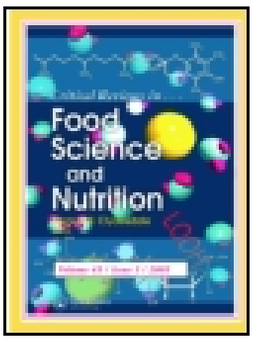

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REVIEW

The impact of exercise training versus caloric restriction on inflammation markers: a systemic review and meta-analysis

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ABSTRACT

Obesity is associated with an increased risk of chronic, low-grade systematic inflammation for which exercise training (EX) and caloric restriction (CR) are potential treatments. We therefore performed a systematic meta-analysis to compare the effect of EX vs. CR and EX + CR vs. CR on inflammation markers in overweight and obese individuals. PubMed, Scopus, Web of Science and the Cochrane were searched up to April 2020 for EX vs. CR or EX + CR vs. CR interventions studies on inflammatory makers i.e. CRP, IL-6 and TNF-α in overweight and obese individuals. Standardized mean differences and 95% confidence intervals were calculated. Thirty two articles (reporting 38 trials) involving 2108 participants were included in the meta-analysis. Based on studies that directly compared EX and CR, there were no evidence for an effect of EX on IL-6 ($p = 0.20$) and TNF-α ($p = 0.58$), when compared with a CR. However, when compared to EX, CR has a statistically greater benefit on CRP ($p = 0.01$). In those studies, directly comparing EX + CR and CR, EX + CR caused a larger decrease in TNF-α ($p = 0.002$) and IL-6 ($p = 0.02$) and tended to decrease CRP ($p = 0.06$) when compared with CR. These results suggest that a combination of EX and CR may be more effective than CR alone at reducing inflammatory cytokines and CRP in overweight and obese individuals.

KEYWORDS

Caloric restriction; exercise training; inflammation; obesity; weight loss

Introduction

Obesity promotes the development of metabolic diseases such as type 2 diabetes (T2D) and cardiovascular disease (CVD), which are rapidly becoming more prevalent, worldwide. Chronic, low-grade systematic inflammation (CLGSI) is recognized as an important risk factor in the pathogenesis of these obesity-related diseases, which is due to obesity enhancing the secretion of adipocytokines (Guzik, Mangalat, and Korbut 2006; Dandona, Aljada, and Bandyopadhyay 2004). The concomitant pathological expansion of adipose tissue (AT) is mediated by adipocyte hypertrophy and hyperplasia, which results in the infiltration of inflammatory cells and activation of AT macrophages (Chait and den Hartigh 2020; Boutens et al. 2018). Raised circulating pro-inflammatory adipocytokines, predominately interleukin 6 (IL-6) and tumor necrosis factor-α (TNF-α) with obesity (Park, Park, and Yu 2005), suppresses the release of anti-inflammatory adipocytokines (Gil-Campos, Cañete, and Gil 2004), and are therefore important candidate molecules in the prevention and treatment of obesity related diseases (Blüher 2014; Donath 2014).

Current therapeutic approaches for treatment of obesity focus on increasing energy expenditure and/or reducing energy intake through exercise training (EX) and/or caloric restriction (CR), with established beneficial effects on obesity-related disease such as T2D (Gil-Campos, Cañete, and Gil 2004; Van Gaal and Scheen 2015; Villareal et al. 2011). Previous results from meta-analysis studies, demonstrated EX decreases inflammatory markers in both overweight and obese individuals (Yu et al. 2017; García-Hermoso et al. 2017) and patients with chronic disease such as T2D (Villareal et al. 2011) or CVD (Villareal et al. 2011; Hammonds et al. 2016). Furthermore, CR and weight loss reduces systemic inflammation in obesity (Ott et al. 2017). However, currently, no meta-analyses have comprehensively compared the effect of EX with CR on circulating markers of inflammation, or examined whether a combination of EX and CR promotes a greater effect. Therefore, the aim of this meta-analysis was to clarify the effects of EX vs. CR as well as EX + CR vs. CR in overweight and obese individuals.

Methods

Search strategy

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement guidelines (Moher et al. 2009) and Cochrane Handbook of Systematic Reviews of

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Interventions. PubMed, Scopus, Web of Science and the Cochrane were searched up to April 2020 by two independent researchers (M.K. and M.E.S.) for EX vs CR or EX + CR vs CR interventions studies that reported the measurement of inflammation markers. Articles were retrieved using the following search criteria: exercise or exercise training or physical activity and caloric restriction or weight loss or diet or dietary and inflammation or cytokines or adipokines or IL-6 or TNF-α or CRP. In addition, reference lists of all retrieved studies were searched for additional reports and to ensure that no relevant articles had been missed. Then, after removing duplicate publications, title and abstracts of articles identified were assessed for their suitability. The full texts of potentially eligible article were then reviewed to determine if the study would be included in the review. Figure 1 presents the flow of papers through the study selection process.

Inclusion and exclusion criteria

Studies were considered to be eligible for inclusion according to the following criteria: (1) an English language articles; (2) comparison between EX vs. CR or EX + CR vs. CR; (3) measurement of at least one of the inflammation markers defined as CRP, IL-6 and TNF-α; (4) involving human subjects; (5) participants with overweight or obesity; (6) involved an intervention of ≥4 weeks in duration In our report, studies were included as CR intervention if they used a consistent pattern of reducing average daily caloric intake or used low and very low calorie diet. Also, studies that used low calorie diet, alternate daily fasting, a hypocaloric diet, counseling or dietary advice with the aim of body weight loss included as part of a weight loss intervention. The followings were considered as exclusion criteria: (1) non-original research (case studies, conference proceedings, dissertations, letters to the editor, reviews and meta-

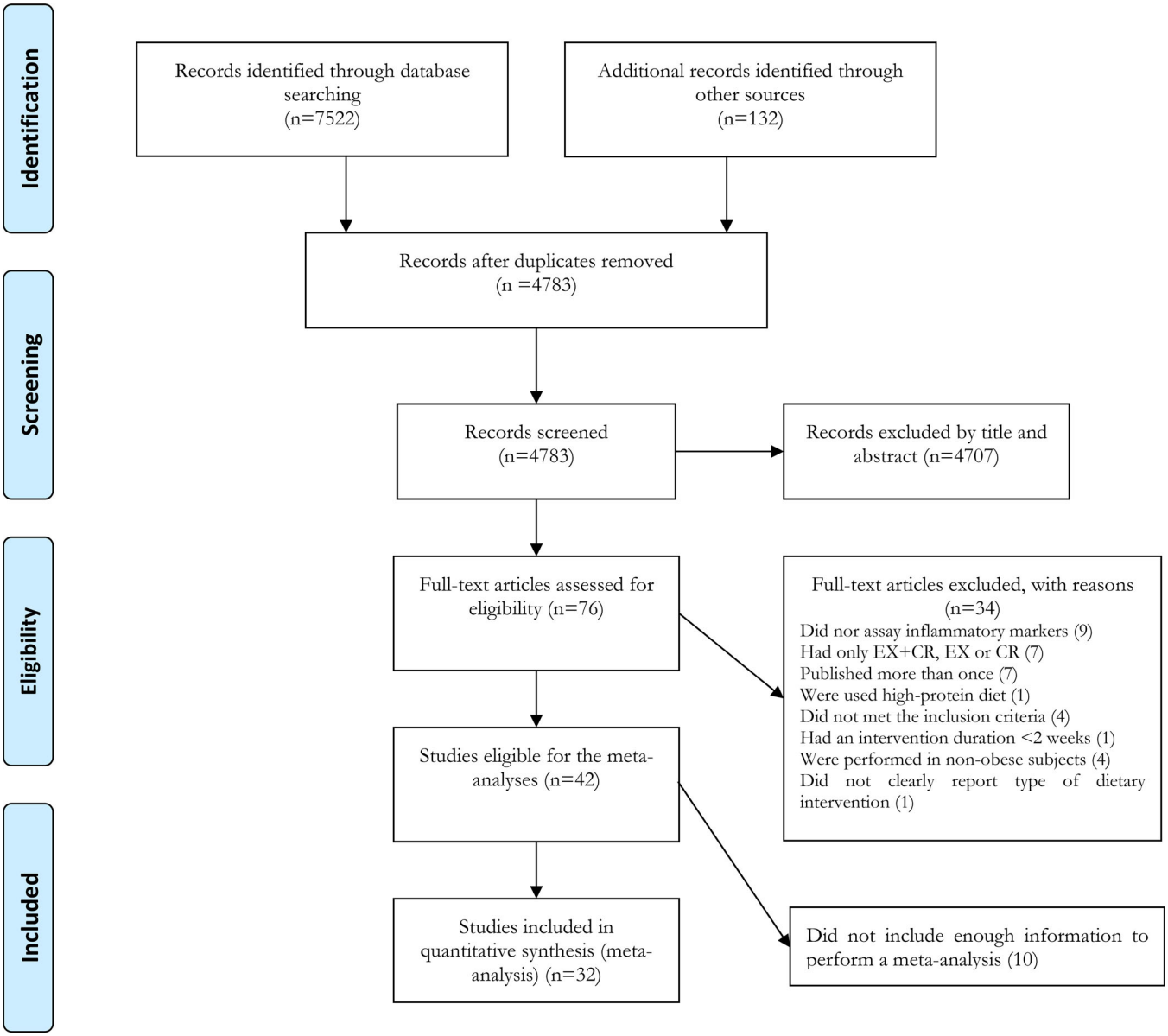

Figure 1. Flow diagram of systematic literature search.

analysis); (2) animal studies; (3) studies in the non-English language; and (4) interventions only include EX, CR or EX + CR. Also, due to a small number of studies, the authors decided to not include the results for MCP-1, IL-1β, IL-10, IL-8, IL-15, and IL-18 in the manuscript. In addition, comparison between EX + CR vs. EX were searched. However, due to a small number of studies, a meta-analysis was not performed.

Data extraction

Primary study characteristics were extracted by two independent reviewers (M.K. and A.A.) and any disagreements were resolved by discussion with other reviewer (M.E.S.) and included (1) study design; (2) characteristics of the participants including age, sex, weight, BMI, sample size; (3) EX intervention characteristics including type and duration; (4) CR intervention characteristics including duration and amount (kcal/day); (5) outcome variables including circulating inflammation markers. For studies that included two type of EX, both were included. When employing two trials of EX + CR and EX vs. CR, both were included. For studies have mid-intervention or follow-up data, end of the intervention were included. For each outcome of interest, the pre- and post-intervention values (mean and standard deviation) or mean differences and associated standard deviations were entered into the meta-analyses to generate forest plots. However, if means and standard deviations were not reported, they were calculated from standard errors, median, range and/or interquartile range (Wan et al. 2014; Hozo, Djulbegovic, and Hozo 2005; Higgins et al. 2019). Also, when required, the Getdata Graph Digitizer software was used for the extraction of data from figures. For studies that reported intent-to-treat (ITT) and efficacy subset analyses, ITT analyses was select. When insufficient information was available for the meta-analysis from the published studies, the corresponding author was contacted.

Quality assessment and sensitivity analyses

Study quality was assessed using the eight item checklist adapted from the PRISMA statement (Costigan et al. 2015), based on the following criteria: eligibility criteria were specified, participants were randomly allocated to groups, groups were similar at baseline, there was blinding of all assessors who measured the primary outcome(s), ITT analysis, drop-out for primary outcome(s) was described, with <15% drop-out of participants, (7) sample size calculation explained, between group statistical difference reported for primary outcome (see supplementary Table 1). The maximum score that can be received is 8. Sensitivity analyses were performed to evaluate the robustness of the results by removing each study individually. Also, to determine if findings were influenced by age of participants, we performed sensitivity analyses by excluding studies on children/adolescents.

Statistical analyses

All the data analyses were performed using the comprehensive meta-analysis software to calculate the standardized mean difference (SMD), weight mean difference (WMD) and 95% confidence intervals (CIs) through the random or fixed-effects models. The effect size was calculated to assess the following comparisons (1) EX vs. CR, (2) EX + CR vs. CR on inflammation markers. Intervention duration (duration of <16 vs. ≥16 weeks), participants BMI (BMI <30 vs. ≥30 kg/m^2) and training type (aerobic, resistance and combined training) were assessed as a categorical variable. Heterogeneity was assessed by using the I^2 statistic. Interpretation of the I^2 statistic was in accordance with Cochrane guidelines as following: I^2 values of <25%, 25%–50%, and >50% are considered to represent small, medium, and large amounts of inconsistency. Based on I^2 values results, the fixed-effects models were used if no or small heterogeneity was present and the random-effects models used if moderate or high heterogeneity were present. Publication bias was detected using visual interpretation of funnel plot, if publication bias was apparent, Egger tests were used as a secondary determinant; significant publication bias was deemed apparent if $p < 0.1$ (Egger et al. 1997).

Results

Included studies

Our search strategy resulted in 7654 studies. After eliminating duplicates and screening the title/abstract, and full text, 76 articles were subjected to further evaluation. After further reviewing the full text, 44 studies were excluded for the following reasons: (1) nine did not assay inflammatory markers (circulating CRP, IL-6, and TNF-α), (2) seven had only EX + CR, EX or CR, (3) one used high-protein diet, (4) seven published more than once with different classifications or main outcomes, (5) four did not met the inclusion criteria, (6) one had an intervention duration <2 weeks, (7) four were performed in non-obese or in both obese and non-obese subjects, (8) one did not clearly report type of dietary intervention and amount CR, (9) 10 did not include enough information to perform a meta-analysis. CRP and (You et al. 2004) IL-6 and TNF-α (Silverman, Nicklas, and Ryan 2009) data of one study were extracted from two separate articles. Finally, a total of 32 articles (38 trials) were included in the review (see Figure 1).

Participant characteristics

The participants' characteristics are summarized in Table 1. A total of 2108 overweight or obese participants were included and the number of participants per study varied from 16 (Lambert et al. 2008; Lam et al. 2016) to 202 (Nicklas et al. 2004). The mean age and BMI ranged from 13.1 (Ounis et al. 2009) to 70 (Bouchonville et al. 2014) years, and 26.9 (Cho et al. 2019) to 44 kg/m^2 (Cooper et al. 2012), respectively. In our meta-analysis, participants were overweight or obese exhibited a wide range of health and

Table 1. Characteristics of participants[1].

Source, year	Sample size	Group	Markers	Sex	Participants characteristics	Age (y)	BMI (kg/m^2)
Bouchonville et al. (2014)	80	EX vs. CR EX + CR vs. CR	CRP	F M	Obese-older adults	EX: 70 ± 4 EX + CR: 70 ± 4 CR: 70 ± 4	EX: 36.9 ± 5.4 EX + CR: 37.2 ± 5.4 CR: 37.2 ± 4.5
Christiansen et al. (2010)	59	EX vs. CR EX + CR vs. CR	IL-6	F M	Obese	EX: 37.2 ± 7 EX + CR: 37.5 ± 8 CR: 35.6 ± 7	EX: 33.3 ± 4 EX + CR: 34.2 ± 3 CR: 35.3 ± 4
Fayh et al. (2013)	35	EX + CR vs. CR	CRP	F M	Obese	EX + CR: 32.4 ± 7 CR: 30.1 ± 5.5	EX + CR: 34.7 ± 2.4 CR: 34.7 ± 2.4
Fisher et al. (2011) a	58	EX + CR vs. CR	IL-6, TNF-α, and CRP	F	Overweight	20–41	EX + CR: 28 ± 1 CR: 28 ± 1
Fisher et al. (2011) b	68	EX + CR vs. CR	IL-6, TNF-α, and CRP	F	Overweight	20–41	EX + CR: 28 ± 1 CR: 28 ± 1
Freitas et al. (2017)	51	EX + CR vs. CR[2]	IL-6, TNF-α, and CRP	F M	Obese adults with asthma	EX + CR: 45.9 ± 7.7 CR: 48.5 ± 9.6	EX + CR: 38.1 ± 2.8 CR: 37.2 ± 2.1
Giannopoulou et al. (2005)[3]	33	EX vs. CR EX + CR vs. CR	CRP, IL-6, and TNF-α	F	Postmenopausal women with type 2 diabetes	EX: 55.5 ± 1.7 EX + CR: 57.4 ± 1.7 CR: 58.5 ± 1.7	EX: 35.9 ± 1.9 EX + CR: 33.7 ± 1.9 CR: 34.3 ± 1.9
Lakhdar et al. (2013)	30	EX vs. CR EX + CR vs. CR	IL-6 and TNF-α	F	Obese	EX: 36.20 ± 5.00 EX + CR: 38.90 ± 4.37 CR: 38.90 ± 3.94	EX: 33.52 ± 3.75 EX + CR: 32.98 ± 2.17 CR: 33.02 ± 1.89
Lambert et al. (2008)	16	EX vs. CR	IL-6, TNF-α, and CRP	F M	Frail obese elderly persons	EX: 68.5 ± 1.4 CR: 69.6 ± 1.4	EX: 37.1 ± 2.8 CR: 38.5 ± 1.7
Loria-Kohen et al. (2013) a	25	EX + CR vs. CR	IL-6, TNF-α, and CRP	F M	Overweight	EX + CR: 36.46 ± 8.9 CR: 36.77 ± 9.24	EX + CR: 29.51 ± 2.00 CR: 28.50 ± 1.29
Loria-Kohen et al. (2013) b	31	EX + CR vs. CR	IL-6, TNF-α, and CRP	F M	Overweight	EX + CR: 35.69 ± 8.07 CR: 36.77 ± 9.24	EX + CR: 28.91 ± 1.78 CR: 28.50 ± 1.29
Loria-Kohen et al. (2013) c	28	EX + CR vs. CR	IL-6, TNF-α, and CRP	F M	Overweight	EX + CR: 36.71 ± 6.99 CR: 36.77 ± 9.24	EX + CR: 28.32 ± 1.54 CR: 28.50 ± 1.29
Nicklas et al. (2004)	202	EX vs. CR EX + CR vs. CR	CRP, IL-6, and TNF-α	F M	Older, obese adults	EX: 69 ± 6 EX + CR: 68 ± 7 CR: 68 ± 5	EX: 34.6 ± 5.8 EX + CR: 33.9 ± 5.6 CR: 34.4 ± 4.9
Ryan et al. (2014)	77	EX + CR vs. CR	CRP	F	Obese	EX + CR: 60 ± 1 CR: 61 ± 1	EX + CR: 32 ± 1 CR: 33 ± 1
Scott et al. (2013)	38	EX vs. CR EX + CR vs. CR	CRP and IL-6	F M	Overweight and obese asthma	EX: 42.2 ± 11.5 EX + CR: 33.9 ± 11.5 CR: 44.7 ± 14.7	EX: 32.8 ± 2.5 EX + CR: 32.7 ± 3.4 CR: 34.7 ± 4.0
Silverman, Nicklas, and Ryan (2009)	86	EX + CR vs. CR	IL-6 and TNF-α	F	Overweight Postmenopausal women	EX + CR: 60 ± 5 CR: 58 ± 5	EX + CR: 32.1 ± 4.2 CR: 32.6 ± 4.6
Snel et al. (2011)	27	EX + CR vs. CR	CRP, IL-6, and TNF-α	F M	Obese, insulin-dependent T2DM patients	EX + CR: 56 ± 2 CR: 59 ± 2	EX + CR: 36.4 ± 1.1 CR: 37.9 ± 1.4
Yoshimura et al. (2014)	72	EX + CR vs. CR	IL-6, TNF-α, and CRP	F M	Adults with Visceral Adiposity	40–75	EX + CR: 27.8 ± 3.8 CR: 28.0 ± 3.4
Brochu et al. (2009)	107	EX + CR vs. CR	CRP	F	Overweight and Obese Postmenopausal Women	EX + CR: 57.2 ± 5.0 CR: 58.0 ± 4.7	EX + CR: 32.6 ± 4.9 CR: 32.2 ± 4.6
Khoo et al. (2015)	80	EX vs. CR	CRP	M	Obese	EX: 43.3 ± 9.0 CR: 41.8 ± 7.2	EX: 32.1 ± 2.6 CR: 32.1 ± 3.0
Ounis et al. (2009)	27	EX vs. CR EX + CR vs. CR	IL-6 and TNF-α	F	Obese adolescents	EX: 13.1 ± 0.9 EX + CR: 13.1 ± 0.8 CR: 13.2 ± 0.3	EX: 30.4 ± 1.8 EX + CR: 31.2 ± 2.1 CR: 30.5 ± 2.2
Galedari, Azarbayjani, and Peeri (2017) a	13	EX + CR vs. CR	TNF-α	M	Overweight	EX + CR: 30.8 ± 7.6 CR: 32.6 ± 6.8	EX + CR: 29.6 ± 1.5 CR: 29.2 ± 2.4
	14	EX + CR vs. CR	TNF-α	M	Overweight		

Galedari, Azarbayjani, and Peeri (2017) b						EX + CR: 28.8 ± 6.1 CR: 32.6 ± 6.8	EX + CR: 28.9 ± 1.32 CR: 29.2 ± 2.4
Galedari, Azarbayjani, and Peeri (2017) c	13	EX + CR vs. CR	TNF-α	M	Overweight	EX + CR: 31.7 ± 7.7 CR: 32.6 ± 6.8	EX + CR: 29.0 ± 2.9 CR: 29.2 ± 2.4
You et al. (2004)	34	EX + CR vs. CR	CRP[4]	F	Overweight or Obese Postmenopausal Women	EX + CR: 59 ± 1 CR: 57 ± 1	25–40
Rejeski et al. (2019) a	84	EX + CR vs. CR	CRP and IL-6	F M	Overweight and obesity-cardiometabolic disease	66.9 ± 4.7	33.5 ± 3.5
Rejeski et al. (2019) b	86	EX + CR vs. CR	CRP and IL-6	F M	Overweight and obesity-cardiometabolic disease	66.9 ± 4.7	33.5 ± 3.5
Weiss et al. (2016)	52	EX vs. CR EX + CR vs. CR	CRP	F M	Overweight	EX: 56 ± 6 EX + CR: 57 ± 7 CR: 57 ± 5	EX: 27 ± 1.5 EX + CR: 28.3 ± 1.8 CR: 27.7 ± 1.7
Lam et al. (2016)	16	EX + CR vs. CR	TNF-α, IL-6, and CRP	F M	Overweight	EX + CR: 37.9 ± 1.8 CR: 39.0 ± 2.1	EX + CR: 27.9 ± 0.6 CR: 27.7 ± 0.5
García-Unciti et al. (2012)	25	EX + CR vs. CR	IL-6	F	Obese	EX + CR: 48.6 ± 6.4 CR: 51.4 ± 5.5	EX + CR: 35 ± 3.1 CR: 34.6 ± 3.4
Cho et al. (2019)	26	EX vs. CR EX + CR vs. CR	CRP[3]	F M	Overweight or obese	EX: 38.6 ± 8.2 EX + CR: 34.5 ± 5.7 CR: 33.5 ± 5.0	EX: 26.9 ± 3.9 EX + CR: 28.0 ± 2.6 CR: 27.8 ± 3.4
Pedersen et al. (2016)	55	EX vs. CR	TNF-α and CRP	F M	Overweight population with stable coronary artery disease	EX: 62.3 ± 5.7 CR: 63.6 ± 6.8	EX: 32.03 ± 4.07 CR: 31.13 ± 2.41
Rokling-Andersen et al. (2007)	151	EX vs. CR EX + CR vs. CR	TNF-α, IL-6, and CRP	M	Over weight with several risk factors for diabetes and cardiovascular disease	45.1 ± 2.5	EX: 28.5 ± 3.3 EX + CR: 28.4 ± 3.4 CR: 29.2 ± 3.8
Cooper et al. (2012)	90	EX + CR vs. CR	CRP	F M	Severely obese adults	EX + CR: 46.8 ± 6.5 CR: 47.5 ± 6.2	EX + CR: 43.8 ± 4.8 CR: 44 ± 6.6
Wiklund et al. (2014)	83	EX vs. CR	IL-6	F	Overweight and obese	EX: 41.9 ± 7.3 CR: 42.2 ± 7.5	EX: 28.4 ± 2.1 CR: 31.3 ± 3.1
Oh et al. (2014)	72	EX + CR vs. CR	TNF-α, IL-6, and CRP	M	Overweight with Nonalcoholic Fatty Liver Disease	EX + CR: 49.1 ± 1.3 CR: 53.2 ± 2.1	EX + CR: 29.2 ± 0.4 CR: 28.5 ± 0.8
Auerbach et al. (2013)	24	EX vs. CR	TNF-α, IL-6, and CRP	M	Moderately overweight	20–40	28.1 ± 1.3
Straznicky et al. (2010)	40	EX + CR vs. CR	CRP	M	Obese with Metabolic Syndrome	EX + CR: 54 ± 1 CR: 55 ± 1	EX + CR: 31.8 ± 0.8 CR: 32.2 ± 0.9

[1] Data are presented as Mean±S.D. unless otherwise stated.
[2] Sham exercises.
[3] Data are presented as Mean±S.E.
[4] IL-6 and TNF-α were report by Silverman.

disease characteristics, including stable coronary artery disease (Pedersen et al. 2016) asthma (Scott et al. 2013; Freitas et al. 2017), metabolic syndrome (Straznicky et al. 2010), nonalcoholic fatty liver disease (Oh et al. 2014), and T2D (Giannopoulou et al. 2005; Snel et al., 2011). The training status of the participants were similar as they were all inactive or sedentary.

Intervention characteristics

The interventions are summarized in Table 2. Intervention duration ranged from 6 weeks (Wiklund et al. 2014) to 18 months (Nicklas et al. 2004; Rejeski et al. 2019), with 3 and 6 months adopted in the majority of studies. In 5 studies EX vs. CR (Lambert et al. 2008; Pedersen et al. 2016; Wiklund et al. 2014; Auerbach et al. 2013; Khoo et al. 2015), 17 EX + CR vs. CR (You et al. 2004; Silverman, Nicklas, and Ryan 2009; Lam et al. 2016; Cooper et al. 2012; Freitas et al. 2017; Straznicky et al. 2010; Oh et al. 2014; Snel et al., 2011; Rejeski et al. 2019; Fayh et al. 2013; Ryan et al. 2014; Yoshimura et al. 2014; Brochu et al. 2009; Galedari, Azarbayjani, and Peeri 2017; García-Unciti et al. 2012; Fisher et al. 2011; Loria-Kohen et al. 2013) and 10 EX + CR vs. CR and EX vs. CR (Nicklas et al. 2004; Ounis et al. 2009; Bouchonville et al. 2014; Cho et al. 2019; Scott et al. 2013; Giannopoulou et al. 2005; Christiansen et al. 2010; Lakhdar et al. 2013; Weiss et al. 2016; Rokling-Andersen et al. 2007) were compared. Of the 32 studies, 19 used aerobic training (You et al. 2004; Silverman, Nicklas, and Ryan 2009; Lam et al. 2016; Cooper et al. 2012; Straznicky et al. 2010; Oh et al. 2014; Giannopoulou et al. 2005; Snel et al., 2011; Wiklund et al. 2014; Auerbach et al. 2013; Khoo et al. 2015; Fayh et al. 2013; Ryan et al. 2014; Yoshimura et al. 2014; Christiansen et al. 2010; Lakhdar et al. 2013; Weiss et al. 2016; Rokling-Andersen et al. 2007), two resistance training (Brochu et al. 2009; García-Unciti et al. 2012), one aerobic interval training (Pedersen et al. 2016), six combined training (aerobic, resistance, flexibility and physical therapy) (Lambert et al. 2008; Nicklas et al. 2004; Bouchonville et al. 2014; Cho et al. 2019; Scott et al. 2013; Freitas et al. 2017). Moreover, two studies used aerobic and resistance training (Rejeski et al. 2019; Fisher et al. 2011), one aerobic, resistance and combined training (Loria-Kohen et al. 2013) and one high intensity interval training, moderate intensity interval training and resistance training (Galedari, Azarbayjani, and Peeri 2017), in separate trials. In one study the training used was not clearly described (Ounis et al. 2009). For subgroup analysis, Nordic walking, jogging, moderate intensity running or cycling, endurance training and aerobic interval training were considered as aerobic training and aerobic training plus resistance training with and without flexibility or physical therapy were considered as combined training. Supervised, unsupervised or both exercise training protocols were performed. In the case of CR, in most studies, calorie intake was reduced by a wide range of 250 to 1000 kcal/day of pre-restriction total energy intake. Other dietary interventions included low energy diet (800 kcal) until a BMI <25 (Fisher et al. 2011) or targeted to lose 3 kg of body weight in 6 weeks (Wiklund et al. 2014), dietary advice to achieve weight reduction of 0.5 to 2 kg/month (Rokling-Andersen et al. 2007), 25% CR of baseline energy requirements or expenditure (Lam et al. 2016; Loria-Kohen et al. 2013) or low caloric diet including 885–1170 (Scott et al. 2013), 450 (Snel et al., 2011), 600–800 (Christiansen et al. 2010) or 800–100 (Pedersen et al. 2016), 1680 (Oh et al. 2014) kcal/day or target energy intake was 25 kcal/kg of ideal body weight (Yoshimura et al. 2014). Also one study used alternate day fasting intervention (Cho et al. 2019).

Inflammatory markers

In our meta-analysis, the following inflammatory markers were included: CRP or hs-CRP, IL-6, and TNF-α. IL-6 in 20 studies (Silverman, Nicklas, and Ryan 2009; Lambert et al. 2008; Lam et al. 2016; Nicklas et al. 2004; Ounis et al. 2009; Scott et al. 2013; Freitas et al. 2017; Oh et al. 2014; Giannopoulou et al. 2005; Snel et al., 2011; Wiklund et al. 2014; Rejeski et al. 2019; Auerbach et al. 2013; Yoshimura et al. 2014; García-Unciti et al. 2012; Fisher et al. 2011; Loria-Kohen et al. 2013; Christiansen et al. 2010; Lakhdar et al. 2013; Rokling-Andersen et al. 2007), TNF-α in a 16 (Lambert et al. 2008; Lam et al. 2016; Nicklas et al. 2004; Pedersen et al. 2016; Freitas et al. 2017; Oh et al. 2014; Giannopoulou et al. 2005; Snel et al., 2011; Auerbach et al. 2013; Yoshimura et al. 2014; Galedari, Azarbayjani, and Peeri 2017; Fisher et al. 2011; Loria-Kohen et al. 2013; Lakhdar et al. 2013; Rokling-Andersen et al. 2007) and CRP in 25 (You et al. 2004; Lambert et al. 2008; Lam et al. 2016; Nicklas et al. 2004; Bouchonville et al. 2014; Cho et al. 2019; Cooper et al. 2012; Pedersen et al. 2016; Scott et al. 2013; Freitas et al. 2017; Straznicky et al. 2010; Oh et al. 2014; Giannopoulou et al. 2005; Snel et al., 2011; Rejeski et al. 2019; Auerbach et al. 2013; Khoo et al. 2015; Fayh et al. 2013; Ryan et al. 2014; Yoshimura et al. 2014; Brochu et al. 2009; Fisher et al. 2011; Loria-Kohen et al. 2013; Weiss et al. 2016; Rokling-Andersen et al. 2007).

Meta-analysis

EX vs. CR

Based on those studies that directly compared EX and CR, there were no evidence for an effect of EX on IL-6 [0.12 (95% CI: −0.06 to 0.31), $p = 0.20$; $I^2 = 0.00$, p for heterogeneity = 0.61; 9 trials, Figure 2] and TNF-α [0.06 (95% CI: −0.15 to 0.27), $p = 0.58$; $I^2 = 0.00$, p for heterogeneity = 0.93; 7 trials, Figure 3] when compared with a CR. However, when compared to EX, CR have statistically greater benefits on CRP [−0.21 (95% CI: −0.38 to −0.04), $p = 0.01$; $I^2 = 0.00$, p for heterogeneity = 0.55; 11 trials, Figure 4].

EX + CR vs. CR

Based on the studies that directly compared EX + CR and CR, EX + CR caused a larger decrease in IL-6 [−0.15 (95% CI: −0.27 to −0.02), $p = 0.02$; $I^2 = 0.00$, p for heterogeneity

Table 2. Characteristics of interventions.

	Training characteristics					
Source, year	Type	Intensity	Supervised or non-supervised	Frequency (time a week)	Dietary intervention	Intervention durations
Bouchonville et al. (2014)	Combined	AT: % of HR[1] peak RT: 65%–85% of 1RM[2]	Supervised	3	Calorie-restricted diet (500–750 kcal deficit)	12 months
Christiansen et al. (2010)	Aerobic	—	Supervised	3	CR: very low energy diet (600 kcal per day) EX + CR: very low energy diet (800 kcal per day) followed by a weight maintenance diet	12 weeks
Fayh et al. (2013)	Aerobic	75% of the HRR[3]	Supervised	3	Calorie-restricted diet (500–100 kcal deficit)	CR: ∼79.7 days EX: ∼65.9 days
Fisher et al. (2011) a	Aerobic	65%–80% of HRmax	Supervised	3	Calorie restriction and exercise training was applied until a BMI <25	—
Fisher et al. (2011) b	Resistance	80% of 1RM	Supervised	3	Calorie restriction and exercise training was applied until a BMI <25	—
Freitas et al. (2017)	Combined	AT: 50%–75% of Vo2peak RT: 50%–70% of 1RM	Supervised	2	Hypocaloric diet counseling sessions and supported by behavioral techniques	3 months
Giannopoulou et al. (2005)	Aerobic	65%–70% of Vo2peak	Supervised	3–4	CR: Calorie-restricted diet (∼2510 kJ deficit) EX + CR: Calorie-restricted diet (∼1460 kJ deficit from the diet and ∼1050 kJ deficit from the exercise, in non-exercise days a ∼ 2510 kJ deficit from the diet alone).	14 weeks
Lakhdar et al. (2013)	Aerobic	55%–80% of HRmax	—	3	Calorie-restricted diet (500 kcal deficit)	24 weeks
Lambert et al. (2008)	Combined	AT: 75%–90% of HRpeack RT: 65%–80% of 1RM	Supervised	3	Calorie-restricted diet (500–750 kcal deficit) with a goal of 1%–2% loss of body weight per week	12 weeks
Loria-Kohen et al. (2013) a	Resistance	50%–60% of 15RM	Supervised	3	Calorie-restricted diet (25% less energy than the baseline daily energy)	22 weeks
Loria-Kohen et al. (2013) b	Aerobic	50%–60% of HRR	Supervised	3	Calorie-restricted diet (25% less energy than the baseline daily energy)	22 weeks
Loria-Kohen et al. (2013) c	Combined	50%–60% of 15RM and HRR	Supervised	3	Calorie-restricted diet (25% less energy than the baseline daily energy)	22 weeks
Nicklas et al. (2004)	Combined	AT: 50%–75% of HRR RT: —	Non-Supervised	3	Calorie-restricted diet (500 kcal deficit), allowing for a loss of 0.5 kg body weigh per week.	18 months
Ryan et al. (2014)	Aerobic	50%–85% HRR	Supervised	3	Calorie-restricted diet (300–500 kcal deficit)	6 months
Scott et al. (2013)	Combined	—	Supervised	at least 3	Low energy diet (885–1170 kcal per day)	10 weeks
Silverman, Nicklas, and Ryan (2009)	Aerobic	50%–75% of HRR	Supervised and non-supervised	3	Calorie-restricted diet (250–350 kcal deficit)	6 months
Snel et al. (2011)	Aerobic	70% of Vo2max	Supervised and non-supervised	5	Very low calorie diet (450 kcal per day)	4 months
Yoshimura et al. (2014)	Aerobic	At lactate threshold	Supervised	3	Target energy intake was 25 kcal/kg of ideal body weigh	12 weeks
Brochu et al. (2009)	Resistance	60%–80% of 1RM	Supervised	3	Calorie-restricted diet (500–800 kcal were subtracted from baseline resting metabolic rate)	6 months

(*continued*)

Table 2. Continued.

	Training characteristics					
Source, year	Type	Intensity	Supervised or non-supervised	Frequency (time a week)	Dietary intervention	Intervention durations
Khoo et al. (2015)	Aerobic	AT: 60%–80% HRmax RT: N/A	Supervised and non-supervised	3	Calorie-restricted diet (500 kcal deficit)	24 weeks
Ounis et al. (2009)	Exercise	Corresponded to Lipoxmax	Supervised	Less than 4	Calorie-restricted diet (500 kcal deficit)	8 weeks
Galedari, Azarbayjani, and Peeri (2017) a	HIIT[4]	90%–95% HRmax	Supervised	3	CR: Calorie-restricted diet (3000–3500 kcal deficit per week) EX + CR: Calorie-restricted diet (1500–2500 kcal deficit per week)	12 weeks
Galedari, Azarbayjani, and Peeri (2017) b	MICT[5]	65%–70% HRmax	Supervised	3	CR: Calorie-restricted diet (3000–3500 kcal deficit per week) EX + CR: Calorie-restricted diet (1500–2500 kcal deficit per week)	12 weeks
Galedari, Azarbayjani, and Peeri (2017) c	Resistance	60%–80% of 1RM	Supervised	3	CR: Calorie-restricted diet (3000–3500 kcal deficit per week) EX + CR: Calorie-restricted diet (1500–2500 kcal deficit per week)	12 weeks
You et al. (2004)	Aerobic	50%–70% of HRR	Supervised and non-supervised	3	Calorie-restricted diet (250–350 kcal deficit) with a goal of 0.5–1 kg weight loss per week	6 months
Rejeski et al. (2019) a	Aerobic	At a RPE of 12 to 14 on the Borg RPE scale	—	4	Caloric goal for individuals with weight <250 lb was 1200 to 1500 kcal/d, and for those with weight ≥250 lb, it was 1500 to 1800 kcal/d	18 months
Rejeski et al. (2019) b	Resistance	40%–75% of 1RM	—	4	Caloric goal for individuals with weight <250 lb was 1200 to 1500 kcal/d, and for those with weight ≥250 lb, it was 1500 to 1800 kcal/d	18 months
Weiss et al. (2016)	Aerobic	—	Non-supervised	—	CR: Calorie-restricted diet (Reduce energy intake by 20%) EX + CR: Calorie-restricted diet (Reduce energy intake by 20% using a combination of CR and EX)	12–14 weeks
Lam et al. (2016)	Aerobic	—	Supervised and non-supervised	5	CR: Calorie-restricted diet (25% calorie restriction of baseline energy) EX + CR: Calorie-restricted diet (12.5% calorie restriction plus 12.5% increase in energy expenditure by structured exercise)	6 months
García-Unciti et al. (2012)	Resistance	50%–80% of 1RM	Supervised	2	Calorie-restricted diet (500 kcal deficit)	16 weeks
Cho et al. (2019)	Combined	—	—	At least 3	Alternate day fasting diet	8 weeks
Pedersen et al. (2016)	Aerobic interval training	85%–90% of VO2peak	Supervised	3	Low energy diet (800–1000 kcal per day)	12 weeks
Rokling-Andersen et al. (2007)	Aerobic	—	Supervised	3	Dietary advice to achieve weight reduction of 0.5 to 2 kg per month	12 months
Cooper et al. (2012)	Aerobic	—	Non-supervised	5	Energy intake was between1200 and 2100 kcal per day	6 months
Wiklund et al. (2014)	Aerobic	60%–75% of HRmax	Supervised	3–4	Targeting to lose 3 kg of body weight in 6 weeks	6 weeks
Oh et al. (2014)	Aerobic	>40% of HRmax	Supervised	3	Diet program for maintaining a caloric intake of 1680 kcal per	3 months

Auerbach et al. (2013)	Aerobic	Three to four days per week at 85% of HRR and for the remaining sessions at 65% of HRR	Non-supervised	7	Calorie-restricted diet (600 kcal deficit)	12 weeks	
Straznicky et al. (2010)	Aerobic	65% of predetermined HRmax	Supervised and non-supervised	3	Calorie-restricted diet (600 kcal deficit)	12 weeks	

[1] Heart Rate.
[2] One-Repetition-Maximum.
[3] Heart Rate Reserve.
[4] High intensity interval training.
[5] Moderate intensity continuous training.

= 0.64; 21 trials, Figure 5] and TNF-α [−0.22 (95% CI: −0.37 to −0.08), $p = 0.002$; $I^2 = 7.88$, p for heterogeneity = 0.35; 19 trials, Figure 6] and tended to decrease in CRP [−0.10 (95% CI: −0.21 to −0.008), $p = 0.06$; $I^2 = 15.72$, p for heterogeneity = 0.24; 25 trials, Figure 7] when compared with CR.

Body weight

CR caused a larger decrease in body weight [−3.63 (95% CI: −5.78 to −1.49), $p = 0.001$; $I^2 = 80.27$, p for heterogeneity < 0.001; 14 trials, see supplementary Figure 1], when compared to EX. Also, EX + CR caused a larger decrease in body weight [−1.17 (95% CI: −1.79 to −0.56, $p = 0.001$; $I^2 = 6.57$, p for heterogeneity = 0.36; 28 trials, see supplementary Figure 2], when compared to CR.

Subgroup analysis

Subgroup analyses in CR vs. EX by BMI and intervention duration revealed a non-significant effects on CRP. Also, greater decrease of CRP was observed in CR when compared with combined training subgroup ($p = 0.01$) (see supplementary Table 1).

Subgroup analyses in EX + CR vs. CR by intervention duration revealed a significant decrease of IL-6 ($p = 0.001$) by shorter intervention duration and TNF-α by both shorter ($p = 0.005$) and longer intervention ($p = 0.01$), while, a significant decrease of CRP was observed in longer intervention duration ($p = 0.01$). Moreover, in subgroup analyses according to type of training, we observed a significant decrease of TNF-α ($p = 0.03$) and non-significant decrease of IL-6 ($p = 0.05$) for aerobic training. Also, we observed a significant decrease of TNF-α for combined training ($p = 0.01$). Subgroup analyses by BMI revealed a significant decrease of CRP ($p = 0.003$) and TNF-α ($p = 0.002$) for higher BMI (see supplementary Table 2).

Quality assessment, publication bias and sensitivity of analysis

The quality assessment for each study is summarized in supplementary Table 3 and ranged from 1 to 8 (maximum points = 8). In the case of comparing EX vs. CR, visual interpretation of funnel plots suggested publication bias, but, were not apparent for IL-6 ($p = 0.53$) and body weight ($p = 0.14$). Both funnel plots and Egger's test did not suggest publication bias for TNF-α ($p = 0.86$) and CRP ($p = 0.56$). In the case of comparing EX + CR vs. CR, visual interpretation of funnel plots suggested publication bias, but, were not apparent by Egger's test for TNF-α ($p = 0.19$), CRP ($p = 0.12$) and body weight ($p = 0.28$). Also, both funnel plots and Egger's test did not suggest publication bias for IL-6 ($p = 0.89$).

In the case of EX + CR vs. CR, sensitivity analyses indicated that a decrease in TNF-α and IL-6 still remained significant or tended to significant. However, the decrease in body weight did not remain significant. In the case of CR

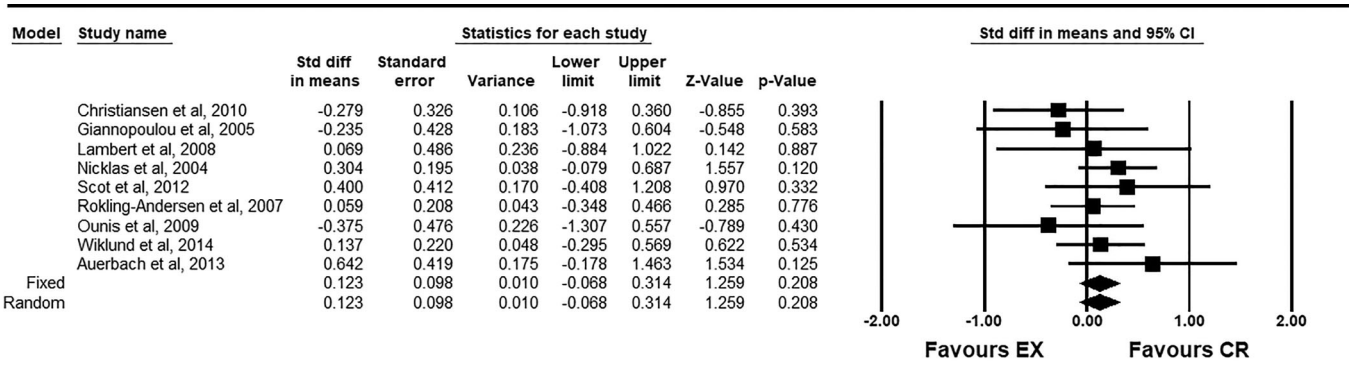

Figure 2. Forest plot of the effects of exercise training (EX) compared with caloric restriction (CR) on interleukin-6 (IL-6). Data are reported as SMD (95% confidence limits). SMD, standardized mean difference.

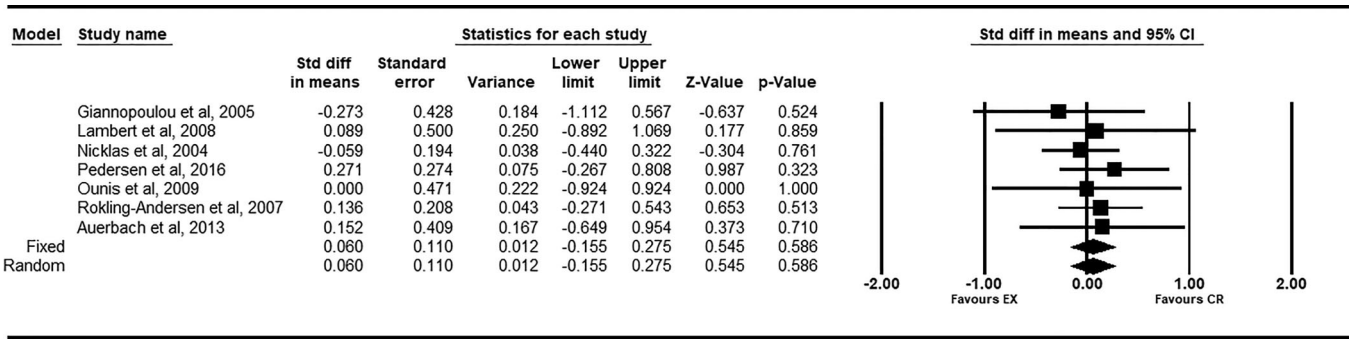

Figure 3. Forest plot of the effects of exercise training (EX) compared with caloric restriction (CR) on tumor necrosis factor alpha (TNF-α). Data are reported as SMD (95% confidence limits). SMD, standardized mean difference.

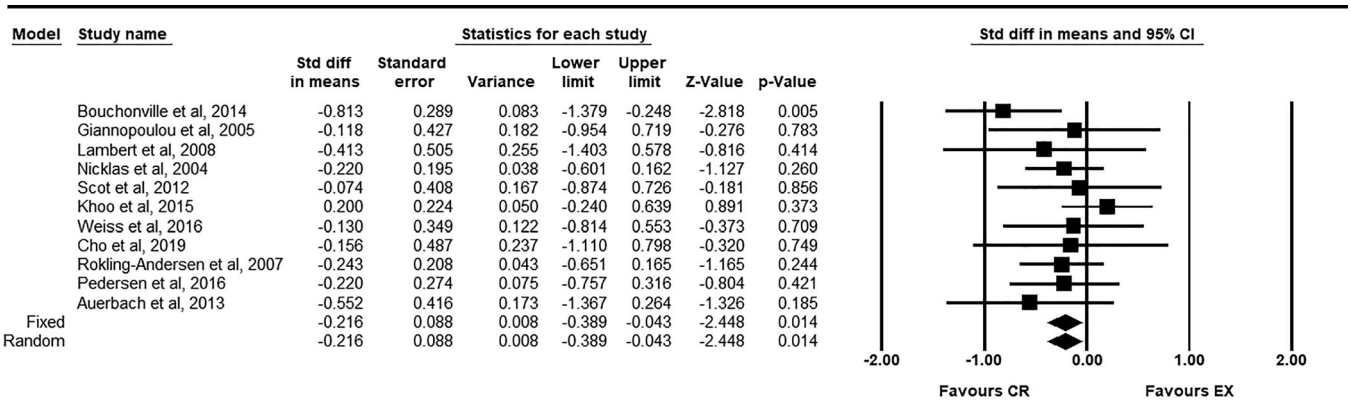

Figure 4. Forest plot of the effects of exercise training (EX) compared with caloric restriction (CR) on C reactive protein (CRP). Data are reported as SMD (95% confidence limits). SMD, standardized mean difference.

vs. EX, in the sensitivity analysis for IL-6 and TNF-α, one study (Lakhdar et al. 2013) was the source of heterogeneity, which was then removed from the analysis. Moreover, sensitivity analyses indicated that a decrease in body weight and CRP (longer intervention) remained significant or tended to significant. Also, in our studies, only one study included in the meta-analysis was performed in adolescents. Sensitivity of analysis in which it was removed indicated that the results remained significant.

Discussion

The present study is the first meta-analysis to compare the effect of EX and CR as well as EX + CR and CR on markers of inflammation in overweight and obese individuals. It suggests that EX + CR is an effective intervention to improve the circulating concentration of inflammation. Moreover, CR was a more effective intervention to improve CRP compared to EX.

Lifestyle interventions including EX and/or CR are generally recommended for over-coming obesity as they not only

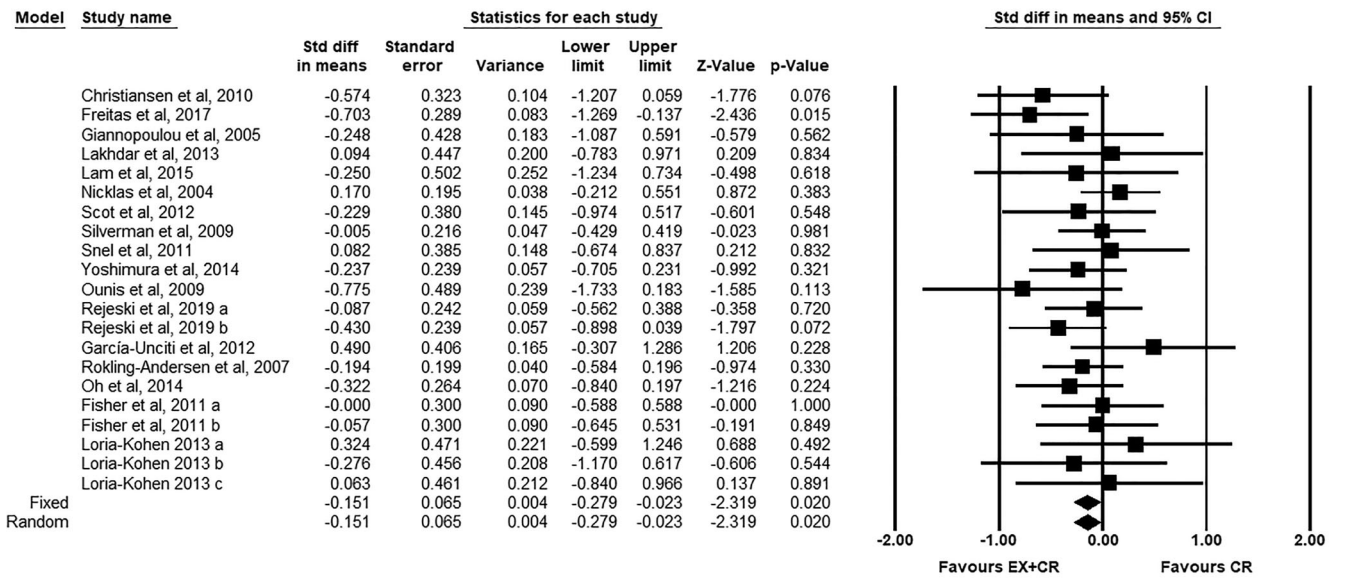

Figure 5. Forest plot of the effects of exercise training plus caloric restriction (EX + CR) compared with caloric restriction (CR) on interleukin-6 (IL-6). Data are reported as SMD (95% confidence limits). SMD, standardized mean difference.

modify energy balance but also induce immune (Collao et al. 2020; Pietrocola et al. 2016) and metabolic adaptations in AT, especially visceral depots (Villareal et al. 2011; Bruun et al. 2006; Miller, Koceja, and Hamilton 1997; Ross 2000). EX has anti-inflammatory effects that has been linked to weight loss and the down regulation of inflammatory cytokine-mediated signaling in adipocytes (Gleeson et al. 2011). An improvement in circulating cytokines was shown in a previous meta-analyses in patients with obesity (Sirico et al. 2018), T2D (Hayashino et al. 2014) and coronary artery disease (Swardfager et al. 2012). The effect of EX, however, has not been compared to CR. Weight loss is an important factor in the improvement of inflammatory cytokine release, because visceral fat, together with macrophages and T cells primarily regulate the secretion of IL-6 and TNFα (Chait and den Hartigh 2020; Fantuzzi 2005; Pessin and Kwon 2013). Nevertheless, we show that despite a greater weight loss with CR compered to EX, it does not relate to a decrease in either IL-6 or TNF-α. On other hand, EX + CR had significant effects on reducing IL-6 and TNF-α compered to CR alone. This can be explained by the fact that EX can reduce adiposity and visceral fat mass despite total body weight remaining unchanged (Verheggen et al. 2016; Thompson et al. 2012) and weight loss does not necessarily reflect changes in visceral fat (Verheggen et al. 2016). Therefore, adding EX to CR interventions may play a potential role in reducing of visceral AT, which will be critical for improving inflammation. EX can reduce adiposity by enhancing lipolysis mediated by elevated catecholamines and β-adrenergic receptor sensitivity (Crampes et al. 1986) within AT (Collins and Surwit 2001). In our study, treatment duration ranged from 6 weeks to 18 months and subgroup analysis indicated that intervention duration moderated the IL-6 and TNF-α response in EX + CR vs. CR. This suggests a greater effect of EX + CR <16 weeks and that inflammatory responses are labile. Regarding the type of training added to CR, aerobic training tended to promote a greater effect on reducing IL-6 and TNF-α for which a possible mechanism underlying these adaptions could relate to the central role of aerobic training in reducing visceral fat (Ismail et al. 2012). Moreover, regarding the BMI of participants, our analysis demonstrated that adding EX to CR is effective at reducing TNF-α as well as CRP in individuals with obesity. These observation is significant as inflammatory cytokines are related to increased risk for CVD and T2D with obesity (Maachi et al. 2004; de Mello et al. 2009; Yudkin et al. 2000; Mirza et al. 2012).

CRP as a marker of CLGSI is produced in the liver (Bian et al. 2014) in response to pro-inflammatory cytokines such as IL-6 and TNF-α. Obesity increases CRP (Park, Park, and Yu 2005), but decreases with weight loss (Dietrich and Jialal 2005), and beneficial effects of EX and CR on CRP are established clinically (Dietrich and Jialal 2005; Fedewa, Hathaway, and Ward-Ritacco 2017; Steckhan et al. 2016), including in participants with coronary artery disease (Thompson et al. 2020) or T2D (Hayashino et al. 2014). Weight loss is the main mechanism by which EX and/or CR induce a reduction in CRP (Fedewa, Hathaway, and Ward-Ritacco 2017). Across lifestyle and surgical interventions, following a 1 kg of weight loss, CRP declines by −0.13 mg/L (Selvin, Paynter, and Erlinger 2007). Our results therefore confirm previous data, that a greater decrease in CRP occurs with CR compared to EX when accompanied with weight loss. Nevertheless, adding EX to CR and compared with CR tended to decrease CRP, suggesting that combined therapy may be a more effective treatment approach. This adaptation may be explained in part with the potential role of adding EX to CR in causing weight loss and reducing AT mass (Verheggen et al. 2016; Thompson et al. 2012) as well as inflammatory cytokines (present study). An association between CRP and AT is established (Park, Park, and Yu 2005; Forouhi, Sattar, and McKeigue 2001; Lemieux et al.

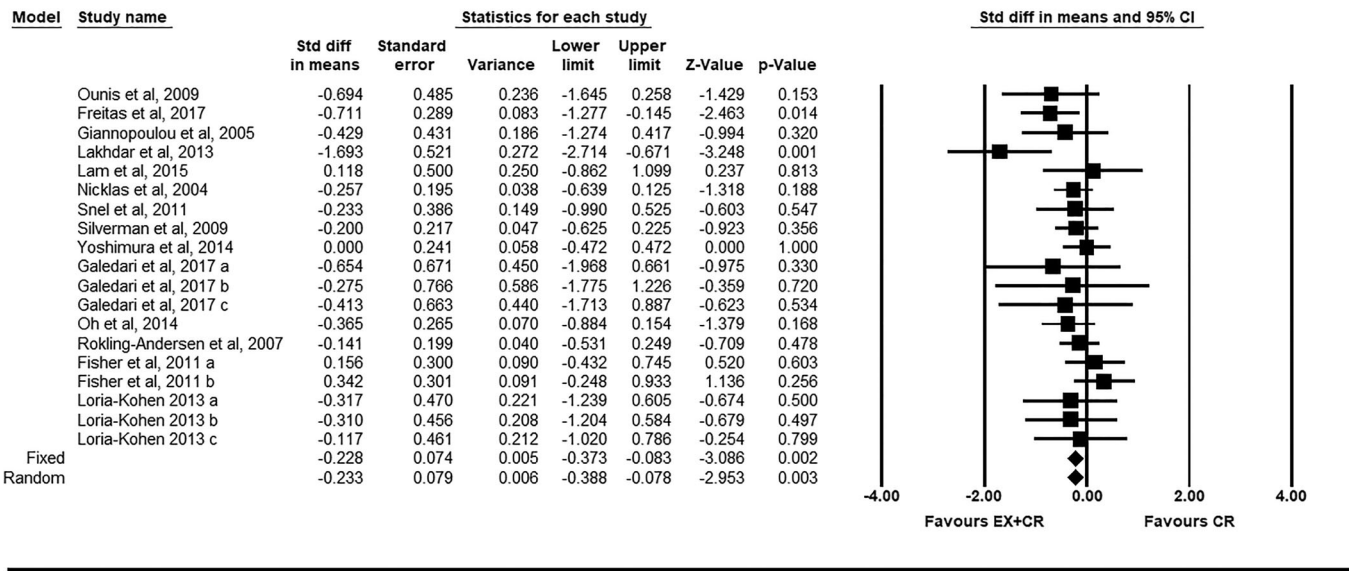

Figure 6. Forest plot of the effects of exercise training plus caloric restriction (EX + CR) compared with caloric restriction (CR) on tumor necrosis factor alpha (TNF-α). Data are reported as SMD (95% confidence limits). SMD, standardized mean difference.

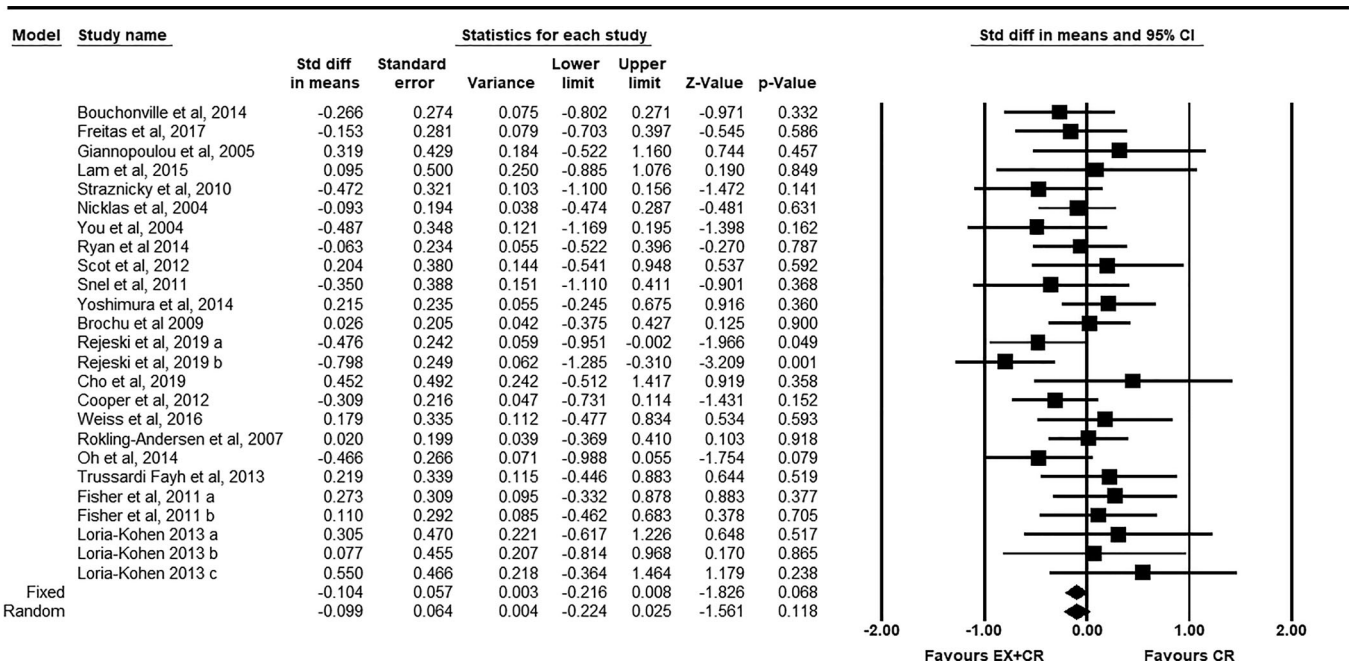

Figure 7. Forest plot of the effects of exercise training plus caloric restriction (EX + CR) compared with caloric restriction (CR) on C reactive protein (CRP). Data are reported as SMD (95% confidence limits). SMD, standardized mean difference.

2001), with accumulation of AT directly (Anty et al. 2006; Ouchi et al. 2003; Calabro et al. 2005) or indirectly (Maachi et al. 2004; Castell et al. 1990) (through the release of pro-inflammatory cytokines such as IL-6) contribute to an increase in circulating CRP. Moreover, our results suggest long-term interventions are effective in improving CRP.

Strength and limitations

The current study has several strengths. According to our knowledge, it is first systematic review and meta-analysis that directly compared CR vs. EX or EX + CR vs. CR on inflammatory cytokine and CRP. In addition, it was performed on individuals that were overweight or obese and were affected by chronic inflammation. Also, subgroup analysis was conducted based on the BMI of participants, type of exercise and duration of interventions. Our study added novel findings to the literature, however, it has several limitations. The study protocol was not registered in any database. Some studies included overweight and obese individuals with comorbidities such as type 2 diabetes which could affect the baseline biochemical parameters and the way participants responded to the intervention. The wide amount and type of caloric restriction used in the studies included in the meta-analysis is also a limitation. A number of studies did not provide sufficient information on the

intervention and some may not have been retrieved during the literature search. Most of the studies used aerobic training and further studies with resistance and combined training are needed. Most of the studies used moderate intensity training and consequently subgroup analysis could not be performed separately according intensity of training.

Conclusions

Our meta-analysis demonstrated that EX + CR have superior effects on reducing inflammatory cytokines and CRP compared with CR in overweight and obese individuals. In addition, aerobic training can be indicated as an effective therapeutic approach for adding CR.

Conflict of interest

The authors declare that they have no conflict of interest.

Authors' contributions

M.K., A.A., and M.E.S. carried out the screenings and reviews, plus the analysis of the articles. M.K. and M.E.S. drafted and revised the manuscript. All authors read and approved the final manuscript.

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