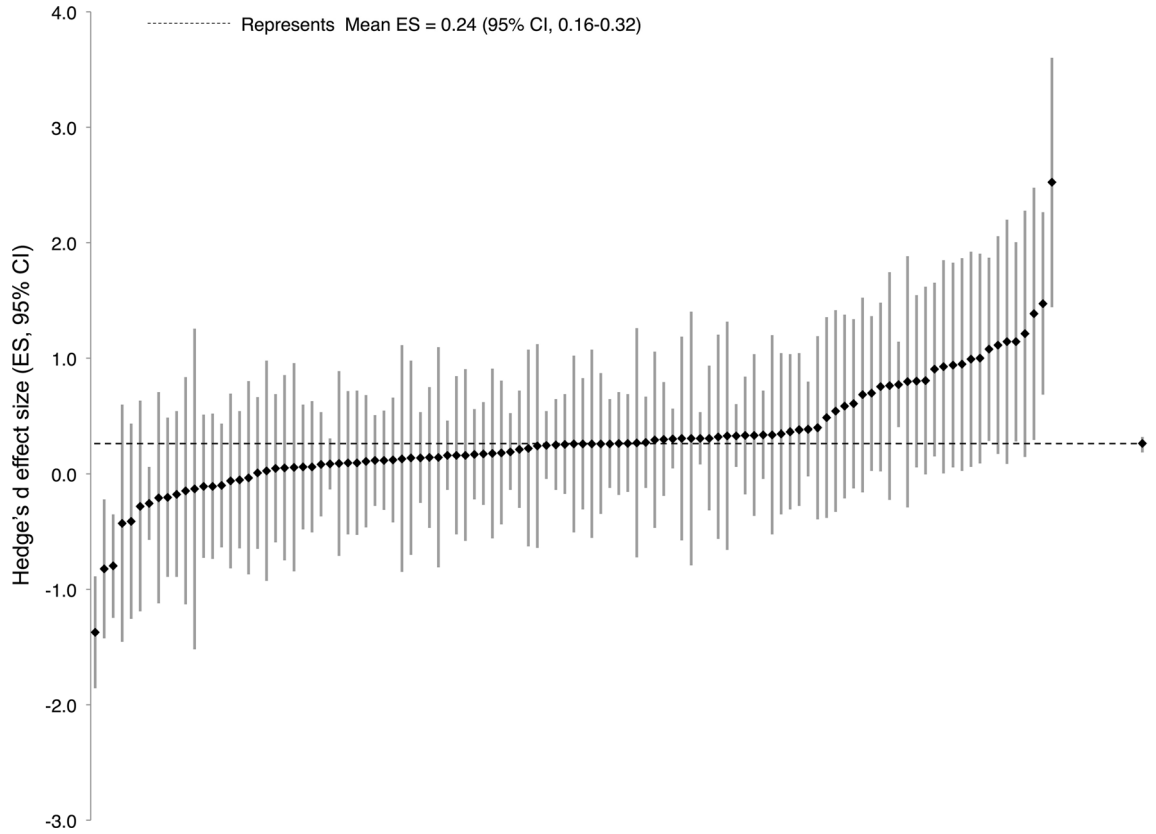


**Fig. 2** Forest plot of Hedges' *d* effect sizes. The aggregated Hedges' *d* is the random-effects mean effect size for chronic exercise training on leptin weighted by the inverse variance. Data are presented as effect size and 95% CI. *CI* confidence interval, *ES* effect size

significantly associated with the change in leptin after adjusting for the nesting of effects within studies.

### 3.4 Assessment of Bias

Twenty-nine effects (27.1%) were obtained from high-quality studies, with overall quality of scores for effects in the current analysis ranging from 1 to 4 (1.9 ± 0.9). All 107 effects (100%) were randomized, with 29 effects (27.1%) gathered from studies that provided a description of the randomization process used and that the current authors deemed appropriate (table of random numbers, computer-generated order, etc.). A complete description of participants who were enrolled in the study but did not complete the observation period or who were not included in the analysis was provided for 53 effects (49.5%). Although it is often not possible to 'blind' participants to an exercise treatment condition, 12 effects (11.2%) described the procedures used to blind researchers during data collection and analysis.

The number of unpublished or unretrieved null effects needed to overturn the significant results was estimated using a fail-safe $N^+$ [53]. The fail-safe $N^+$ for the effect of exercise training on leptin using a random-effects model collapsed to a fixed-effects model after one iteration, and yielded $N^+ = 1708.4$ effects. The robust fail-safe $N^+$ indicated that publication bias can be 'safely ignored' [48]. A funnel plot was created by scattering the treatment ES exercise training on leptin against their SE [54], as recommended when using a standardized mean difference ES [54–56]. These data are presented in Fig. 3 and indicate low likelihood of potential bias. In addition, 10 of the 107 effects (9.3%) outside of the 95% CI were identified using the funnel plot to identify potential outliers. Sensitivity analysis removing these 10 effects had minimal effect on our estimate of the effect of exercise on leptin (ES 0.2408, 95% CI 0.1854–0.2962, $p < 0.001$) for the remaining 97 effects, but reduced the observed heterogeneity in effects ($Q_{96} = 63.7201$, $p = 0.9955$, $I^2 = 0.00\%$). Finally, potential publication bias was addressed using Egger's test [49]. Further supporting the fail-safe $N^+$, funnel plot, and sensitivity analysis, Egger's test indicated that the effect of exercise training on leptin was not subject to bias [$F(1, 105) = 0.196$, $p = 0.659$].

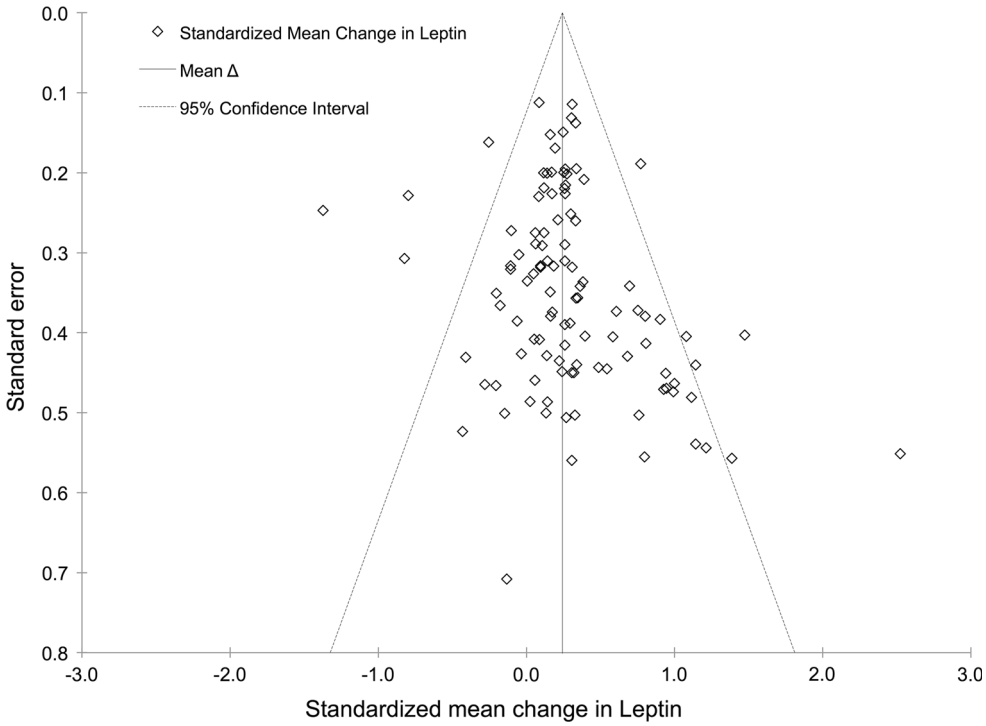


**Fig. 3** Funnel plot of Hedges' *d* effect size versus study standard error. The aggregated Hedges' *d* is the random-effects mean effect size for chronic exercise training on leptin plotted against the standard error

## 4 Discussion

The cumulative evidence gathered from peer-reviewed research published between 1998 and 2016 indicates that chronic exercise training (≥ 2 weeks) is associated with a decrease in plasma leptin. Our results provide an estimate of the magnitude of the effect of chronic exercise training on leptin levels, and indicate that a decrease in leptin occurs as a result of chronic exercise training, regardless of age and sex. Aerobic, resistance, and concurrent exercise training all yielded a significant decrease in leptin, with no differences noted between the modes of exercise. In addition, exercise intensity, duration, frequency, and program length were not associated with a change in leptin. Although a decrease in %Fat appears to be one of the most significant factors associated with a decrease in leptin levels, chronic exercise training appears to elicit an independent and significant decrease in leptin levels regardless of change in adiposity.

Dietary interventions have consistently led to a decrease in circulating leptin levels and appear to yield similar decreases in leptin levels when compared with exercise training [57]. While either may be effective stand-alone treatment options, combined diet and exercise training treatments have been associated with the largest decrease in leptin levels, especially when accompanied by weight loss and decrease in %Fat [22, 43, 58]. The physiologic impact of this decrease in leptin on weight loss success during diet and exercise interventions remains unclear. Previous research has indicated that while higher leptin levels may decrease feelings of hunger and increase energy expenditure in normal-weight individuals, obese individuals appear to be leptin-resistant, where higher circulating leptin levels may not be able to induce these same responses [9]. The acute decrease in leptin concentration in response to an energy deficit may serve as a protective mechanism to control energy expenditure during periods of low energy availability [59]. During an exercise program, these mechanisms may counteract a weight loss program in order to keep total daily energy expenditure within a narrow physiologic range. These protective mechanisms may be partly responsible for weight regain as previously obese individuals tend to have lower leptin levels when compared with their normal weight, 'never obese' peers [60]. On the other hand, the decrease in leptin following chronic exercise training observed in the current study may be due to improved leptin sensitivity [61–63], and may represent the body establishing a new physiologic 'set point'. As this analysis was limited to exercise interventions longer than 2 weeks, the improved leptin sensitivity may enhance further weight loss during periods of negative energy balance as %Fat explained only a portion of the variation in the change in leptin following exercise training [64].

Combined dietary and exercise interventions show promise when treating obesity and may compliment pharmaceutical interventions [65, 66]. When elevated plasma leptin levels do not effectively reduce energy intake, this often leads to further weight gain, and ultimately increases leptin resistance [67]. Although somewhat speculative, previous researchers have argued that improved leptin sensitivity would result in weight loss almost exclusively

due to decreased adiposity [68] as exogenous leptin administration produced a decrease in fat mass that explained over 95% of weight loss, during the 24-week study period, in obese participants [16]. The increased leptin sensitivity of a combined treatment program including diet, exercise, and pharmaceutical treatment could potentially induce greater weight loss than any treatment independently, and would have tremendous clinical significance when coupled with the improvements in fat-free mass that occur as a result of exercise training. However, due to the exploratory nature of this analysis, an attempt should be made to explore these hypotheses in future experimental studies.

The result of the subgroup analysis indicated that the effect of chronic exercise training varied by the clinical population being studied, however only two of the clinical populations studied (pregnancy and knee osteoarthritis) presented negative mean ES. In addition, 10 of the 14 clinical populations studied yielded fewer than three effects, and group ES ranged from $-0.7979$ to 0.8035. The largest number of effects came from three distinct populations (healthy, overweight/obese, and type 2 diabetes mellitus participants). Evidence supporting the hypothesis that the effect of chronic exercise training varies by clinical population is somewhat inconclusive despite the observed, and perhaps spurious, significant between-group differences. Rather, these results should highlight the need for further research examining whether the presence of a specific disease or condition alters the efficacy of exercise training.

Based on the current results, improvements in body composition were the strongest predictors of the observed mean effect. Determining the best treatment strategy for overweight/obese patients or participants is paramount. As no single component of the exercise prescription was associated with the observed decrease in leptin, practitioners are encouraged to design their physical activity and exercise training interventions based on the current guidelines for weight loss and weight management, and accumulate at least 250 min of moderate-intensity physical activity per week [69]. The current study also indicates that aerobic and resistance training may yield a similar decrease in leptin, which aligns with previous evidence that has suggested both modes of exercise can yield similar weight loss, especially when accompanied by a restricted-calorie dietary program [70]. Perhaps when working with individuals to achieve weight loss, health-fitness professionals should emphasize a holistic approach to human movement combining structured exercise training with increased lifestyle-based physical activity. Taken together, physical activity is generally better than none at all, more physical activity is often better than less, and including higher-volume or higher-intensity activities is appropriate when under the guidance of a trained professional [71, 72].

### 4.1 Limitations

Because of the nature of meta-analysis and reviews of secondary data, the current review is not without limitations. First, the current study calculated a standardized mean effect of exercise training using summary data from published peer-reviewed manuscripts. Using raw individual participant data rather than summary descriptive statistics may have provided added precision for the current analysis, however this approach was not feasible due to the large number of publications and wide range of years included in our electronic search [73]. Second, the current study was limited to peer-review publications and excluded 'grey literature' from conference abstracts, dissertations, and other non-peer-reviewed sources. Although grey literature was not included in order to limit the current analysis to studies of high methodological quality, excluding these other sources has been shown to have little impact on the overall estimated ES [74–76]. As with all systematic reviews, it is difficult to estimate the extent to which unpublished, unidentified, and unretrieved studies may have potentially influenced the results of the current study [53]. The authors feel confident that this review identified the vast majority of the relevant publications as 97.3% of the publications were identified using the electronic database search, as well as identifying additional articles using a manual search of references [77–80]. It should be noted that fewer than half of the studies in the current review included a complete description of participant randomization, attrition, and missingness (46.9%). Improved transparency when reporting data management and analysis should be a priority in future studies.

Specific to the current analysis, the authors made the decision to include children/adolescents in the current review a priori because it was unclear how much research had examined the effect of chronic exercise training on leptin within this age group. In the end, only six effects were collected from articles with an average age $< 20$ years. A sensitivity analysis removing children/adolescents did not impact the overall mean effect (ES 0.2430, 95% CI 0.1647–0.3212, $p < 0.0001$ in the original manuscript vs. ES 0.2558, 95% CI 0.1841–0.3275, $p < 0.0001$ when excluding children/adolescents). In addition, excluding children had no impact on the results of the moderator analysis comparing 'younger' and 'older' adults (0.2715, 95% CI 0.1777–0.3653 vs. 0.2296, 95% CI 0.1310–0.3281, respectively; $p = 0.5457$). The magnitude of decrease in leptin following chronic exercise training appear to be much larger in 'younger' and 'older' adults, however caution should be used when interpreting the between-group differences based on age due to the relatively small number of studies involving children/adolescents. Based on the available data, it is unclear if these apparent differences

represent the true effect of chronic exercise training on leptin in the population or represent a statistical artifact due to the paucity of research in children. As such, we recommend that future high-quality original research should further examine the effect of chronic exercise training on leptin in children/adolescents.

## 5 Conclusions

Based on the cumulative results from peer-reviewed research published between 1998 and 2016, chronic exercise training ($\geq$ 2 weeks) produces a small but consistent decrease in plasma leptin levels regardless of age and sex. The effect of exercise training appears to be largely driven by improvements in body composition, specifically a decrease in %Fat. However, the decrease also appears to suggest increased leptin sensitivity, even in the absence of weight loss or decrease in %Fat. These results further support the role of exercise training as part of an effective weight management program.

**Author Contributions** MVF conceptualized and designed the study, coded and analyzed effects, carried out the initial analysis, drafted the initial manuscript, and approved the final manuscript as submitted. EDH coded and analyzed effects, reviewed and revised the initial manuscript, and approved the final manuscript as submitted. CLW-R coded and analyzed effects, reviewed and revised the initial manuscript, and approved the final manuscript as submitted. TDW coded and analyzed effects, reviewed and revised the initial manuscript, and approved the final manuscript as submitted. WCD coded and analyzed effects, reviewed and revised the initial manuscript, and approved the final manuscript as submitted.

**Compliance with Ethical Standards**

**Data Availability Statement** Data used for these analyses are available in a public repository through the University of Alabama, which does not issue datasets with DOIs (non-mandated deposition). The data can be downloaded directly from http://ir.ua.edu/handle/123456789/3480 in SPSS or Microsoft Excel file format.

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## References

1. Kelly T, Yang W, Chen C, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. Int J Obes. 2008;32(9):1431–7.
2. Ogden CL, Carroll MD, Fryar CD, Flegal KM. Prevalence of obesity among adults and youth: United States, 2011–2014. NCHS Data Brief. 2015;219:1–8.
3. Pi-Sunyer FX, Becker DM, Bouchard C, Carleton R, Colditz G, Dietz W, et al. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. Am J Clin Nutr. 1998;68(4):899–917.
4. Benjamin RM. The Surgeon General's vision for a healthy and fit nation. Public Health Rep. 2010;125(4):514.
5. Klem ML, Wing RR, McGuire MT, Seagle HM, Hill JO. A descriptive study of individuals successful at long-term maintenance of substantial weight loss. Am J Clin Nutr. 1997;66(2):239–46.
6. Thorogood A, Mottillo S, Shimony A, Filion KB, Joseph L, Genest J, et al. Isolated aerobic exercise and weight loss: a systematic review and meta-analysis of randomized controlled trials. Am J Med. 2011;124(8):747–55.
7. Pontzer H. Constrained total energy expenditure and the evolutionary biology of energy balance. Exerc Sport Sci Rev. 2015;43(3):110–6.
8. Schwartz MW, Woods SC, Porte D, Seeley RJ, Baskin DG. Central nervous system control of food intake. Nature. 2000;404(6778):661–71.
9. Klok MD, Jakobsdottir S, Drent ML. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. Obes Rev. 2007;8(1):21–34.
10. Galic S, Oakhill JS, Steinberg GR. Adipose tissue as an endocrine organ. Mol Cell Endocrinol. 2010;316(2):129–39.
11. Hilton LK, Loucks AB. Low energy availability, not exercise stress, suppresses the diurnal rhythm of leptin in healthy young women. Am J Physiol Endocrinol Metab. 2000;278(1):E43–9.
12. Mars M, de Graaf C, de Groot CP, van Rossum CT, Kok FJ. Fasting leptin and appetite responses induced by a 4-day 65%-energy-restricted diet. Int J Obes (Lond). 2006;30(1):122–8.
13. Keim NL, Stern JS, Havel PJ. Relation between circulating leptin concentrations and appetite during a prolonged, moderate energy deficit in women. Am J Clin Nutr. 1998;68(4):794–801.
14. Rosenbaum M, Murphy EM, Heymsfield SB, Matthews DE, Leibel RL. Low dose leptin administration reverses effects of sustained weight-reduction on energy expenditure and circulating concentrations of thyroid hormones. J Clin Endocrinol Metab. 2002;87(5):2391–4.
15. Rosenbaum M, Goldsmith R, Bloomfield D, Magnano A, Weimer L, Heymsfield S, et al. Low-dose leptin reverses skeletal muscle, autonomic, and neuroendocrine adaptations to maintenance of reduced weight. J Clin Investig. 2005;115(12):3579–86.
16. Heymsfield SB, Greenberg AS, Fujioka K, Dixon RM, Kushner R, Hunt T, et al. Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. JAMA. 1999;282(16):1568–75.
17. Myers MG Jr, Leibel RL, Seeley RJ, Schwartz MW. Obesity and leptin resistance: distinguishing cause from effect. Trends Endocrinol Metab. 2010;21(11):643–51.
18. Git KC, Adan RA. Leptin resistance in diet-induced obesity: the role of hypothalamic inflammation. Obes Rev. 2015;16(3):207–24.
19. Hulver MW, Houmard JA. Plasma leptin and exercise: recent findings. Sports Med. 2003;33(7):473–82.
20. Mezghanni N, Mnif M, Chtourou H, Chaabouni K, Masmoudi L, Lassoued A, et al. Effect of aerobic training on insulin resistance and C-reactive protein (CRP) levels and subcutaneous abdominal in obese women. Sport Sci Health. 2014;10(2):111–8.
21. Fatouros IG, Tournis S, Leontsini D, Jamurtas AZ, Sxina M, Thomakos P, et al. Leptin and adiponectin responses in overweight inactive elderly following resistance training and

detraining are intensity related. J Clin Endocrinol Metab. 2005;90(11):5970–7.
22. Shalitin S, Ashkenazi-Hoffnung L, Yackobovitch-Gavan M, Nagelberg N, Karni Y, Hershkovitz E, et al. Effects of a twelve-week randomized intervention of exercise and/or diet on weight loss and weight maintenance, and other metabolic parameters in obese preadolescent children. Horm Res. 2009;72(5):287–301.
23. Lambert CP, Sullivan DH, Evans WJ. Effects of testosterone replacement and/or resistance training on interleukin-6, tumor necrosis factor alpha, and leptin in elderly men ingesting megestrol acetate: a randomized controlled trial. J Gerontol A Biol Sci Med Sci. 2003;58(2):165–70.
24. Lucotti P, Monti LD, Setola E, Galluccio E, Gatti R, Bosi E, et al. Aerobic and resistance training effects compared to aerobic training alone in obese type 2 diabetic patients on diet treatment. Diabetes Res Clin Pract. 2011;94(3):395–403.
25. Kraemer RR, Chu H, Castracane VD. Leptin and exercise. Exp Biol Med. 2002;227(9):701–8.
26. Bouassida A, Zalleg D, Bouassida S, Zaouali M, Feki Y, Zbidi A, et al. Leptin, its implication in physical exercise and training: a short review. J Sports Sci Med. 2006;5(2):172–81.
27. Bouassida A, Chamari K, Zaouali M, Feki Y, Zbidi A, Tabka Z. Review on leptin and adiponectin responses and adaptations to acute and chronic exercise. Br J Sports Med. 2010;44(9):620–30.
28. Jürimäe J, Jürimäe T. Leptin responses to short term exercise in college level male rowers. Br J Sports Med. 2005;39(1):6.
29. Legakis IN, Mantzouridis T, Saramantis A, Lakka-Papadodima E. Rapid decrease of leptin in middle-aged sedentary individuals after 20 minutes of vigorous exercise with early recovery after the termination of the test. J Endocrinol Investig. 2004;27(2):117–20.
30. Zafeiridis A, Smilios I, Considine RV, Tokmakidis SP. Serum leptin responses after acute resistance exercise protocols. J Appl Physiol. 2003;94(2):591–7.
31. Gomez-Merino D, Chennaoui M, Drogou C, Bonneau D, Guezennec CY. Decrease in serum leptin after prolonged physical activity in men. Med Sci Sports Exerc. 2002;34(10):1594–9.
32. Moher D, Liberati A, Tetzlaff J, Altman D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:332–6.
33. Hasson RE, Adam TC, Davis JN, Kelly LA, Ventura EE, Byrd-Williams CE, et al. Randomized controlled trial to improve adiposity, inflammation, and insulin resistance in obese African-American and Latino youth. Obesity (Silver Spring). 2012;20(4):811–8.
34. Mason C, Foster-Schubert KE, Imayama I, Xiao LR, Kong A, Campbell KL, et al. History of weight cycling does not impede future weight loss or metabolic improvements in post-menopausal women. Metab Clin Exp. 2013;62(1):127–36.
35. Straznicky NE, Lambert EA, Grima MT, Eikelis N, Nestel PJ, Dawood T, et al. The effects of dietary weight loss with or without exercise training on liver enzymes in obese metabolic syndrome subjects. Diabetes Obes Metab. 2012;14(2):139–48.
36. Nuri R, Moghaddasi M, Darvishi H, Izadpanah A. Effect of aerobic exercise on leptin and ghrelin in patients with colorectal cancer. J Cancer Res Ther. 2016;12(1):169–74.
37. Foster-Schubert KE, McTiernan A, Frayo RS, Schwartz RS, Rajan KB, Yasui Y, et al. Human plasma ghrelin levels increase during a one-year exercise program. J Clin Endocrinol Metab. 2005;90(2):820–5.
38. Kim HJ, Lee S, Kim TW, Kim HH, Jeon TY, Yoon YS, et al. Effects of exercise-induced weight loss on acylated and unacylated ghrelin in overweight children. Clin Endocrinol. 2008;68(3):416–22.
39. Loria-Kohen V, Fernandez-Fernandez C, Bermejo LM, Morencos E, Romero-Moraleda B, Gomez-Candela C, et al. Effect of different exercise modalities plus a hypocaloric diet on inflammation markers in overweight patients: a randomised trial. Clin Nutr. 2013;32(4):511–8.
40. Marinho SM, Mafra D, Pelletier S, Hage V, Teuma C, Laville M, et al. In hemodialysis patients, intradialytic resistance exercise improves osteoblast function: a pilot study. J Ren Nutr. 2016;26(5):341–5.
41. de Piano A, de Mello MT, Sanches PD, da Silva PL, Campos RMS, Carnier J, et al. Long-term effects of aerobic plus resistance training on the adipokines and neuropeptides in nonalcoholic fatty liver disease obese adolescents. Eur J Gastroenterol Hepatol. 2012;24(11):1313–24.
42. Volpe SL, Kobusingye H, Bailur S, Stanek E. Effect of diet and exercise on body composition, energy intake and leptin levels in overweight women and men. J Am Coll Nutr. 2008;27(2):195–208.
43. Abbenhardt C, McTiernan A, Alfano CM, Wener MH, Campbell KL, Duggan C, et al. Effects of individual and combined dietary weight loss and exercise interventions in postmenopausal women on adiponectin and leptin levels. J Intern Med. 2013;274(2):163–75.
44. Hedges L, Olkin I. Statistical methods for meta-analysis. 6th ed. San Diego: Academic Press; 1985. p. 79–201.
45. Gutin B, Ramsey L, Barbeau P, Cannady W, Ferguson M, Litaker M, et al. Plasma leptin concentrations in obese children: changes during 4-mo periods with and without physical training. Am J Clin Nutr. 1999;69(3):388–94.
46. Barbeau P, Gutin B, Litaker Ramsey LT, Cannady WE, Allison J, et al. Influence of physical training on plasma leptin in obese youths. Can J Appl Physiol. 2003;28(3):382–96.
47. Gutin B, Owens S. Role of exercise intervention in improving body fat distribution and risk profile in children. Am J Hum Biol. 1999;11(2):237–47.
48. Rosenthal R. Meta-analytic procedures for social research. 2nd ed. Newbury Park: SAGE Publications; 1991.
49. Egger M, Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629–34.
50. Hox J. Multilevel analysis: techniques and applications. 2nd ed. New York: Taylor & Francis; 2010. p. 205–32.
51. Singer JD, Using SAS. PROC MIXED to fit multilevel models, hierarchical models, and individual growth models. J Educ Behav Stat. 1998;23(4):323–55.
52. Higgins J, Thompson S, Deeks J, Altman D. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60.
53. Rosenberg M. The file-drawer problem revisited: a general weighted method for calculating fail-safe numbers in meta-analysis. Evolution. 2005;59(2):464–8.
54. Sterne JAC, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. 2011;343:1–8.
55. Begg CB, Berlin JA. Publication bias: a problem in interpreting medical data. J R Stat Soc Ser A Stat Soc. 1988;151(3):419–63.
56. Sterne JAC, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J Clin Epidemiol. 2001;54(10):1046–55.
57. Klimcakova E, Kovacikova M, Stich V, Langin D. Adipokines and dietary interventions in human obesity. Obes Rev. 2010;11(6):446–56.
58. Figueroa A, Vicil F, Sanchez-Gonzalez MA, Wong A, Ormsbee MJ, Hooshmand S, et al. Effects of diet and/or low-intensity resistance exercise training on arterial stiffness, adiposity, and

lean mass in obese postmenopausal women. Am J Hypertens. 2013;26(3):416–23.
59. Bereket A, Kiess W, Lustig RH, Muller HL, Goldstone AP, Weiss R, et al. Hypothalamic obesity in children. Obes Rev. 2012;13(9):780–98.
60. Filozof C, Gonzalez C. Predictors of weight gain: the biological-behavioural debate. Obes Rev. 2000;1(1):21–6.
61. Lau PW, Kong Z, Choi C-R, Clare C, Chan DF, Sung RY, et al. Effects of short-term resistance training on serum leptin levels in obese adolescents. J Exerc Sci Fit. 2010;8(1):54–60.
62. Zhao J, Tian Y, Xu J, Liu D, Wang X, Zhao B. Endurance exercise is a leptin signaling mimetic in hypothalamus of Wistar rats. Lipids Health Dis. 2011;10:225.
63. Guadalupe-Grau A, Perez-Gomez J, Olmedillas H, Chavarren J, Dorado C, Santana A, et al. Strength training combined with plyometric jumps in adults: sex differences in fat-bone axis adaptations. J Appl Physiol. 2009;106(4):1100–11.
64. Miller GD, Nicklas BJ, Davis CC, Ambrosius WT, Loeser RF, Messier SP. Is serum leptin related to physical function and is it modifiable through weight loss and exercise in older adults with knee osteoarthritis? Int J Obes Relat Metab Disord. 2004;28(11):1383–90.
65. Farr OM, Gavrieli A, Mantzoros CS. Leptin applications in 2015: what have we learned about leptin and obesity? Curr Opin Endocrinol Diabetes Obes. 2015;22(5):353–9.
66. Paz-Filho G, Wong ML, Licinio J. Ten years of leptin replacement therapy. Obes Rev. 2011;12(5):e315–23.
67. Pan H, Guo J, Su Z. Advances in understanding the interrelations between leptin resistance and obesity. Physiol Behav. 2014;130:157–69.
68. Brinkoetter M, Magkos F, Vamvini M, Mantzoros CS. Leptin treatment reduces body fat but does not affect lean body mass or the myostatin–follistatin–activin axis in lean hypoleptinemic women. Am J Physiol Endocrinol Metab. 2011;301(1):E99–104.
69. Donnelly JE, Blair SN, Jakicic JM, Manore MM, Rankin JW, Smith BK. 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):459–71.
70. 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):441–7.
71. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc. 2011;43(7):1334–59.
72. United States Department of Health and Human Services. 2008 physical activity guidelines for Americans. Washington, DC; 2008. http://www.health.gov/PAGuidelines. Accessed 12 Dec 2017.
73. Stewart LA, Tierney JF. To IPD or not to IPD? Advantages and disadvantages of systematic reviews using individual patient data. Eval Health Prof. 2002;25(1):76–97.
74. McAuley L, Pham B, Tugwell P, Moher D. Does the inclusion of grey literature influence estimates of intervention effectiveness reported in meta-analyses? Lancet. 2000;356(9237):1228–31.
75. Hopewell S, McDonald S, Clarke MJ, Egger M. Grey literature in meta-analyses of randomized trials of health care interventions. Cochrane Database Syst Rev. 2007;(2):MR000010.
76. Conn VS, Valentine JC, Cooper HM, Rantz MJ. Grey literature in meta-analyses. Nurs Res. 2003;52(4):256–61.
77. Lemeshow AR, Blum RE, Berlin JA, Stoto MA, Colditz GA. Searching one or two databases was insufficient for meta-analysis of observational studies. J Clin Epidemiol. 2005;58(9):867–73.
78. Whiting P, Westwood M, Burke M, Sterne J, Glanville J. Systematic reviews of test accuracy should search a range of databases to identify primary studies. J Clin Epidemiol. 2008;61(4):357–64.
79. Papaioannou D, Sutton A, Carroll C, Booth A, Wong R. Literature searching for social science systematic reviews: consideration of a range of search techniques. Health Info Libr J. 2010;27(2):114–22.
80. Linder SK, Kamath GR, Pratt GF, Saraykar SS, Volk RJ. Citation searches are more sensitive than keyword searches to identify studies using specific measurement instruments. J Clin Epidemiol. 2015;68(4):412–7.
81. Ackel-D'Elia C, Carnier J, Bueno CR, Campos RMS, Sanches PL, Clemente APG, et al. Effects of different physical exercises on leptin concentration in obese adolescents. Int J Sports Med. 2014;35(2):164–71.
82. Afshar R, Emany A, Saremi A, Shavandi N, Sanavi S. Effects of intradialytic aerobic training on sleep quality in hemodialysis patients. Iran J Kidney Dis. 2011;5(2):119–23.
83. Ahmadizad S, Ghorbani S, Ghasemikaram M, Bahmanzadeh M. Effects of short-term nonperiodized, linear periodized and daily undulating periodized resistance training on plasma adiponectin, leptin and insulin resistance. Clin Biochem. 2014;47(6):417–22.
84. Akbarpour M. The effect of aerobic training on serum adiponectin and leptin levels and inflammatory markers of coronary heart disease in obese men. Biol Sport. 2013;30(1):21–7.
85. Almenning I, Rieber-Mohn A, Lundgren KM, Løvvik TS, Garnæs KK, Moholdt T. Effects of high intensity interval training and strength training on metabolic, cardiovascular and hormonal outcomes in women with polycystic ovary syndrome: a pilot study. PLoS One. 2015;10(9):e0138793.
86. Ara I, Perez-Gomez J, Vicente-Rodriguez G, Chavarren J, Dorado C, Calbert JAL, et al. Serum free testosterone, leptin and soluble leptin receptor changes in a 6-week strength-training programme. Br J Nutr. 2006;96(6):1053–9.
87. Arciero PJ, Baur D, Connelly S, Ormsbee MJ. Timed-daily ingestion of whey protein and exercise training reduces visceral adipose tissue mass and improves insulin resistance: the PRISE study. J Appl Physiol. 2014;117(1):1–10.
88. Arciero PJ, Gentile CL, Pressman R, Everett M, Ormsbee MJ, Martin J, et al. Moderate protein intake improves total and regional body composition and insulin sensitivity in overweight adults. Metabolism. 2008;57(6):757–65.
89. Arikawa AY, Thomas W, Schmitz KH, Kurzer MS. Sixteen weeks of exercise reduces C-reactive protein levels in young women. Med Sci Sports Exerc. 2011;43(6):1002–9.
90. Balducci S, Zanuso S, Nicolucci A, Fernando F, Cavallo S, Cardelli P, et al. Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss. Nutr Metab Cardiovasc Dis. 2010;20(8):608–17.
91. Bijeh N, Hosseini SA, Hejazi K. The effect of aerobic exercise on serum C—reactive protein and leptin levels in untrained middle-aged women. Iran J Public Health. 2012;41(9):36–41.
92. Boudou P, Sobngwi E, Mauvais-Jarvis F, Vexiau P, Gautier JF. Absence of exercise-induced variations in adiponectin levels despite decreased abdominal adiposity and improved insulin sensitivity in type 2 diabetic men. Eur J Endocrinol. 2003;149(5):421–4.
93. Christensen JO, Svendsen OL, Hassager C, Christiansen C. Leptin in overweight postmenopausal women: no relationship with metabolic syndrome X or effect of exercise in addition to diet. Int J Obes Relat Metab Disord. 1998;22(3):195–9.

94. Chyu M-C, Dagda RY, Doctolero S, Chaung E, Von Bergen V, Zhang Y, et al. Effects of martial arts exercise on body composition, serum biomarkers and quality of life in overweight/obese premenopausal women: a pilot study. Clin Med Insights Womens Health. 2013;6:55–65.
95. Colakoglu S, Colakoglu M, Taneli F, Cetinoz F, Turkmen M. Cumulative effects of conjugated linoleic acid and exercise on endurance development, body composition, serum leptin and insulin levels. J Sports Med Phys Fit. 2006;46(4):570–7.
96. Daryanoosh F, Mehrabani G, Shikhani H. The effect of aerobic and resistance exercises on hormonal changes in non-athlete students at Shiraz University, Southern Iran. Iran Red Crescent Med. 2010;12(2):127–32.
97. Dede ND, Ipekci SH, Kebapcilar L, Arslan M, Kurban S, Yildiz M, et al. Influence of exercise on leptin, adiponectin and quality of life in type 2 diabetics. Turk J Endocrinol Metab. 2015;19(1):7–13.
98. Deibert P, Solleder F, König D, Vitolins MZ, H-h Dickhuth, Gollhofer A, et al. Soy protein based supplementation supports metabolic effects of resistance training in previously untrained middle aged males. Aging Male. 2011;14(4):273–9.
99. Dong-il SEO, Wi-Young SO, Dong Jun S. Changes in insulin resistance and adipokines in obese women following a 12-week programme of combined exercise training. S Afr J Res Sport Phys Educ Recreat. 2016;38(1):139–47.
100. Eftekhari E, Zafari A, Gholami M. Physical activity, lipid profiles and leptin. J Sports Med Phys Fit. 2016;56(4):465–9.
101. Fazelifar S, Ebrahim K, Sarkisian V. Effect of exercise training and detraining on serum leptin levels in obese young boys. Med Sport. 2013;66(3):325–37.
102. Frank LL, Sorensen BE, Yasui Y, Tworoger SS, Schwartz RS, Ulrich CM, et al. Effects of exercise on metabolic risk variables in overweight postmenopausal women: a randomized clinical trial. Obes Res. 2005;13(3):615–25.
103. Friedenreich CM, Neilson HK, Woolcott CG, McTiernan A, Wang Q, Ballard-Barbash R, et al. Changes in insulin resistance indicators, IGFs, and adipokines in a year-long trial of aerobic exercise in postmenopausal women. Endocr Relat Cancer. 2011;18(3):357–69.
104. García-Unciti M, Izquierdo M, Idoate F, Gorostiaga E, Grijalba A, Ortega-Delgado F, et al. Weight-loss diet alone or combined with progressive resistance training induces changes in association between the cardiometabolic risk profile and abdominal fat depots. Ann Nutr Metab. 2012;61(4):296–304.
105. Giannopoulou I, Fernhall B, Carhart R, Weinstock RS, Baynard T, Figueroa A, et al. Effects of diet and/or exercise on the adipocytokine and inflammatory cytokine levels of postmenopausal women with type 2 diabetes. Metabolism. 2005;54(7):866–75.
106. Heyman E, Toutain C, Delamarche P, Berthon P, Briard D, Youssef H, et al. Exercise training and cardiovascular risk factors in type 1 diabetic adolescent girls. Pediatr Exerc Sci. 2007;19(4):408–19.
107. Hopkins SA, Baldi JC, Cutfield WS, McCowan L, Hofman PL. Effects of exercise training on maternal hormonal changes in pregnancy. Clin Endocrinol (Oxf). 2011;74(4):495–500.
108. Karim S, Afiq A. Does regular aerobic training affect basal leptin level (difference between male and female)? Afr J Microbiol Res. 2011;5(31):5591–5.
109. Kelly AS, Steinberger J, Olson TP. Denael. In the absence of weight loss, exercise training does not improve adipokines or oxidative stress in overweight children. Metabolism. 2007;56(7):1005–9.
110. Kerksick C, Thomas A, Campbell B, Taylor L, Wilborn C, Marcello B, et al. Effects of a popular exercise and weight loss program on weight loss, body composition, energy expenditure and health in obese women. Nutr Metab (Lond). 2009;6:23.
111. Kim YS, Nam JS, Yeo DW, Kim KR, Suh SH, Ahn CW. The effects of aerobic exercise training on serum osteocalcin, adipocytokines and insulin resistance on obese young males. Clin Endocrinol. 2015;82(5):686–94.
112. Ko IG, Choi PB. Regular exercise modulates obesity factors and body composition in sturdy men. J Exerc Rehabil. 2013;9(2):256–62.
113. Kosydar-Piechna M, Bilińska M, Janas J, Piotrowicz R. Influence of exercise training on leptin levels in patients with stable coronary artery disease: a pilot study. Cardiol J. 2010;17(5):477–81.
114. Ku YH, Han KA, Ahn H, Kwon H, Koo BK, Kim HC, et al. Resistance exercise did not alter intramuscular adipose tissue but reduced retinol-binding protein-4 concentration in individuals with type 2 diabetes mellitus. J Int Med Res. 2010;38(3):782–91.
115. Ligibel JA, Giobbie-Hurder A, Olenczuk D, Campbell N, Salinardi T, Winer EP, et al. Impact of a mixed strength and endurance exercise intervention on levels of adiponectin, high molecular weight adiponectin and leptin in breast cancer survivors. Cancer Causes Control. 2009;20(8):1523–8.
116. Loimaala A, Groundstroem K, Rinne M, Nenonen A, Huhtala H, Parkkari J, et al. Effect of long-term endurance and strength training on metabolic control and arterial elasticity in patients with type 2 diabetes mellitus. Am J Cardiol. 2009;103(7):972–7.
117. Markofski MM, Carrillo AE, Timmerman KL, Jennings K, Coen PM, Pence BD, et al. Exercise training modifies ghrelin and adiponectin concentrations and is related to inflammation in older adults. J Gerontol A Biol Sci Med Sci. 2014;69(6):675–81.
118. Mason C, Xiao L, Imayama I, Duggan CR, Campbell KL, Kong A, et al. The effects of separate and combined dietary weight loss and exercise on fasting ghrelin concentrations in overweight and obese women: a randomized controlled trial. Clin Endocrinol. 2015;82(3):369–76.
119. McNeil J, Schwartz A, Rabasa-Lhoret R, Lavoie JM, Brochu M, Doucet E. Changes in leptin and peptide YY do not explain the greater-than-predicted decreases in resting energy expenditure after weight loss. J Clin Endocrinol Metab. 2015;100(3):E443–52.
120. Mendham A, Duffield R, Marino F, Coutts A. Small-sided games training reduces CRP, IL-6 and leptin in sedentary, middle-aged men. Eur J Appl Physiol. 2014;114(11):2289–97.
121. Mendham AE, Duffield R, Marino F, Coutts AJ. A 12-week sports-based exercise programme for inactive Indigenous Australian men improved clinical risk factors associated with type 2 diabetes mellitus. J Sci Med Sport. 2015;18(4):438–43.
122. Okada S, Hiuge A, Makino H, Nagumo A, Takaki H, Konishi H, et al. Effect of exercise intervention on endothelial function and incidence of cardiovascular disease in patients with type 2 diabetes. J Atheroscler Thromb. 2010;17(8):828–33.
123. Pil-Byung C, Shin-Hwan Y, Il-Gyu K, Gwang-Suk H, Jae-Hyun Y, Han-Joon L, et al. Effects of exercise program on appetite-regulating hormones, inflammatory mediators, lipid profiles, and body composition in healthy men. J Sports Med Phys Fit. 2011;51(4):654–63.
124. Reseland JE, Anderssen SA, Solvoll K, Hjermann I, Urdal P, Holme I, et al. Effect of long-term changes in diet and exercise on plasma leptin concentrations. Am J Clin Nutr. 2001;73(2):240–5.
125. Rokling-Andersen MH, Reseland JE, Veieroed MB, Anderssen SA, Jr Jacobs, Urdal P, et al. Effects of long-term exercise and diet intervention on plasma adipokine concentrations. Am J Clin Nutr. 2007;86(5):1293–301.

126. Rosety-Rodriguez M, Camacho A, Rosety I, Fornieles G, Rosety MA, Diaz AJ, et al. Low-grade systemic inflammation and leptin levels were improved by arm cranking exercise in adults with chronic spinal cord injury. Arch Phys Med Rehabil. 2014;95(2):297–302.
127. Sardar MA, Hejazi SM, Abedini R. The effects of an eight-week aerobic exercise training program on serum leptin and cardiovascular risk factors among obese men with type II diabetes. Life Sci J. 2012;9(3):2518–23.
128. Shah K, Armamento-Villareal R, Parimi N, Chode S, Sinacore DR, Hilton TN, et al. Exercise training in obese older adults prevents increase in bone turnover and attenuates decrease in hip bone mineral density induced by weight loss despite decline in bone-active hormones. J Bone Miner Res. 2011;26(12):2851–9.
129. Sheikholeslami-Vatani D, Siahkouhian M, Hakimi M, Ali-Mohammadi M. The effect of concurrent training order on hormonal responses and body composition in obese men. Sci Sport. 2015;30(6):335–41.
130. Straznicky NE, Lambert EA, Nestel PJ, McGrane MT, Dawood T, Schlaich MP, et al. Sympathetic neural adaptation to hypocaloric diet with or without exercise training in obese metabolic syndrome subjects. Diabetes. 2010;59(1):71–9.
131. Suksom D, Phanpheng Y, Soogarun S, Sapwarobol S. Step aerobic combined with resistance training improves cutaneous microvascular reactivity in overweight women. J Sports Med Phys Fit. 2015;55(12):1547–54.
132. Tan S, Wang J, Cao L, Guo Z, Wang Y. Positive effect of exercise training at maximal fat oxidation intensity on body composition and lipid metabolism in overweight middle-aged women. Clin Physiol Funct Imaging. 2016;36(3):225–30.
133. Trapp EG, Chisholm DJ, Freund J, Boutcher SH. The effects of high-intensity intermittent exercise training on fat loss and fasting insulin levels of young women. Int J Obes. 2008;32(4):684–91.
134. Turner JE, Markovitch D, Betts JA, Thompson D. Nonprescribed physical activity energy expenditure is maintained with structured exercise and implicates a compensatory increase in energy intake. Am J Clin Nutr. 2010;92(5):1009–16.
135. van Gemert WA, May AM, Schuit AJ, Oosterhof BY, Peeters PH, Monninkhof EM. Effect of weight loss with or without exercise on inflammatory markers and adipokines in postmenopausal women: the SHAPE-2 trial, a randomized controlled trial. Cancer Epidemiol Biomark Prev. 2016;25(5):799–806.
136. Venojärvi M, Wasenius N, Manderoos S, Heinonen OJ, Hernelahti M, Lindholm H, et al. Nordic walking decreased circulating chemerin and leptin concentrations in middle-aged men with impaired glucose regulation. Ann Med. 2013;45(2):162–70.
137. Villareal DT, Shah K, Banks MR, Sinacore DR, Klein S. Effect of weight loss and exercise therapy on bone metabolism and mass in obese older adults: a one-year randomized controlled trial. J Clin Endocrinol Metab. 2008;93(6):2181–7.
138. Winzer BM, Paratz JD, Whitehead JP, Whiteman DC, Reeves MM. The feasibility of an exercise intervention in males at risk of oesophageal adenocarcinoma: a randomized controlled trial. PLoS One. 2015;10(2):e0117922.
139. Yang C, Chen J, Wu F, Li J, Liang P, Zhang H, et al. Effects of 60-day head-down bed rest on osteocalcin, glycolipid metabolism and their association with or without resistance training. Clin Endocrinol. 2014;81(5):671–8.