IJC Heart & Vasculature 47 (2023) 101234

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

The impacts of exercise interventions on inflammaging markers in overweight/obesity patients with heart failure: A systematic review and meta-analysis of randomized controlled trials

Abbas Malandish [a,*], Martha Gulati [b]

[a] Department of Exercise Physiology, Faculty of Sport Sciences, Urmia University, No. 19, Shams Tabrizi St., Velayat Ave., Keikhali Zone, Yamchi, East Azerbaijan, Urmia, Iran

[b] Barbra Streisand Women's Heart Center, Smidt Heart Institute, Cedars Sinai Medical Center, 127 S. San Vicente Blvd, Suite A3600, Los Angeles, CA 90048, USA

A R T I C L E I N F O

Keywords:
Aerobic training
Resistance training
Concurrent exercise
Inflammaging
Heart failure
Meta-analysis

A B S T R A C T

Objectives: The purpose of this *meta*-analysis was to investigate the association of aerobic, resistance and concurrent exercises vs. control group on inflammaging markers [tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), IL-1-beta, IL-8, and high sensitivity C-reactive protein (hs-CRP)] in overweight or obesity patients with heart failure (HF).

Methods: The databases of Scopus, PubMed, Web of Science and Google Scholar were searched until August 31, 2022 for exercise interventions vs. control group on circulating inflammaging markers in patients with HF. Only randomized controlled trial (RCT) articles were included. Standardized mean difference (SMD) and 95% confidence intervals (95%CIs) were calculated (registration code = CRD42022347164).

Results: Forty-six full-text articles (57 intervention arms and 3693 participants) were included. A significant reduction was occurred in inflammaging markers of IL-6 [SMD-0.205(95% CI:-0.332 to −0.078),p = 0.002] and hs-CRP [SMD −0.379 (95% CI:-0.556 to −0.202), p = 0.001] with exercise training in patients with HF. Analysis of subgroup by age, body mass index (BMI), type, intensity, duration of exercise and mean left ventricular ejection fraction (LVEF) revealed that there was a significant reduction in TNF-α for middle-aged (p = 0.031), concurrent training (p = 0.033), high intensity (p = 0.005), and heart failure with reduced ejection fraction (HFrEF) (p = 0.007) compared to the control group. There was a significant reduction in IL-6 for middle-aged (p = 0.006), overweight (p = 0.001), aerobic exercise (p = 0.001), both high and moderate intensities (p = 0.037 and p = 0.034), short-term follow-up (p = 0.001), and heart failure with preserved ejection fraction (HFpEF) (p = 0.001) compared to the control group. There was a significant reduction in hs-CRP for middle-aged (p = 0.004), elderly-aged (p = 0.001), overweight (p = 0.001), aerobic exercise (p = 0.001), concurrent training (p = 0.031), both high and moderate intensities (p = 0.017 and p = 0.001), short-term (p = 0.011), long-term (p = 0.049), and very long-term (p = 0.016) follow-ups, HFrEF (p = 0.003) and heart failure with mildly reduced ejection fraction (HFmrEF) (p = 0.048) compared to the control group.

Conclusions: The results confirmed that aerobic exercise and concurrent training interventions were effective to improve inflammaging markers of TNF-α, IL-6, and hs-CRP. These exercise-related anti-inflammaging responses were observed across ages (middle-aged and elderly-aged), exercise intensities, duration of follow-ups, and mean LVEFs (HFrEF, HFmrEF and HFpEF) in overweight patients with HF.

1. Introduction

Inflammaging and obesity are chronic low-grad inflammation statuses during aging [1,2] as well as risk factors for cardiovascular diseases (CVDs), especially heart failure (HF) [2]. HF is a heterogeneous pathophysiological syndrome of ventricular dysfunction [3,4], which is associated with high circulating chronic inflammatory cytokines, low-grad inflammation, systemic inflammation, and obesity [3–6]. Chronic inflammatory cytokines (tumor-necrosis-factor-alpha [TNF-α], interleukin-6 [IL-6], IL-1-beta, IL-8) and low-grad inflammation (high

* Corresponding author at: Ph.D. of Exercise Physiology, Department of Exercise Physiology, Faculty of Sport Sciences, Urmia University, Urmia, Iran.
E-mail addresses: malandish@gmail.com (A. Malandish), martha.gulati@csmc.edu (M. Gulati).

https://doi.org/10.1016/j.ijcha.2023.101234
Received 20 March 2023; Received in revised form 22 May 2023; Accepted 18 June 2023

Table 1
Risk of bias assessment.

Author et al., yr	eligibility criteria specified	Random allocation of participants	allocation concealed	groups similar at baseline	assessors blinded	outcome measures assessed in 85% of participants*	intention to treat analysis	reporting of between group statistical comparison#	point measures and measures of variability reported for main effects	Activity monitoring in control group	Relative exercise intensity reviewed	Supervised /Non-supervised	**Total PEDRO score**	**Risk of bias**
Abolahrari-Shirazi et al., 2018	✓	✓	✓	✓	✓	✓✓✓	✓	✓✓	✓	✓	✓	✓	15	Low
Adamopoulos et al., 2002	✓	✓	✓	✓	✓	✓✓✓	–	✓✓	✓	✓	✓	–	13	Low
Adamopoulos et al., 2014	✓	✓	✓	✓	–	✓✓	–	✓✓	✓	✓	✓	✓	12	Low
Ahmad et al., 2014	✓	✓	✓	✓	✓	✓✓	–	✓✓	✓	–	✓	✓	12	Low
Aksoy et al., 2015	✓	✓	–	✓	–	–	–	✓✓	✓	–	–	✓	7	Some
Balen et al., 2008	✓	✓	–	✓	–	✓✓	✓	✓✓	✓	✓	✓	✓	12	Low
Butts et al., 2018	✓	✓	–	✓	–	✓✓	✓	✓✓	✓	✓	✓	✓	12	Low
Byrkjeland et al., 2011	✓	✓	–	✓	–	✓✓	✓	✓✓	✓	✓	✓	✓	12	Low
Conraads, et al., 2002	✓	–	–	✓	–	✓✓	✓	✓✓	✓	–	✓	✓	10	Low
de Meirelles et al., 2014	✓	✓	–	✓	–	✓✓	✓	✓✓	✓	–	✓	✓	11	Low
Eleuteri et al., 2013	✓	✓	✓	✓	–	✓✓✓	✓	✓✓	✓	–	✓	✓	13	Low
Erbs et al., 2010	✓	✓	–	✓	✓	✓✓✓	✓	✓✓	✓	–	✓	✓	13	Low
Feiereisen et al., 2013	✓	✓	–	✓	–	✓✓	✓	✓✓	✓	–	✓	✓	11	Low
Fernandes-Silva et al., 2017	✓	✓	✓	✓	✓	✓✓	✓	✓✓	✓	–	–	✓	12	Low
Fu et al., 2013	✓	✓	–	✓	–	✓✓	–	✓✓	✓	–	✓	✓	10	Low
Giallauria et al., 2011	✓	✓	✓	✓	✓	✓✓✓	–	✓✓	✓	✓	✓	✓	14	Low
Gielen et al., 2012	✓	✓	✓	✓	✓	✓✓✓	✓	✓✓	✓	–	✓	✓	14	Low
Isaksen et al., 2019	✓	✓	✓	✓	✓	✓✓✓	–	✓✓	✓	–	✓	✓	13	Low
Karavidas et al., 2006	✓	✓	✓	✓	✓	✓✓	✓	✓✓	✓	–	–	✓	12	Low
Kim et al., 2008	✓	–	–	✓	–	✓✓	✓	✓✓	✓	–	✓	✓	10	Low
Kim et al., 2011	✓	–	–	✓	–	✓✓✓	✓	✓✓	✓	✓	✓	✓	12	Low
Kobayashi et al., 2003	✓	✓	–	✓	–	✓✓✓	✓	✓✓	✓	–	–	✓	11	Low
Lara Fernandes et al., 2011	✓	✓	–	✓	–	✓✓	✓	✓✓	✓	✓	✓	✓	12	Low
Larsen et al., 2001	✓	–	–	✓	–	✓✓✓	✓	✓	✓	–	✓	✓	10	Low
Linke et al., 2005	✓	✓	–	✓	–	✓✓	–	✓✓	✓	–	✓	✓	10	Low

(*continued on next page*)

Table 1 (*continued*)

Author et al., yr	eligibility criteria specified	Random allocation of participants	allocation concealed	groups similar at baseline	assessors blinded	outcome measures assessed in 85% of participants*	intention to treat analysis	reporting of between group statistical comparison#	point measures and measures of variability reported for main effects	Activity monitoring in control group	Relative exercise intensity reviewed	Supervised /Non-supervised	**Total PEDRO score**	**Risk of bias**
Marco et al., 2013	✓	✓	✓	✓	✓	✓✓	✓	✓✓	✓	–	–	✓	12	Low
Masterson-Creber et al., 2015	✓	✓	✓	✓	–	✓✓	–	✓✓	✓	–	✓	✓	11	Low
Mc Dermott et al., 2004	✓	✓	–	✓	–	✓✓	✓	✓✓	✓	–	–	✓	10	Low
Melo et al., 2019	✓	✓	✓	✓	–	✓	✓	✓✓	✓	–	✓	✓	11	Low
Milani et al., 2004	✓	–	–	✓	–	✓✓	✓	✓✓	✓	–	–	✓	9	Low
Munk et al., 2011	✓	✓	✓	✓	✓	✓✓✓	✓	✓✓	✓	–	✓	✓	14	Low
Myers et al., 2010	✓	✓	–	✓	✓	✓✓✓	✓	✓✓	✓	–	✓	✓	13	Low
Niebauer et al., 2005	✓	✓	–	✓	–	✓✓	–	✓✓	✓	–	✓	✓	10	Low
Parrinello et al., 2010	✓	✓	–	✓	–	✓✓	✓	✓✓	✓	✓	–	✓	11	Low
Pierce et al., 2008	✓	✓	–	✓	–	✓✓	–	✓✓	✓	✓	–	✓	10	Low
Prescott et al., 2009	✓	✓	–	✓	–	✓✓	–	✓✓	✓	–	✓	✓	10	Low
Pullen et al., 2008	✓	✓	–	✓	✓	✓✓✓	✓	✓✓	✓	–	–	✓	12	Low
Racca et al., 2020	✓	–	–	✓	–	✓✓	✓	✓✓	✓	–	✓	✓	10	Low
Ranković et al., 2009	✓	–	–	✓	–	✓✓	–	✓✓	✓	–	✓	✓	9	Low
Redwine et al., 2020	✓	✓	✓	✓	✓	✓✓✓	✓	✓✓	✓	–	–	✓	13	Low
Shin et al., 2006	✓	–	–	✓	–	✓✓	✓	✓✓	✓	–	✓	✓	10	Low
Tisi et al., 1997	✓	✓	✓	✓	–	✓✓✓	✓	✓✓	✓	✓	–	✓	13	Low
Trippel et al., 2017	✓	✓	–	✓	–	✓✓	✓	✓✓	✓	–	✓	✓	11	Low
Tsarouhas et al., 2011	✓	–	–	✓	–	✓✓	✓	✓✓	✓	–	✓	✓	10	Low
Walther et al., 2008	✓	✓	✓	✓	✓	✓✓✓	✓	✓✓	✓	–	–	✓	13	Low
Yeh et al., 2011	✓	✓	–	✓	–	✓✓	✓	✓✓	✓	–	–	✓	10	Low

Note: Total PEDRO score out of 15 points; (✓) = one point; (-) = not reported or unclear; *Three points possible—one point if adherence greater than 85%, one point if adverse events reported, one point if exercise attendance is reported; #Two points possible—one point if primary outcome is reported, one point if all other outcomes reported. Low risk of bias = 8–15 Pedro scores, some risk of bias = 5–7 Pedro scores, and high risk of bias = Pedro score of less than 5 (excluded articles).

sensitivity C-reactive protein [hs-CRP]) during aging are inflammaging biomarkers that can be translated to metabolic disorders such as clinical HF [1,2]. However, the mechanisms of inflammaging and obesity in the development of clinical HF are unclear. It has been reported that inflammatory cytokines, vascular adhesion molecules, and systemic inflammation increase significantly in response to pathophysiological conditions, especially clinical HF [5,6]. The most important approaches for primary and secondary prevention of HF and/or inflammaging include risk factor modifications, medical therapies, and importantly, lifestyle and exercise interventions [7]. To date, the role of the inflammaging process in clinical HF remains unknown. The American Heart Association (AHA) endorses the use of exercise-based cardiac rehabilitation as a class-1 recommendation for clinical HF [4,7]. Numerous studies demonstrated that regular exercise training reduces chronic inflammatory cytokines, systemic inflammation and cardiovascular peptides [4], and improves restore endothelial function [8], cardiorespiratory fitness (CRF) [9], cardiac function, and clinical progression and survival in patients with HF [4,8,9]. Data has been conflicting regarding the impacts of exercise interventions and the inflammaging process in HF, with some studies reporting that aerobic [10,11], resistance [12] and concurrent [13,14] interventions reduced inflammatory cytokines in patients with HF, whereas other studies did not report any significant changes [5,15–17]. Previous *meta*-analyses-based evidence supported a reducing effect on chronic inflammatory markers in men, women and patients with metabolic disorders [6,18,19], but not in patients with HF. Therefore, the purpose of our *meta*-analysis was to determine the effects of types of concurrent, resistance and aerobic exercise interventions on serum or plasma levels of inflammaging markers (TNF-α, IL-6, IL-1-beta, IL-8, and hs-CRP) in overweight and obese patients with HF.

2. Methods

2.1. Search strategy

Our systematic review and *meta*-analysis protocol was registered in PROSPERO at the University of York [registration code = CRD42022347164]. The PRISMA guidelines were used in this *meta*-analysis [20]. The electronic databases of searching including Scopus, PubMed, Web of Science, and Google Scholar were searched until August 31, 2022 by two corresponding authors (A M and M G). The search strategy for exercise interventions, inflammaging markers, and overweight or obesity patients with HF included the keywords as follows: [concurrent OR combined OR combination OR circuit AND resistance OR strength OR power AND aerobic OR endurance OR HIIT OR high intensity interval training OR SIT OR sprint interval training OR continuous AND training OR exercise OR exercise training OR physical activity OR cardiac rehabilitation AND inflammaging OR inflammageing OR inflamm-ageing OR inflammation OR inflammatory OR cytokines OR hsCRP OR CRP OR C-reactive protein OR TNF-α OR TNF-alpha OR Tumor necrosis factor OR IL-6 OR interlukin-6 OR IL-1-beta OR interleukin-1-beta OR IL-8 OR interleukin-8 AND Overweight OR Obesity AND HFrEF OR heart-failure-with-reduced-ejection-fraction OR HFpEF OR heart-failure-with-preserved-ejection-fraction OR heart-failure OR acute-heart-failure OR chronic-heart-failure OR PAD OR peripheral-artery-disease OR peripheral-arterial-disease OR intermittent-claudication OR vascular-claudication]. The titles and abstracts of all articles were screened after removing duplicate publications and then full-text of articles were assessed for eligibility process by two corresponding authors (A M and M G).

2.2. Study selection

Only randomized controlled trial exercise interventions were considered for eligibility of inclusion criteria as follows: (a) only English language original RCT articles, (b) original articles with human participants, (c) patients with HF and overweight (body mass index/ BMI $\geq$ 25 kg/m^2) or obesity (BMI $\geq$ 30 kg/m^2) aged $\geq$ 18 yrs, (d) overweight/obesity HF with maintaining routine medications, standard and usual care, home-based exercise, optimal medical therapy (e) measuring serum or plasma of TNF-α, IL-6, IL-1-beta, IL-8, and hs-CRP at baseline and after intervention, (f) duration of follow-up $\geq$ 2 weeks, (g) having at least one exercise group (concurrent, resistance, and aerobic) with HF vs. control group with HF participants (h) usual care or routine medications for control group with and without exercise intervention and/or home-based exercise. The type of exercise in this *meta*-analysis included concurrent ('concurrent training', combined training; aerobic + resistance), resistance ('resistance training; functional electrical stimulation; weight training'), and aerobic ('aerobic training; endurance training; aerobic exercise-based cardiac rehabilitation; cardiac rehabilitation program; physical training; aerobic interval training; Tai Chi'). There were no restrictions on the duration of exercise follow-up or study protocols in RCT studies. Exclusion criteria included (a) non-original articles (letters to the editors, short reports, case studies, methodologies, review articles and systematic review & *meta*-analysis articles), (b) non-English language articles, (c) animal studies, (d) studies without exercise group, (e) studies without control group, (f) studies with caloric restrictions in exercise group and/or control group, (g) studies with dietary interventions, (h) studies with normal BMI participants, (i) studies with exacerbate HF-related medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), calcium channel blockers (CCBs), and most antiarrhythmic drugs.

2.3. Data extraction

Data extraction process was performed by corresponding author (A M) and any disagreement was resolved by discussion among corresponding authors (A M and M G). The characteristics of the data for each article were extracted as follows: (a) study design, (b) participant characteristics including age, gender, BMI and sample size, (c) study characteristics including exercise interventions (type, frequency, duration, training protocol, and supervised/unsupervised) and control group, (d) outcome inflammaging markers including TNF-α, IL-6, IL-1-beta, IL-8, and hs-CRP. The pre- and post-test values (mean and standard deviation [SD]) were entered into the *meta*-analysis in order to generate forest plots. All data and values of standard-errors, median, range and interquartile-ranges were converted to mean and SD based on statistical formulas [21,22]. The Getdata Graph Digitizer software was used for the data extraction from graphs and figures. If studies had multiple arms of exercise interventions, data for aerobic, resistance and concurrent vs. control group were included (control group was divided by the number of intervention arms to avoid multiple sample size counting). In addition, for the studies with more than one evaluated post-test intervention, only the last post-test intervention was considered. When insufficient information was available from the articles and/or additional information was required, the corresponding author was contacted by e-mail.

2.4. Quality assessment and sensitivity analysis

The Pedro scale was used to assess the methodological quality of included-studies (Pedro scores ranged 7 to 15 with maximum 15 scores) and risk of bias (high risk of bias = Pedro score of less than 5; excluded articles) [22] (Table 1), which included as follows: (a) eligibility criteria specified, (b) random allocation of participants, (c) allocation concealed, (d) groups similar at baseline, (e) assessors blinded, (f) outcome measures assessed in 85% of participants, (g) intention to treat analysis, (h) comparing between-groups for statistical differences, (i) point measures and measures of variability reported for main effects, (j) activity monitoring in control group, (k) relative exercise intensity reviewed (l) supervised or non-supervised (Table 1).

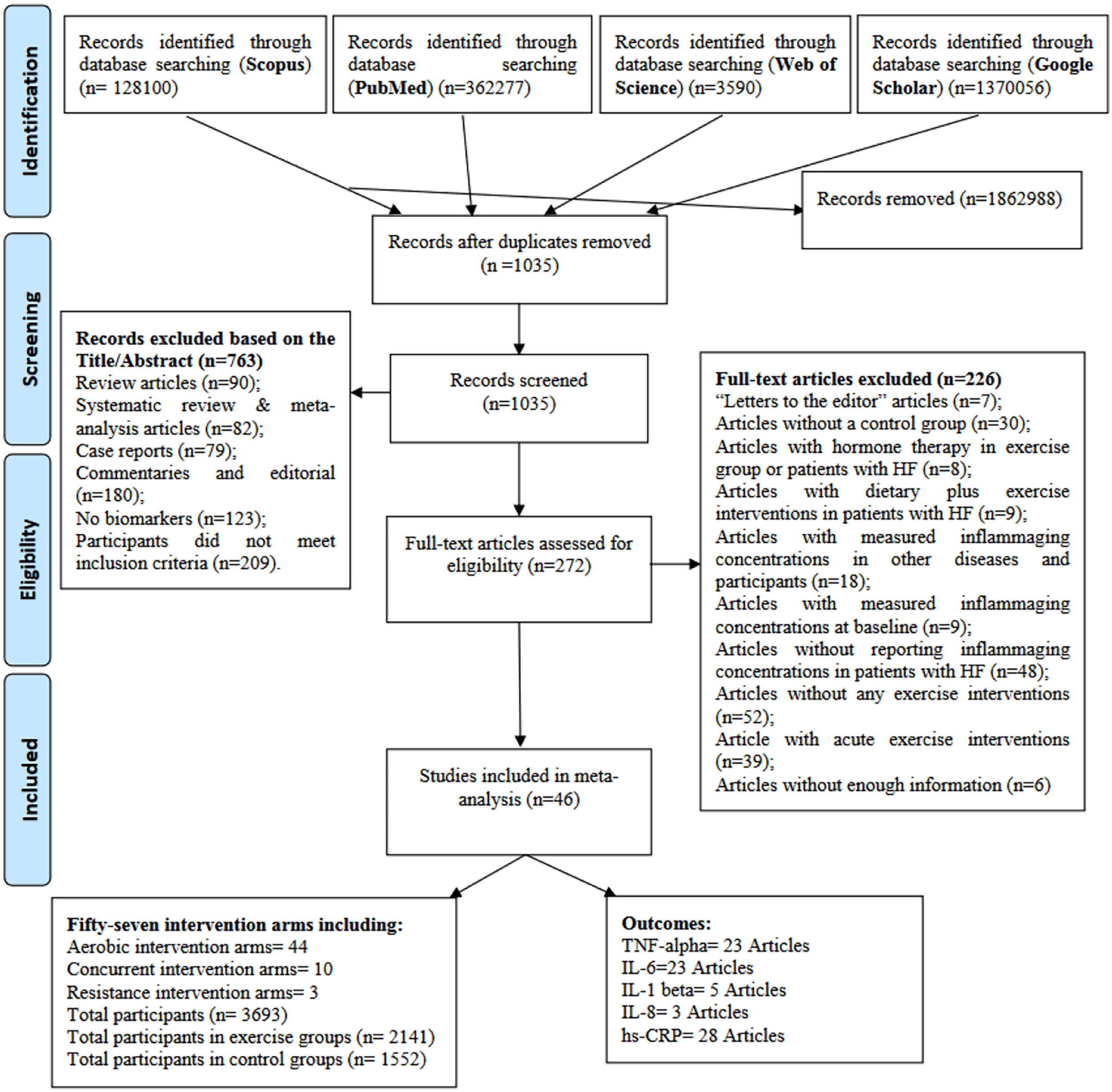

Fig. 1. Flowchart of study selection. ***Note.*** HF = Heart failure.

2.5. Statistical analysis

Comprehensive *meta*-analysis (CMA) software was used for data analysis and calculating the standardized mean difference (SMD) and 95% confidence intervals (CIs) by fixed and random-effect models. Significance level was considered at a P less than 0.05. The effect size was calculated to compare the effects of exercise interventions vs. control group on circulating inflammaging markers. For interpreting effect sizes were considered the Cochrane guidelines including small (0.2–0.49), medium (0.5–0.79), and large (more than 0.8) effect sizes [23]. Heterogeneity was assessed by using the I-squared (I^2) statistic. In addition, for interpretation of I^2 statistic was used of Cochrane guidelines as follows: low heterogeneity (25%), medium heterogeneity (50%), and high heterogeneity (75%). The visual interpretation of funnel plots and Egger's test were considered to identify publication bias, as P-value less than 0.1 was considered for significant level of publication bias [24].

3. Results

3.1. Included studies

The initial search in the electronic databases of Scopus, PubMed, Web of Science, and Google Scholar identified 128100, 362277, 3590, and 1,370,056 articles, respectively. After removing duplicates and screening articles based on the title and abstract, 272 full-text articles were included for final screening based on the inclusion and exclusion criteria. Of those 272 articles, 46 full-text articles met the inclusion criteria and 226 articles were excluded with reasons as follows: (a) letters to the editor articles (n = 7), (b) articles without a control group (n = 30), (c) articles with hormone therapy in exercise group or patients with HF (n = 8), (d) articles with dietary plus exercise interventions in patients with HF (n = 9), (e) articles with measured inflammaging concentrations in other diseases and participants (n = 18), (f) articles with measured inflammaging concentrations at baseline (n = 9), (g) articles without reporting inflammaging concentrations in patients with HF (n = 48); (h) articles without any exercise interventions (n = 52), (i)

Table 2
Participant characteristics at baseline.

Source, yrs	Country	Exercise + Control = Total sample size (Baseline)	Gender	Participants characteristics	Groups	Age (yrs) (Baseline) Mean ± SD	BMI (kg/m^2) (Baseline) Mean ± SD	Inflammaging markers (TNF-α, IL-6, IL-1 beta, IL-8, hs-CRP)
Abolahrari-Shirazi et al., 2018	Iran	25(Concurrent) + 25(Aerobic) + 25(Control) =75	Male/ Female	Patients with heart failure (NYHA Class I-III)	Concurrent Aerobic Control	Concurrent: 56.76 ± 8.71 Aerobic: 57.64 ± 7.85 Control: 57.32 ± 9.41	Concurrent: 25.69 ± 3.65 Aerobic: 26.71 ± 2.91 Control: 26.10 ± 3.86	hs-CRP
Adamopoulos et al., 2002	Greece	24 + 20 = 44	Unknown	Patients with chronic heart failure (NYHA Class II-III)	Aerobic Control	Aerobic: 55.0 ± 9.79 Control: Unknown	Unknown	TNF-alpha, IL-6
Adamopoulos et al., 2014	Belgium	21 + 22 = 43	Male/ Female	Patients with chronic heart failure (NYHA Class I-III)	Concurrent Control	Concurrent: 57.8 ± 11.7 Control: 58.3 ± 13.2	Concurrent: 28.6 ± 6.7 Control: 27.2 ± 2.9	CRP
Ahmad et al., 2014	England	477 + 451 = 928	Male/ Female	Patients with chronic heart failure (NYHA Class II-IV)	Aerobic Control	Aerobic: 59.36 ± 12.41 Control: 59.23 ± 12.86	Unknown	hs-CRP
Aksoy et al., 2015	Turkey	15(Continuous) + 15(Intermittent) + 15(Control) =45	Male/ Female	patients with chronic heart failure (NYHA Class II-III)	Aerobic Control	Aerobic: Continuous 63.7 ± 8.8 Intermittent 59.6 ± 6.9 Control: 57.5 ± 11.2	Aerobic: Continuous 28.4 ± 4.9 Intermittent 30.1 ± 5.1 Control: 29.1 ± 4.2	CRP
Balen et al., 2008	Croatia	30 + 30 = 60	Male/ Female	Patients with myocardial infarction	Aerobic Control	Aerobic: 59 ± 9 Control: 61 ± 10	Aerobic: 28.8 ± 3.8 Control: 28 ± 3.8	hs-CRP, IL-8, TNF-alpha
Butts et al., 2018	USA	38 + 16 = 54	Male/ Female	Patients with heart failure (NYHA Class II-III)	Aerobic Control	Aerobic: 60 ± 8.7 Control: 58.19 ± 12.8	Aerobic: 31.51 ± 7.1 Control: 31.03 ± 6.1	IL-1β
Byrkjeland et al., 2011	Norway	40 + 40 = 80	Male/ Female	Patients with chronic heart failure (NYHA Class I-IIIB)	Aerobic Control	Aerobic: 68.8 ± 7.9 Control: 71.5 ± 7.8	Unknown	CRP, TNF-alpha, IL-6
Conraads, et al., 2002	Belgium	23 + 18 = 41	Male/ Female	Patients with chronic heart failure and coronary artery disease (NYHA Class I–II/ III–IV)	Concurrent Control	Concurrent: 54.75 ± 13.22 Control: 62.0 ± 14.27	Unknown	IL-6, TNF-α
de Meirelles et al., 2014	Brazil	15 + 15 + 30	Male/ Female	Patients with heart failure (NYHA class II and III)	Concurrent Control	Concurrent 54 ± 3 Control: 55 ± 2	Concurrent 28.6 ± 0.9 Control: 27.9 ± 0.7	CRP, IL-6, TNF-alpha
Eleuteri et al., 2013	Italy	11 + 10 = 21	Male	Patients with chronic heart failure (NYHA class II)	Aerobic Control	Aerobic: 66 ± 2 Control: 63 ± 2	Unknown	IL-6, CRP
Erbs et al., 2010	Germany	18 + 19 = 37	Male	Patients with advanced chronic heart Failure (NYHA Class IIIB)	Aerobic Control	Aerobic: 60 ± 11 Control: 62 ± 10	Unknown	TNF-α
Feiereisen et al., 2013	Luxembourg	15(Concurrent) + 15(Resistance) + 15(Aerobic) + 15(Control) =60	Unknown	Patients with chronic heart failure (NYHA class II-III)	Concurrent Resistance Aerobic Control	Concurrent: 60.6 ± 5.6 Resistance: 57.9 ± 5.8 Aerobic: 59.4 ± 6.5 Control: 55.5 ± 7.5	Unknown	TNF-α, IL-6
Fernandes-Silva et al., 2017	Brazil	28 + 16 = 44	Male/ Female	Patients with heart failure (NYHA Class IV)	Aerobic Control	Aerobic: 51 ± 7 Control: 48 ± 7	Aerobic: 29 ± 4 Control: 28 ± 4	IL-6, TNF-alpha
Fu et al., 2013	Taiwan	15(Aerobic interval) + 15(Aerobic continuous)	Male/ Female	patients with heart failure (NYHA Class II-III)	Aerobic Interval Continuous Control	Aerobic: Interval 67.5 ± 1.8 Continuous 66.3 ± 2.1	Unknown	IL-6

(continued on next page)

Table 2 (*continued*)

Source, yrs	Country	Exercise + Control = Total sample size (Baseline)	Gender	Participants characteristics	Groups	Age (yrs) (Baseline) Mean ± SD	BMI (kg/m^2) (Baseline) Mean ± SD	Inflammaging markers (TNF-α, IL-6, IL-1 beta, IL-8, hs-CRP)
		+ 15(Control) =45				Control: 67.8 ± 2.5		
Giallauria et al., 2011	Italy	37 + 38 = 75	Male/ Female	Patients with acute myocardial infarction (AHA Class IIB or III)	Aerobic Control	Aerobic: 61 ± 7 Control: 60 ± 8	Aerobic: 27.3 ± 2.2 Control: 28.2 ± 2.8	hsCRP
Gielen et al., 2012	Germany	15 + 15 = 30 15 + 15 = 30	Male/ Female	Patients with chronic heart failure ≤ 55 yrs and ≥ 65 yrs (NYHA Class II-III)	Aerobic Control Aerobic Control	Aerobic: 50 ± 19.36 Control: 49 ± 19.36 Aerobic: 72 ± 15.49 Control: 72 ± 11.61	Aerobic: 29 ± 7.74 Control: 30 ± 11.61 Aerobic: 28 ± 11.61 Control: 28 ± 7.74	TNF-alpha
Isaksen et al., 2019	Norway	19 + 11 = 30	Male	Patients with ischemic heart failure (LVEF < 40%)	Aerobic Control	Aerobic: 69 ± 9 Control: 66 ± 9	Aerobic: 27.3 ± 4.2 Control: 27.2 ± 3.8	hs-CRP
Karavidas et al., 2006	Greece	16 + 8 = 24	Male/ Female	Patients with chronic heart failure (NYHA Class II-III)	Resistance/ Functional electrical stimulation Control	Resistance: 57.4 ± 15.3 Control: 63.8 ± 8.1	Resistance: 26.57 ± 4.80 Control: 28.07 ± 3.68	TNF-alpha, IL-6
Kim et al., 2008	Korea	29 + 10 = 39	Male/ Female	Patients with coronary artery disease	Aerobic Control	Aerobic: 59.9 ± 8.61 Control: 52.8 ± 11.70	Aerobic: 25.6 ± 3.23 Control: 26.6 ± 2.21	hs-CRP, TNF-α, IL-1β, IL-6
Kim et al., 2011	Korea	69 + 72 = 141	Male/ Female	Patients with acute myocardial infarction	Aerobic Control	Aerobic: 61.93 ± 10.67 Control: 64.49 ± 9.31	Unknown	hs-CRP
Kobayashi et al., 2003	Japan	14 + 14 = 28	Male/ Female	Patients with chronic heart failure (NYHA Class II-III)	Aerobic Control	Aerobic: 55 ± 7.48 Control: 62 ± 7.48	Unknown	IL-6
Lara Fernandes et al., 2011	Brazil	15 + 19 = 34	Male/ Female	Patients with coronary artery disease	Aerobic Control	Aerobic: 60.7 ± 6.7 Control: 59.5 ± 7.3	Aerobic: 28.6 ± 5.9 Control: 27.6 ± 3.6	CRP
Larsen et al., 2001	Norway	28 + 16 = 44	Male	Patients with heart failure (NYHA Class II-III)	Aerobic Control	Aerobic: 67 ± 8 Control: 62 ± 5	Unknown	TNF-alpha, IL-6
Linke et al., 2005	Germany	12 + 11 = 23	Male	Patients with chronic heart failure (NYHA Class II-III)	Aerobic Control	Aerobic: 55 ± 6.92 Control: 52 ± 9.94	Unknown	TNF-α, IL-1β
Marco et al., 2013	Spain	11 + 11 = 22	Male/ Female	patients with chronic heart failure (NYHA class II-III)	Concurrent Control	Concurrent: 68.5 ± 8.88 Control: 70.1 ± 10.75	Concurrent: 28.4 ± 3.64 Control: 26.3 ± 2.4	hs-CRP
Masterson-Creber et al., 2015	USA	163 + 157 = 320	Male/ Female	Patients with chronic heart failure (NYHA Class II-IV)	Aerobic Control	58.66 ± 11.91	Unknown	hsCRP
Mc Dermott et al., 2004	USA	24 + 8 = 34	Male/ Female	Peripheral arterial patients	Aerobic Control	Aerobic: 69.4 ± 9.6 Control: 65.9 ± 6.2	Aerobic: 28.6 ± 5.1 Control: 28.8 ± 6.1	hs-CRP, IL-6
Melo et al., 2019-a	Portugal	7 + 9 = 16	Male/ Female	Patients with chronic heart failure (atrial fibrillation) (NYHA Class II-IV)	Aerobic Control	69.4 ± 7.2	28.2 ± 4.8	TNF-alpha, IL-6
Melo et al., 2019-b	Portugal	11 + 10 = 21	Male/ Female	Patients with chronic heart failure (sinus rhythm) (NYHA Class II-IV)	Aerobic Control	66.2 ± 14.57	26.7 ± 4.58	TNF-alpha, IL-6
Milani et al., 2004	USA	235 + 42 = 277	Male/ Female	Patients with coronary heart disease	Aerobic Control	Aerobic: 66.7 ± 11 Control: 63.9 ± 11.1	Aerobic: 27.9 ± 4.9 Control: 29.2 ± 5	hs-CRP

(*continued on next page*)

Table 2 (*continued*)

Source, yrs	Country	Exercise + Control = Total sample size (Baseline)	Gender	Participants characteristics	Groups	Age (yrs) (Baseline) Mean ± SD	BMI (kg/m^2) (Baseline) Mean ± SD	Inflammaging markers (TNF-α, IL-6, IL-1 beta, IL-8, hs-CRP)
Munk et al., 2011	Norway	18 + 18 = 36	Male/ Female	Patients with angina pectoris	Aerobic Control	Aerobic: 59.5 ± 10 Control: 60.7 ± 9	Aerobic: 26.1 ± 4 Control: 28.4 ± 3.3	IL-6, TNF-alpha, IL-8
Myers et al., 2010	USA	26 + 31 = 57	Male/ Female	Patients with abdominal aortic aneurysm	Concurrent Control	Concurrent: 73.1 ± 6 Control: 70.4 ± 9	Concurrent: 28.2 ± 4.4 Control: 26.9 ± 3.4	CRP
Niebauer et al., 2005	UK	18 + 9 = 27	Male/ Female	Patients with chronic heart failure	Concurrent Control	Concurrent: 53.6 ± 9.2 Control: 51.3 ± 6.9	Unknown	TNF-alpha, IL-6
Parrinello et al., 2010	Italy	11 + 11 = 22	Male/ Female	Patients with compensated congestive heart failure (NYHA Class II-III)	Aerobic Control	Aerobic: 62.3 ± 4.9 Control: 63.2 ± 5	Unknown	CRP
Pierce et al., 2008	USA	8 + 6 = 14	Male/ Female	Patients with heart transplant recipients	Aerobic Control	Aerobic: 53.5 ± 13.6 Control: 54.2 ± 6.4	Aerobic: Unknown Control: 25.8 ± 3.8	CRP, IL-6, TNF-α
Prescott et al., 2009	Denmark	20 + 23 = 43	Male/ Female	Patients with chronic systolic heart failure (NYHA Class II–IV)	Concurrent Control	Concurrent: 68 ± 11 Control: 66.9 ± 12.5	Concurrent: 27.7 ± 4.12 Control: 27.7 ± 5.92	hsCRP, IL-6, TNF-alpha
Pullen et al., 2008	USA	9 + 10 = 19	Male/ Female	Patients with chronic heart failure (NYHA Class II-III)	Aerobic Control	Aerobic: 52.1 ± 3.3 Control: 50.5 ± 12.8	Unknown	IL-6, hs-CRP
Racca et al., 2020	Italy	47(Aerobic) + 35(Aerobic) + 14(Aerobic) + 40(Control) =136	Male/ Female	Patients with not experience atrial fibrillation (NoAF) Patients with postoperative atrial fibrillation (POAF) Patients with permanent atrial fibrillation (AF)	Aerobic Aerobic Aerobic Control	Aerobic: 71 ± 6 Aerobic: 71 ± 5 Aerobic: 77.5 ± 6.5 Control: 66.2 ± 10.6	Aerobic: 24.1 ± 2.6 Aerobic: 25.8 ± 2.2 Aerobic: 26.4 ± 2.4 Control: 25.1 ± 4.2	IL-1β, IL-6, TNFα, IL-8
Ranković et al., 2009	Serbia	22 + 30 = 52	Male/ Female	Patients with ischemic heart disease	Aerobic Control	Aerobic: 62.7 ± 7.1 Control: 58.4 ± 7.6	Aerobic: 29.3 ± 3.2 Control: 29.1 ± 2.7	hs-CRP
Redwine et al., 2020	USA	24(Aerobic) + 22(resistance) + 23(Control) =69	Male/ Female	Patients with heart failure (AHA Class III)	Aerobic Resistance Control	Aerobic: 63 ± 9 Resistance: 65 ± 9 Control: 67 ± 7	Aerobic: 32 ± 8 Resistance: 33 ± 8 Control: 31 ± 6	CRP, IL-6, TNF-alpha
Shin et al., 2006	Korea	15(Aerobic) + 14(Aerobic) + 10(Control) =39	Male/ Female	Patients with coronary artery disease/ acute myocardial infarction	Aerobic Aerobic Control	Aerobic: 59.3 ± 6.97 Aerobic: 60.6 ± 9.72 Control: 52.5 ± 12.64	Aerobic: 25.7 ± 3.48 Aerobic: 25.8 ± 2.61 Control: 26.6 ± 2.21	hs-CRP, IL-6
Tisi et al., 1997	UK	67 + 15 = 82	Male/ Female	Patients with intermittent claudication	Aerobic Control	69.3 66.2	Unknown	CRP
Trippel et al., 2017	Germany	43 + 19 = 62	Male/ Female	Patients with heart failure	Concurrent Control	64.4 ± 7.2	Unknown	TNF-alpha, IL-1β, IL-6
Tsarouhas et al., 2011	*Greece*	27 + 12 = 39	Male/ Female	Patients with chronic heart failure (NYHA Class II-III)	Aerobic Control	Aerobic: 66.8 ± 13.1 Control: 67 ± 5.6	Aerobic: 24.1 ± 7.1 Control: 25.5 ± 4.5	TNF-α
Walther et al., 2008	Germany	51 + 50 = 101	Male	Patients with coronary artery disease	Aerobic Control	Aerobic: 62 ± 7.14 Control: 60 ± 7.07	Aerobic: 27.2 ± 2.85 Control: 28 ± 3.53	hs-CRP, IL-6
Yeh et al., 2011	USA	50 + 50 = 100	Male/ Female	Patients with chronic heart failure (NYHA Class I-III)	Aerobic Control	Aerobic: 68.1 ± 11.9 Control: 66.6 ± 12.1	Unknown	CRP, TNF-alpha

Note: American heart association (AHA), Canadian cardiovascular society (CCS), high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), interleukin-1 beta (IL-1-beta), interleukin-8 (IL-8), New York heart association (NYHA), tumor necrosis factor alpha (TNF-α), Left ventricular ejection fraction (LVEF).

Table 3
Study characteristics in overweight/ obesity patients with heart failure.

Source, yr	Exercise group					Control group
	Type	Frequency (days/ week)	Follow-up (Duration)	Training protocol	Supervised or Unsupervised	
Abolahrari-Shirazi et al., 2018-a	Combined (cycle + weight training)	3	7 weeks	Combined = endurance + resistance. Endurance training = 45 min at 40%–70% peak VO2 predicted; exercising on a cycle ergometer for 20 min, an arm ergometer for 10 min, and a treadmill for 15 min; Resistance training = knee extension, knee flexion, elbow flexion, and shoulder abduction. Initial intensity was set as 40% one repetition maximum (1RM) and then increased gradually to 60% 1RM. The total duration of the resistance exercise protocol was approximately 15 min.	Supervised	Control group only received a pamphlet for daily exercising at home including ten types of active exercises, 10 repetitions and each exercise session at home lasted 15–20 min.
Abolahrari-Shirazi et al., 2018-b	Endurance (cycle)	3	7 weeks	Endurance training = 45 min at 40%–70% peak VO2 predicted; exercising on a cycle ergometer for 20 min, an arm ergometer for 10 min, and a treadmill for 15 min.	Supervised	Control group only received a pamphlet for daily exercising at home including ten types of active exercises, 10 repetitions and each exercise session at home lasted 15–20 min.
Adamopoulos et al., 2002	Aerobic (bicycle)	5	12 weeks	Home-based bicycle exercise training program: The training program consisted of five days per week, 30 min per day; patients and normal control subjects were instructed to exercise at 50 rpm to keep their continuously monitored heart rate in the range of 60% to 80% of their previously determined maximal heart rate.	Unknown	Control group was performed home-based bicycle exercise training programme similar to the aerobic group.
Adamopoulos et al., 2014	Concurrent (cycle + inspiratory muscle training)	3	12 weeks	Patients in the Concurrent group underwent aerobic training for 45 min on an ergometer at 70–80% HRmax with warm-up and cool down periods lasted 5 min. resistance training including an inspiratory-incremental resistive loading device was performed at 60% of individual sustained maximal inspiratory pressure (SPImax) with six inspiratory efforts at each level. Initially, the first level presented templates at 60 s rest intervals over its six inspiratory efforts, but at the second level through to the sixth level, this rest period was reduced to 45, 30, 15, 10, and 5 sec. After the sixth level, the rest period was kept at 5 sec. The duration of training was 30 min.	Supervised	Patients in control group underwent aerobic + resistance trainings similar to the exercise group with only 10% of their sustained maximal inspiratory pressure (SPImax).
Ahmad et al., 2014	Aerobic (walking, treadmill or cycling)	3	12 weeks	Patients in aerobic group performed walking, treadmill, or stationary cycling as their primary training mode. Aerobic exercise was initiated at 15 to 30 min per session at a heart rate corresponding to 60% of heart rate reserve. Patients in the aerobic group were also provided home exercise equipment, and home exercise adherence and amount were formally measured	Supervised	Patients in the usual care group, received detailed self-management educational materials that included information on medications, fluid management, symptom exacerbation, sodium intake, and amount of activity recommended.
Aksoy et al., 2015	Aerobic (cycle)	3	10 weeks	Aerobic training: Intermittent aerobic + Continuous aerobic: Both group started with power attained at 50% of peak VO2 and continued with increments of power in every 2 wks until achievement of power attained at 75% of peak VO2; a single session consisted of 35 min of aerobic exercise (by ergometers with an electromagnetic brake at a constant pedal rate of 50 revolutions per min) including 10 min of warm-up and cool down. Intermittent aerobic: worked for 60-sec bouts of cycling at a determined intensity and worked for 30-sec intervals	Supervised	Control group was on optimal medical therapy without any particular regular physical activity before.

(continued on next page)

Table 3 (*continued*)

Source, yr	Exercise group					Control group
	Type	Frequency (days/ week)	Follow-up (Duration)	Training protocol	Supervised or Unsupervised	
				of low intensity cycling at 30 W, making a total of 17 cycles of low- and high-intensity bouts in a session. Continuous aerobic: worked without any change in the intensity of the exercise during a single session.		
Balen et al., 2008	Aerobic (cycle)	3	3 weeks	Aerobic group was performed a 45 min aerobic activity on a cycle-ergometer with exercise intensity reaching a level of heart rate 50–60% VO2peak monitored on ergospirometry. Addition to this training was a daily 30-minute organized program of supervised walking on a standardized track.	Supervised	Control group without active training was provided with standard care.
Butts et al., 2018	Aerobic (walking)	3	3 months	Aerobic group was instructed to walk for 30 min 3 times per week at 60% maximum heart rate for the first two weeks, 45 min 3 times per week at 60% maximum heart rate for weeks three and four, and 45 min 3 times per week at 70% maximum heart rate for the remaining eight weeks.	Supervised	Control group received education and flexibility and stretching exercises to control for the possible confounding variable of receiving attention from a healthcare professional.
Byrkjeland et al., 2011	Aerobic (walking)	2	4 months	Aerobic group was performed three intervals of high intensity (15–18 on the Borg scale) and two periods of moderate intensity (11–13 on the Borg scale), in addition to warm-up and cool-down periods, 50 min walking per session and twice a week.	Supervised	Control group was referred to standard follow-up care by their primary physician and was not discouraged from regular physical activity.
Conraads, et al., 2002	Combined (cycling or jogging + weight training)	3	4 months	Combined group was performed endurance/ resistance exercise programme for 60 min. Endurance = at 90% of the ventilator threshold including 20 min of cycling and/or jogging with a 5 min warming-up or cooling-down and stretching period. Resistance = resistive weight training at 50% of 1-RM, two sets, consisting of 10 repetitions for 30 min.	Supervised	Control group was age- and gender matched patients with comparable disease severity, attending the outpatient heart failure clinic, served as the untrained heart failure.
de Meirelles et al., 2014	Concurrent (walking + weight training)	3	6 months	Concurrent group was performed aerobic, resistance, and stretching exercises for 90 min. Aerobic: 30 min of treadmill exercise with 5–15% above the ventilator threshold. Resistance: whole body skeletal muscle strength with 2–3 sets of 10–15 repetition maximum of 8–10 exercises for the major muscle groups. Stretching: part of cool-down period for the major muscle groups.	Supervised	Control group was on optimal medical therapy and usual care during 6 months.
Eleuteri et al., 2013	Aerobic (cycle)	5	3 months	The training protocol consisted of 5 sessions a week of 30-min cycle ergometry (60 rev/min) at a power and heart rate corresponding to ventilatory anaerobic threshold (VAT), preceded and followed by a 5-min warm-up and cool-down unloaded period, respectively. A ramp incremental cardiopulmonary exercise test was repeated 6 weeks after the start of the study, in order to adjust training stimulus intensity.	supervised	Control group was continued their normal activities without exercise intervention.
Erbs et al., 2010	Aerobic (bicycle)	3–6	12 weeks	During the first 3 weeks, patients exercised 3 to 6 times daily for 5 to 20 min on a bicycle ergometer adjusted to the work load at which 50% of maximum oxygen uptake (VO2max) was reached in-hospital. On discharge, patients were provided with bicycle ergometers for home exercise training (defined as the heart rate reached at 60% of VO2max).	Supervised	Control patients assigned to the control group continued in no exercise intervention

(*continued on next page*)

Table 3 (*continued*)

Source, yr	Exercise group					Control group
	Type	Frequency (days/ week)	Follow-up (Duration)	Training protocol	Supervised or Unsupervised	
Feiereisen et al., 2013-a	Concurrent (bicycle + weight training)	3	14 weeks (40 sessions)	Combined training group executed 20 min of bicycle training and 20 min of strength training on 5 different weight machines. Every training session was preceded by a warm-up period of 5 min of bicycle training at 30% of VO2 peak.	Supervised	Control group was without exercise intervention.
Feiereisen et al., 2013-b	Resistance (weight training)	3	14 weeks (40 sessions)	Strength training group executed 10 different strength exercises on weight machines during 40 min, starting at 60% of previously determined 1 repetition maximum (1RM), and progressively increasing to 75% of 1RM. Every training session was preceded by a warm-up period of 5 min of bicycle training at 30% of VO2 peak.	Supervised	Control group was continued their lifestyle activities without exercise intervention.
Feiereisen et al., 2013-c	Aerobic (bicycle)	3	14 weeks (40 sessions)	Aerobic group trained for 40 min on a bicycle and treadmill, starting at a target heart rate corresponding to 60% of previously determined peak oxygen uptake (VO2 peak), which they progressively adapted to reach 75% of the VO2 peak. Every training session was preceded by a warmup period of 5 min of bicycle training at 30% of V O 2 peak.	Supervised	Control group was continued without exercise activities.
Fernandes-Silva et al., 2017	Aerobic (cycle)	3	12 weeks	Aerobic training was performed in a cycle ergometer during 30 min, added to 5-min warming and cool-down respectively. The perceived effort was also monitored and kept between 11 and 14 in the Borg scale.	Supervised	Control group was under guideline-directed medical therapy without exercise activities.
Fu et al., 2013	Aerobic (cycle)	3	12 weeks	Aerobic training including 2 groups: aerobic interval training (AIT) and moderate continuous training (MCI). The AIT group warmed up for 3 min at 30% of VO2peak [≈30% heart rate reserve (HRR);≈30% · (HRpeak − HRrest) + HRrest] before exercise five 3-minute intervals at 80% of VO2peak (≈80% HRR). Each interval was separated by 3-minute exercise at 40% of VO2peak (≈40% HRR). The exercise session was terminated by 3-minute cool-down at 30% of VO2peak. The MCT group comprised a warm-up at 30% of VO2peak for 3 min, followed by continuous 60% of VO2peak (≈60% HRR) for 30 min, then a cool-down at 30% of VO2peak for 3 min. The two protocols were isocaloric at the same exercise duration.	Supervised	Control group only engaged in general home-based health care
Giallauria et al., 2011	Aerobic (bicycle)	3	6 months	Aerobic exercise was performed for 30 min on a bicycle ergometer with the target of 60% to 70% of the peak oxygen consumption achieved at the initial symptom-limited cardiopulmonary exercise test (CPET) monitored by a wearable device; Each session was preceded by a 5-minute warming-up and followed by a 5-minute cool-down.	Supervised	Control group was discharged with generic instructions for maintaining physical activity and a correct lifestyle.
Gielen et al., 2012	Aerobic (bicycle)	4	4 weeks	The exercise intervention consisted of 4 supervised training sessions per weekday for 20 min each (excluding 5 min of warming-up and cooling down) with the use of a bicycle ergometer at 70% of the symptom-limited maximum oxygen uptake.	Supervised	Control group received usual clinical care by their physicians.
Isaksen et al., 2019	Aerobic (cycling or running)	3	12 weeks	Aerobic exercise consisted of 15-min of warm-up at 60–70% of maximal heart rate (HRmax). The patients then performed four 4-min intervals at 85% of HRmax (Borg scale 15–17 Rate of	Supervised	Control group was without exercise activities.

(*continued on next page*)

Table 3 (*continued*)

Source, yr	Exercise group					Control group
	Type	Frequency (days/ week)	Follow-up (Duration)	Training protocol	Supervised or Unsupervised	
				Perceived Exertion (RPE)). Participants exercised by means of a cycle ergometer or by running on a treadmill. The intervals were interrupted by short periods of active recovery at 60–70% of maximal HR lasting 3 min. Twenty minutes of cool down and stretching concluded each session.		
Karavidas et al., 2006	Resistance (electrical stimulation)	5	6 weeks	Functional electrical stimulation group was trained for 30 min a day. The stimulator was configured to deliver a direct electrical current at 25 Hz for 5 s followed by 5 s of rest. The intensity of the stimulation was adjusted to achieve a visible muscle contraction that was not sufficiently strong to cause discomfort or a significant movement at either the knee or the angle joints. When the muscles of the right leg were contracted, the muscles of the left leg were relaxing and vice versa.	Supervised	Control group was exposed to the same regimen as the functional electrical stimulation group, except that the intensity of stimulation did not lead to visible or palpable contractions, as judged objectively or subjectively.
Kim et al., 2008	Aerobic (treadmill or bicycle)	2	14 weeks	Aerobic exercise included a warm-up, 30- to 40-min exercise on a treadmill or bicycle ergometer, and a cool-down. Exercise intensity in the first stage was increased progressively from 50 to 85% of VO2max determined by exercise test.	Supervised	Control group was followed up with standard care as outpatients.
Kim et al., 2011	Aerobic (treadmill or bicycle)	Unknown	4 months	Aerobic exercise group consisted of a total of 50 min, including warm-up (10 min), exercise (30 min), and cool-down (10 min). Intensity of exercise was adjusted on a test result basis by calculation of heart rate reserve first, followed by the increased target heart rate from 40% to 85% of the value in phases.	Supervised	Control group underwent general activities on exercise or risk factors management and were instructed to maintain their own activities and cardiovascular risk factors management.
Kobayashi et al., 2003	Aerobic (cycle)	2–3	12 weeks	Aerobic group underwent supervised cycle ergometer training in two 15-min sessions. In each session, the exercise speed was adjusted to maintain the heart rate equivalent to the ventilatory threshold level for 15 min.	Supervised	Control group was instructed to continue leading their normal lifestyle without exercise intervention.
Lara Fernandes et al., 2010	Aerobic (cycling)	3	4 months	Aerobic exercise consisted of three 60-min exercise sessions per week (5 min stretching, 40 min of cycling, 10 min of local strengthening and 5 min of cool down). Exercise intensity was calculated for a target heart rate between anaerobic threshold and respiratory compensation point.	Supervised	Control group received recommendations for lifestyle modification without exercise intervention.
Larsen et al., 2001	Aerobic (walking and jogging)	3	12 weeks	Aerobic exercise consisted of 10 min of warmup, 25 min of endurance training, and 10 min of cooling down and stretching. The endurance training was based on callisthenics: low-impact aerobic walking and jogging using the large muscle groups in both the upper and lower extremities at approximately 80% of maximum capacity.	Supervised	Control group participated in no exercise intervention.
Linke et al., 2005	Aerobic (walking and bicycle)	3	6 months	Aerobic exercise close to their target heart rate daily (at 70% of maximum oxygen uptake) for 20 min for a period of 6-month and were expected to participate in one group training session, consisting of walking, noncompetitive ball games, and calisthenics, for 60 min each week. During the first 2 weeks, Aerobic group exercised in hospital 4 to 6 times daily for 10 min each on a bicycle ergometer adjusted to a workload at which 70% of peak oxygen uptake was reached.	Supervised	Control group participated in no exercise intervention.

(*continued on next page*)

Table 3 (*continued*)

Source, yr	Exercise group					Control group
	Type	Frequency (days/ week)	Follow-up (Duration)	Training protocol	Supervised or Unsupervised	
Marco et al., 2013	Concurrent (inspiratory muscle endurance & strength)	7	4 weeks	Concurrent group performed high-intensity inspiratory muscle training for 20 min with 10 consecutive maximal repetitions (10RM), five sets of 10 repetitions followed by 1–2 min of unloaded recovery breathing off the device and training intensity with 100% of their 10RM twice a day.	Supervised	Control group received sham- inspiratory muscle training at an initial workload of 10 cmH2O which was increased 2.5 cmH2O every week.
Masterson-Creber et al., 2015	Aerobic (walking or cycling)	3	12 months	Aerobic group performed walking or cycling at a 60–70% HRmax reserve for 30–35 min.	Supervised	Control group or patients in the usual care group were not provided with a formal exercise prescription.
Mc Dermott et al., 2004	Aerobic (walking)	3	12 weeks	Aerobic exercise included of step back on the treadmill and walk 20 min continuously, the treadmill speed and grade were increased alternately by 0.5 miles per hour and 2%, respectively, to maintain an 11 to 12 rate of perceived exertion. During the first week of training, the total time the participants spent exercising on the treadmill was 30 min. Their total time walking on the treadmill was increased gradually to a maximum of 50 min per session	Supervised	Control group received usual clinical care.
Melo et al., 2019	Aerobic (walking)	2	6 months	HIIT group performed of 4 interval training periods (high intensity: 90–95% of maximal heart rate if below the device threshold, and if not, 90–95% of the device threshold was used) with 3 lower-intensity active periods (moderate intensity: 60–70% of maximal heart rate if below the device threshold) between interval training periods as well as a 10-min warm-up and a 5–7 min cool-down and implemented twice a week, each for 60 min.	Supervised	Control group patients received usual care.
Milani et al., 2004	Aerobic (walking or jogging)	3	3 months	Aerobic group received formalized exercise instruction, 3 times per week for group exercise classes and lasting 20–60 min on the treadmill (walking/jogging), work capacity usually levels out at a maximal level of 5–8 METs for most cardiac rehabilitation participants, and was encouraged to exercise on their own (1–3 times per week) in between sessions. Although compliance with formal rehabilitation and exercise sessions was assessed, but not record compliance with home exercise frequency or duration.	Supervised	Control group participated in no exercise prescription.
Munk et al., 2011	Aerobic (bicycle or running)	3	6 months	Aerobic exercise consisted of a warm-up period, followed by four 4-minute intervals at 80–90% of maximal heart rate, when patients were riding an ergometric bicycle or were running, 3 times a week for 1 h. Intervals were interrupted by 3 min of active recovery at 60–70% of maximal heart rate. Afterwards, there were 5 min cool-down, 10 min abdominal- and spine-resistance exercises, and 5 min of stretching and relaxing.	Supervised	Control group received usual care.
Myers et al., 2010	Concurrent (treadmill, cycling, stair climbing, elliptical training and rowing)	3	12 months	Exercise sessions included treadmill, cycle ergometry, stair climbing, elliptical training, and rowing 3 times weekly for 45 min followed by 10 min of resistance exercise. The initial intensity target was 60% of heart rate reserve estimated from baseline testing, increasing to 80% as tolerated.	Supervised	Control group received usual care.
Niebauer et al., 2005	Concurrent (calisthenics and bicycle)	5	8 weeks	Exercise training consisted of at least 5 days a week of a combination of calisthenics and bicycle ergometry,	Supervised	Control group was without exercise intervention.

(*continued on next page*)

Table 3 (*continued*)

Source, yr	Exercise group					Control group
	Type	Frequency (days/ week)	Follow-up (Duration)	Training protocol	Supervised or Unsupervised	
				performed at home. Participants were asked to do the first nine exercises in the Canadian airforce XBX program (physical fitness program). Participants were loaned a bicycle ergometer and asked to exercise on it for 20 min a day. They were asked to warm up by pedaling at a work load of 25 W at 50 rev/min for 3 min and then to increase the resistance until their pulse rate was between 70% and 80% of the maximum pulse rate achieved on their initial maximal treadmill test. They then pedaled at 50 rev/min for 20 min before decreasing the resistance to 25 W to cool down for 2–3 min.		
Parrinello et al., 2010	Aerobic (walking)	5	10 weeks	Aerobic group performed an aerobic physical training program consisting in mild–moderate walking exercise for 30 min over the usual physical activity.	Supervised	Control group continued their medical therapy and dietary recommendations with routine activities.
Pierce et al., 2008	Aerobic (walking)	7	12 weeks	Aerobic training began with 30 min of continuous treadmill walking and progressed to 35–40 min as tolerated after the initial 4 weeks. Exercise intensity was progressed to an RPE in the 12–14 Borg scale range 'as tolerated' by each participant.	Supervised	Control group received standard of medical care, which included encouragement to engage in regular walking, but they did not participate in 'supervised' exercise training.
Prescott et al., 2009	Concurrent walking, cycling, step machine, and step board + weight training)	2	8 weeks	Concurrent group was performed 1.5-h training session comprised of 20 min warm-up period followed by four 6-min series of aerobic training (walking, cycling, step machine, and step board) and two posts of resistance endurance exercises (leg press and exercises with rubber bands for quadriceps, gluteus/ hamstring region, and arms; three sets of 20 repetitions with each arm/leg). Each patient's training intensity was adjusted to achieve 70–80% of peak oxygen consumption, corresponding to 4–5 on the Modified Borg Scale [range 0 (no breathlessness at all) to 10 (maximal breathlessness)].	Supervised	Control group received usual care
Pullen et al., 2008	Aerobic (yoga)	2	8 weeks	Aerobic group performed a 10-minute warm-up phase, a 40-minute period of standing or seated yoga postures (Asanas), and finally a 20-minute relaxation phase including breathing exercises (pranayama) and meditation.	Supervised	Control group received standard medical therapy.
Racca et al., 2020	Aerobic (cycling)	5	3 weeks	Aerobic group started a standardized therapy protocol of supervised physical training with five daily sessions of cycling for 3 weeks until the discharge. Each session was performed at 70% maximal heart rate for at least 30 min. The sessions duration increased by ten minutes every three days, up to 50 min twice a day.	Supervised	Control group participated in no intervention.
Ranković et al., 2009	Aerobic (treadmill, bicycle or walking)	3	6 weeks	Aerobic training consisted of continual aerobic exercise for 45 min on a treadmill, room bicycle or walking. The intensity of physical exercise was limited to the submaximal physical capacity at the level of 70–80% of maximal heart frequency at the stress test.	Supervised	Control group participated in no exercise intervention.
Redwine et al., 2020-a	Aerobic (Tai Chi)	2	16 weeks	Aerobic group performed Tai Chi Chuan movements (Yang–Style Short Form–First Third) for 60 min per session with warm-up and was also asked to practice at home for 10–20 min per day on non-class days. Participants were	Supervised	Control group as usual care group did not take part in an intervention.

(*continued on next page*)

Table 3 (*continued*)

Source, yr	Exercise group					Control group
	Type	Frequency (days/ week)	Follow-up (Duration)	Training protocol	Supervised or Unsupervised	
				asked to exercise at an intensity using the Borg ratings of perceived exertion (RPE) of 11–13 ("fairly light" to "somewhat hard").		
Redwine et al., 2020-b	Resistance (resistance band)	2	16 weeks	Resistance group performed resistance band exercises (Upper back, Tricep extension, Bicep curl, Chest press, Internal obliques, Standing hip abduction, Standing hip extension, Seated leg extension, Bent over rows, Lateral rows) with 8—10 repetitions on each side) as well as warm-up and stretching exercises and was also asked to practice at home for 10–20 min per day on non-class days. Participants were asked to exercise at an intensity using the Borg ratings of perceived exertion (RPE) of 11–13 ("fairly light" to "somewhat hard").	Supervised	Control group as usual care group did not take part in an intervention.
Shin et al., 2006	Aerobic (treadmill or bicycle)	3	14 weeks	Aerobic training consisted of a warm-up period, 30–40 min on a treadmill or bicycle ergometer, and a cool-down period. The exercise intensity of the first stage was increased progressively from 50% to 85% of VO2max determined by symptom-limited treadmill exercise.	Supervised	Control group received usual clinical care by their physicians.
Tisi et al., 1997	Aerobic (active and passive leg exercises + walking)	7	12 months	Aerobic exercise consisted of a series of active and passive leg exercises performed to the limit of claudication pain. Patients were encouraged to exercise for at least 45 min every day at home, in addition to daily walks of at least 1 mile.	Supervised	Control group participated in no exercise intervention.
Trippel et al., 2017	Concurrent (bicycle + weight training)	3	12 weeks	Concurrent group performed supervised structured endurance/resistance exercise training on top of usual care. The first 4 weeks of training are exclusively endurance training on a bicycle ergometer. Patients start endurance training at 50% peakVO2 in the first 2 weeks and increase intensity up to 70% peak VO2 after 1-month including 10 min for warm-up and cool-down, exercise volume of endurance training increases from 30 min in the first 2 weeks to 60 min after 3 month. After the initial 4 weeks, resistance training is included into a minimum of two of the three training sessions per week, which was performed as a set of seven exercises on weight-training machines to work out the major muscle groups. Each exercise consists of 12–15 repetitions and is performed at 60% of one-repetition-maximum (1-RM) with one repetition lasting 3 s; 1-RM testing is performed regularly. After 3 months of intervention, patients increase resistance training to two sets, allowing 90 s of rest between set.	Supervised	Control group received usual care.
Tsarouhas et al., 2011	Aerobic (walking)	5	12 weeks	Aerobic group performed walking at 40% of HRmax for 10 min progressing to reach 40 min at 60% of HRmax.	Unsupervised	Control group received usual care.
Walther et al., 2008	Aerobic (bicycling)	Unknown	24 months	Aerobic group performed daily bicycling without any supervision.	Unsupervised	Control group received usual care and percutaneous intervention (PCI).
Yeh et al., 2011	Aerobic (Tai Chi)	2	12 weeks	Aerobic group was performed 1-hour tai chi exercises, twice weekly for 12 weeks by standard protocol of a pilot trial in patients with heart failure.	Supervised	Control group patients received time-matched education without exercise intervention.

Model	Study name	Subgroup within study	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Adamopoulos et al., 2002	Aerobic	-0.668	0.311	0.097	-1.277	-0.058	-2.147	0.032
	Balen et al., 2008	Aerobic	0.136	0.258	0.067	-0.370	0.643	0.527	0.598
	Byrkjeland et al., 2011	Aerobic	-0.002	0.224	0.050	-0.440	0.436	-0.009	0.993
	Conraads et al., 2002	Concurrent	-0.301	0.316	0.100	-0.921	0.320	-0.950	0.342
	de Meirelles et al., 2014	Concurrent	-0.627	0.374	0.140	-1.360	0.106	-1.676	0.094
	Erbs et al., 2010	Aerobic	-0.484	0.348	0.121	-1.166	0.198	-1.391	0.164
	Feiereisen et al., 2013-a	Aerobic	-0.365	0.368	0.136	-1.087	0.356	-0.992	0.321
	Feiereisen et al., 2013-b	Concurrent	-0.468	0.370	0.137	-1.194	0.257	-1.266	0.206
	Feiereisen et al., 2013-c	Resistance	-0.504	0.371	0.138	-1.231	0.223	-1.359	0.174
	Fernandes-Silva et al., 2017	Aerobic	-0.042	0.313	0.098	-0.656	0.573	-0.133	0.894
	Gielen et al., 2012-a	Aerobic	-0.039	0.365	0.133	-0.755	0.677	-0.107	0.915
	Gielen et al., 2012-b	Aerobic	0.000	0.365	0.133	-0.716	0.716	0.000	1.000
	Karavidas et al., 2006	Resistance	-0.598	0.442	0.195	-1.463	0.267	-1.355	0.176
	Kim et al., 2008	Aerobic	-0.522	0.371	0.138	-1.250	0.206	-1.406	0.160
	Larsen et al., 2001	Aerobic	-0.195	0.314	0.099	-0.810	0.421	-0.620	0.536
	Linke et al., 2005	Aerobic	-0.321	0.420	0.176	-1.144	0.502	-0.764	0.445
	Melo et a;., 2019-b	Aerobic	-0.493	0.444	0.197	-1.363	0.376	-1.113	0.266
	Melo et al., 2019-a	Aerobic	-0.142	0.505	0.255	-1.131	0.847	-0.281	0.779
	Munk et al., 2011	Aerobic	0.138	0.334	0.111	-0.516	0.792	0.414	0.679
	Niebauer et al., 2005	Concurrent	-0.387	0.412	0.169	-1.194	0.420	-0.940	0.347
	Pierce et al., 2008	Aerobic	-15.235	2.929	8.581	-20.976	-9.494	-5.201	0.000
	Prescott et al 2009	Concurrent	0.103	0.306	0.094	-0.496	0.703	0.338	0.735
	Racca et al., 2020-a	Aerobic	0.336	0.315	0.099	-0.281	0.953	1.066	0.286
	Racca et al., 2020-b	Aerobic	0.099	0.325	0.106	-0.538	0.736	0.305	0.760
	Racca et al., 2020-c	Aerobic	0.125	0.386	0.149	-0.630	0.881	0.325	0.745
	Redwine et al., 2020-a	Aerobic	2.634	0.456	0.207	1.742	3.527	5.783	0.000
	Redwine et al., 2020-b	Resistance	2.504	0.466	0.217	1.591	3.418	5.373	0.000
	Trippel et al., 2017	Concurrent	-0.267	0.277	0.076	-0.809	0.275	-0.967	0.333
	Tsarouhas et al., 2011	Aerobic	-0.276	0.348	0.121	-0.959	0.406	-0.793	0.428
	Yeh et al., 2011	Aerobic	0.167	0.200	0.040	-0.226	0.559	0.832	0.405
Fixed			-0.055	0.062	0.004	-0.176	0.066	-0.897	0.370
Random			-0.061	0.127	0.016	-0.310	0.187	-0.485	0.627

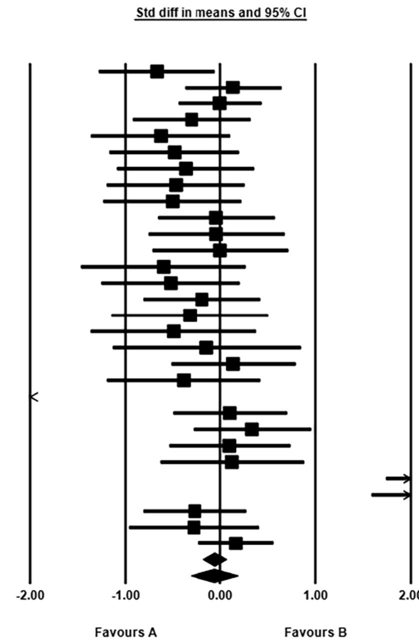

Fig. 2. Forest plot of the impacts of exercise interventions on TNF-alpha. Data are standardized mean difference (SMD) and 95% confidence intervals (95% CIs). (Favours A = exercise and Favours B = control).

article with acute exercise interventions (n = 39), and (j) articles without enough information (n = 6). Two articles included two arms of exercise intervention [25,26]. Two articles included three arms of exercise intervention [27,28] and six articles included two arms of exercise intervention [10,17,25,26,29,30]. A total of 46 full-text articles (57 intervention arms), 10 concurrent intervention arms, three resistance intervention arms, and 44 aerobic intervention arms were included. A total of 3693 participants including exercise groups (n = 2141) and control groups (n = 1552) were included. The flowchart of study selection is shown in Fig. 1.

3.2. Participant characteristics

The participant characteristics of included studies are illustrated in

Model	Study name	Subgroup within study	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Adamopoulos et al., 2002	Aerobic	-0.435	0.306	0.094	-1.035	0.165	-1.420	0.156
	Byrkjeland et al., 2011	Aerobic	0.153	0.224	0.050	-0.286	0.591	0.681	0.496
	Conraads et al., 2002	Concurrent	0.378	0.317	0.101	-0.244	1.001	1.192	0.233
	de Meirelles et al., 2014	Concurrent	-0.140	0.366	0.134	-0.857	0.576	-0.384	0.701
	Eleuteri et al., 2013	Aerobic	0.147	0.438	0.191	-0.710	1.005	0.337	0.736
	Feiereisen et al., 2013-a	Aerobic	-0.447	0.370	0.137	-1.171	0.278	-1.209	0.227
	Feiereisen et al., 2013-b	Concurrent	-0.616	0.374	0.140	-1.348	0.117	-1.648	0.099
	Feiereisen et al., 2013-c	Resistance	-0.545	0.372	0.138	-1.274	0.184	-1.466	0.143
	Ferrandes-Silva et al., 2017	Aerobic	-0.097	0.314	0.098	-0.712	0.518	-0.309	0.757
	Fu et al., 2013-a	Aerobic	-0.494	0.481	0.231	-1.436	0.449	-1.027	0.304
	Fu et al., 2013-b	Aerobic	-0.262	0.482	0.233	-1.207	0.683	-0.544	0.587
	Karavidas et al., 2006	Resistance	-0.129	0.433	0.188	-0.978	0.721	-0.297	0.766
	Kim et al., 2008	Aerobic	-0.158	0.367	0.135	-0.877	0.562	-0.429	0.668
	Kobayashi et al., 2003	Aerobic	-0.105	0.378	0.143	-0.846	0.636	-0.277	0.782
	Larsen et al., 2001	Aerobic	0.039	0.313	0.098	-0.575	0.654	0.126	0.900
	Mc Dermott et al., 2004	Aerobic	-0.454	0.399	0.159	-1.236	0.328	-1.138	0.255
	Melo et al., 2019-a	Aerobic	0.373	0.508	0.258	-0.624	1.369	0.733	0.464
	Melo et al., 2019-b	Aerobic	-0.839	0.456	0.208	-1.732	0.054	-1.842	0.066
	Munk et al., 2011	Aerobic	-0.302	0.335	0.112	-0.959	0.355	-0.901	0.367
	Niebauer et al., 2005	Concurrent	0.333	0.411	0.169	-0.472	1.138	0.810	0.418
	Pierce et al., 2008	Aerobic	-0.957	0.570	0.324	-2.073	0.159	-1.681	0.093
	Prescott et al 2009	Concurrent	-0.131	0.306	0.094	-0.731	0.469	-0.428	0.669
	Pullen et al., 2008	Aerobic	-0.771	0.476	0.227	-1.704	0.163	-1.619	0.106
	Racca et al., 2020-a	Aerobic	-0.821	0.322	0.104	-1.452	-0.189	-2.547	0.011
	Racca et al., 2020-b	Aerobic	-0.966	0.339	0.115	-1.631	-0.300	-2.845	0.004
	Racca et al., 2020-c	Aerobic	-0.477	0.391	0.153	-1.242	0.289	-1.221	0.222
	Redwine et al., 2020-a	Aerobic	0.378	0.336	0.113	-0.281	1.037	1.125	0.261
	Redwine et al., 2020-b	Resistance	-0.071	0.350	0.122	-0.756	0.615	-0.203	0.839
	Shin et al., 2006-a	Aerobic	-0.390	0.412	0.170	-1.197	0.418	-0.946	0.344
	Shin et al., 2006-b	Aerobic	0.097	0.414	0.172	-0.715	0.909	0.234	0.815
	Trippel et al., 2017	Concurrent	-0.037	0.275	0.076	-0.577	0.503	-0.136	0.892
Fixed			-0.205	0.065	0.004	-0.332	-0.078	-3.171	0.002
Random			-0.211	0.068	0.005	-0.345	-0.077	-3.087	0.002

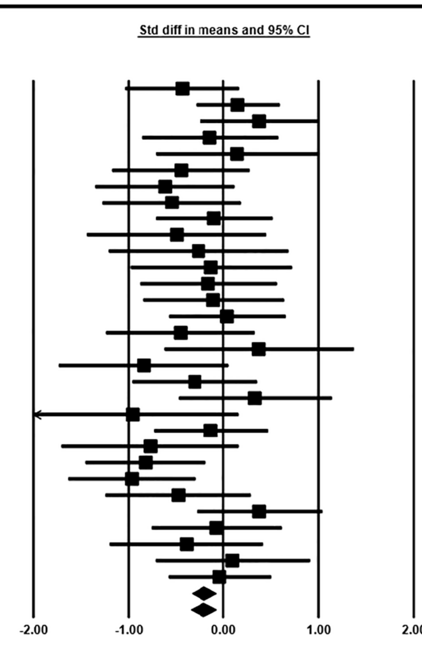

Fig. 3. Forest plot of the impacts of exercise interventions on IL-6. Data are standardized mean difference (SMD) and 95% confidence intervals (95% CIs). (Favours A = exercise and Favours B = control).

Model	Study name	Subgroup within study	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Butts et al., 2018	Aerobic	-0.371	0.300	0.090	-0.959	0.217	-1.236	0.216
	Kim et al., 2008	Aerobic	-0.019	0.367	0.134	-0.738	0.700	-0.052	0.959
	Linke et al., 2005	Aerobic	0.018	0.417	0.174	-0.800	0.836	0.043	0.966
	Racca et al., 2020-a	Aerobic	0.163	0.314	0.098	-0.452	0.778	0.520	0.603
	Racca et al., 2020-b	Aerobic	0.104	0.325	0.106	-0.533	0.741	0.319	0.750
	Racca et al., 2020-c	Aerobic	1.273	0.422	0.178	0.445	2.100	3.014	0.003
	Trippel et al., 2017	Concurrent	-0.441	0.278	0.077	-0.986	0.105	-1.584	0.113
Fixed			-0.001	0.127	0.016	-0.249	0.247	-0.009	0.993
Random			0.054	0.193	0.037	-0.324	0.431	0.279	0.780

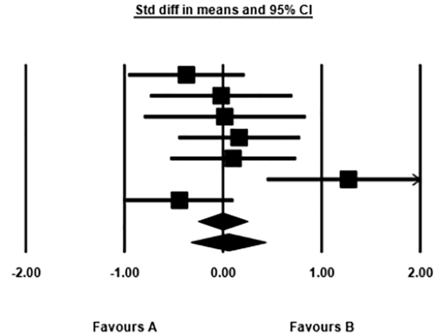

Fig. 4. Forest plot of the impacts of exercise interventions on IL-1 beta. Data are standardized mean difference (SMD) and 95% confidence intervals (95% CIs). (Favours A = exercise and Favours B = control).

Table 2. Total sample sizes including 3693 participants (exercise groups = 2141 and control groups = 1552) were included in our systematic review and *meta*-analysis. The sample size, mean age, and BMI for each original research ranged between 14 and 928 participants [31,32], 48 ± 7 and 77.5 ± 6.5 yrs [33,28], and between 25 and 33 ± 8 kg/m^2 [31,17], respectively. A total of 46 included articles, 39 articles were included both male and female genders, six articles were included only male gender [34–39], and two articles in terms of gender were unknown [27,40].

3.3. Study characteristics in exercise and control groups

The study characteristics in exercise and control groups are illustrated in Table 3. Types of exercise interventions including concurrent training [5,10,13–16,27,41,42], resistance training [12,17,27], and aerobic exercise [10,11,17,25–40,43–60] were studies included. The intensity ranges for concurrent exercises were performed from 40% VO2peak plus 40% of (one-repetition maximum) 1RM [10] to 100% of 10RM [16]. The intensity ranges for aerobic exercises were performed from 40% (VO2peak, HRmax, HRmax reserve) [10,47,59] to 95% HRmax [52], with the most common exercise intensity 60–75% VO2peak, HRmax and/or HRmax reserve [10,11,26–29,32, 35,38,43,45,50,59]. The intensity ranges for resistance exercises were performed from 60% of 1RM [27] to 75% of 1RM [27], with the most common exercise intensity 60–75% of 1RM. [27].

The duration of exercise training protocols was varied from 3 weeks [28,43] to 24 months [39], with the most common period of 3 months (12 weeks) [11,13,25,31–37,40,48,51,53,59,60,61]. The exercise frequency was performed from 2 [17,42,44,46,52,56,60] to 7 [16,31,58] day/week, with the most common exercise frequency of 3 day/week [10,11,13–15;25,27,29,30,32,33,36–38,41,43,45,48–51,53,54,57,61] . The duration per session for concurrent exercises was consisted of 20–30 min [16] to 120 min [13], with the most common session duration of 60 min [10,15,41]. The session duration per session for resistance exercises was consisted of 30 min [12] to 60 min [17], with the most common session duration of 30–60 min [12,17,27]. The duration per session for aerobic exercises was consisted of 20 min [26,35] to 70 min [56], with the most common session duration of 30–45 min [10,11,25,27,29,30–34,36,37,40,43,45,46,48,50,51,55,57,58,59]. The exercise sessions and participants were supervised in 43 included studies, unsupervised in two studies [39,59], and unknown in one study [40].

The control group-related characteristics were considered optimal medical therapy, usual care or standard therapy,[14,17,26,29–33,39, 41–44,46,50,51,52,54–56,59,61] without exercise interventions, [5,27,28,34–38,48,49,53,57,58] general home-based health care,[25] home-based exercise,[40] general activity exercises,[45,47] time-matched education,[60] age- and gender matched patients,[15] pamphlet for daily exercising at home,[10] received education and flexibility and stretching exercises,[11] aerobic plus resistance trainings similar to exercise group at only 10% of their exercise,[13] functional electrical stimulation,[12] and sham-inspiratory muscle training at an initial workload of 10 cmH2O.[16].

3.4. Inflammaging markers

In this systematic review and *meta*-analysis, inflammaging markers in patients with HF including plasma or serum levels of TNF-α in 24

Model	Study name	Subgroup within study	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Balen et al., 2008	Aerobic	-0.383	0.261	0.068	-0.894	0.128	-1.470	0.142
	Munk et al., 2011	Aerobic	-1.174	0.361	0.130	-1.882	-0.467	-3.254	0.001
	Racca et al., 2020-a	Aerobic	0.265	0.311	0.097	-0.345	0.875	0.853	0.394
	Racca et al., 2020-b	Aerobic	-0.135	0.322	0.104	-0.766	0.497	-0.418	0.676
	Raccas et al., 2020-c	Aerobic	-0.156	0.383	0.147	-0.907	0.596	-0.406	0.685
Fixed			-0.290	0.143	0.020	-0.570	-0.011	-2.036	0.042
Random			-0.304	0.225	0.051	-0.745	0.137	-1.349	0.177

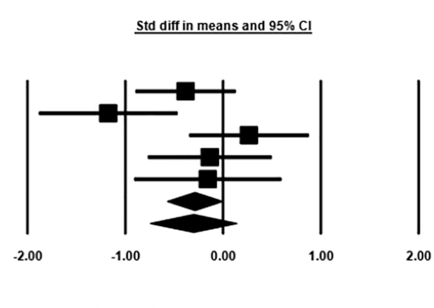

Fig. 5. Forest plot of the impacts of exercise interventions on IL-8. Data are standardized mean difference (SMD) and 95% confidence intervals (95% CIs). (Favours A = exercise and Favours B = control).

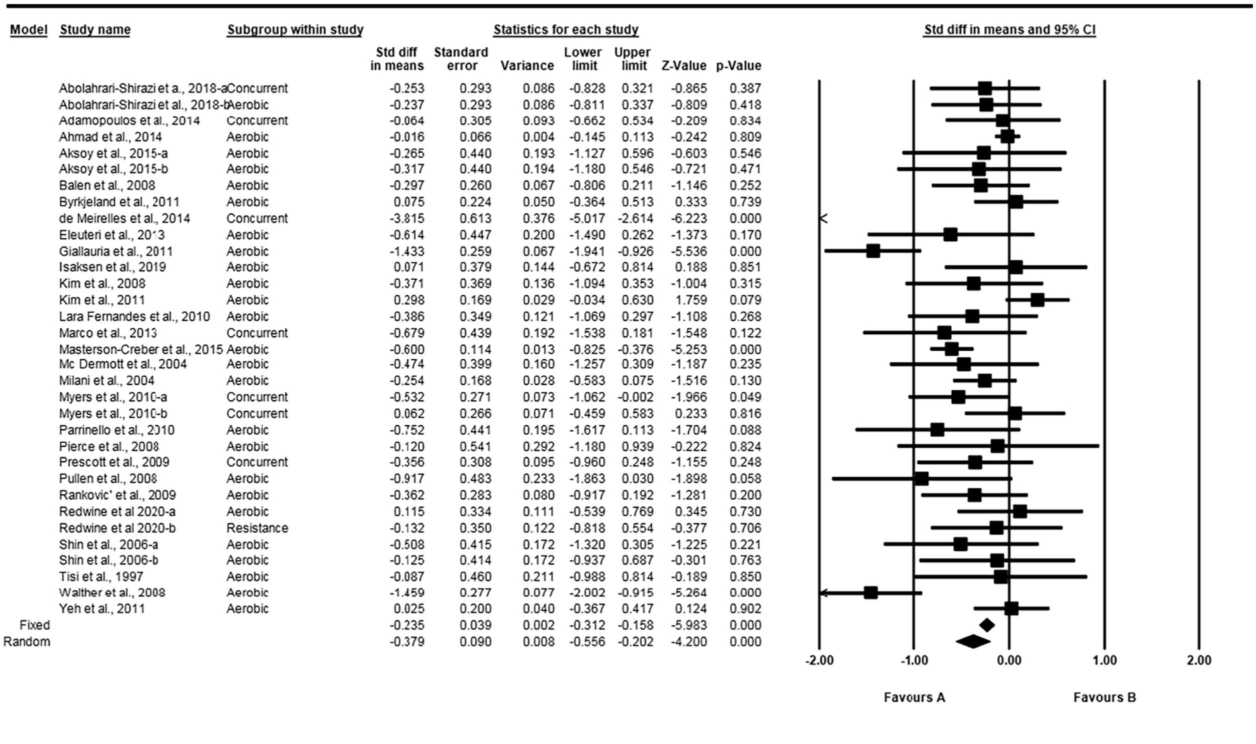

Fig. 6. Forest plot of the impacts of exercise interventions on hs-CRP. Data are standardized mean difference (SMD) and 95% confidence intervals (95% CIs). (Favours A = exercise and Favours B = control).

articles, [5,12,14,15,17,26–28,31,33,35,37,38,40,42–44,46,52,54,59,60,61] IL-1- beta in 5 articles,[11,28,38,46,61] IL-6 in 23 articles,[5,12,14,15,17,25,27,28,30,31,33,34,37,39,40,42,44,46,48,51,52,54,56,61] IL-8 in 3 articles,[28,43,54] and hs-CRP in 28 articles[10,13,14,16,17,29,30–32,34,36,39,41–47,49–51,54–58,60] were measured.

4. Meta-analysis

4.1. TNF-α

According to 30 exercise intervention arms compared to the control group, exercise intervention did not significantly change for TNF-α values [SMD −0.061 and 95% CI: −0.310 to 0.187, p = 0.627] (Fig. 2). There was a significant heterogeneity, thereby I-squared was more than 50% (I-squared = 74.65%, P = 0.001). Analysis of subgroup by age, type of exercise and mean left ventricular ejection fraction (LVEF) revealed that there was a significant reduction in TNF-α marker for middle aged [SMD −0.421 and 95%CI: −0.803 to −0.039, p = 0.031], concurrent training [SMD −0.288 and 95%CI: −0.555 to −0.022, p = 0.033] and HFrEF [SMD −0.261and 95%CI: −0.452 to −0.070, p = 0.007] compared to the control group, whereas aerobic and resistance exercises did not show significant changes in TNF-α [SMD −0.044 and 95%CI:-0.331 to 0.242, p = 0.761] and [SMD 0.455 and 95% CI: −1.443 to

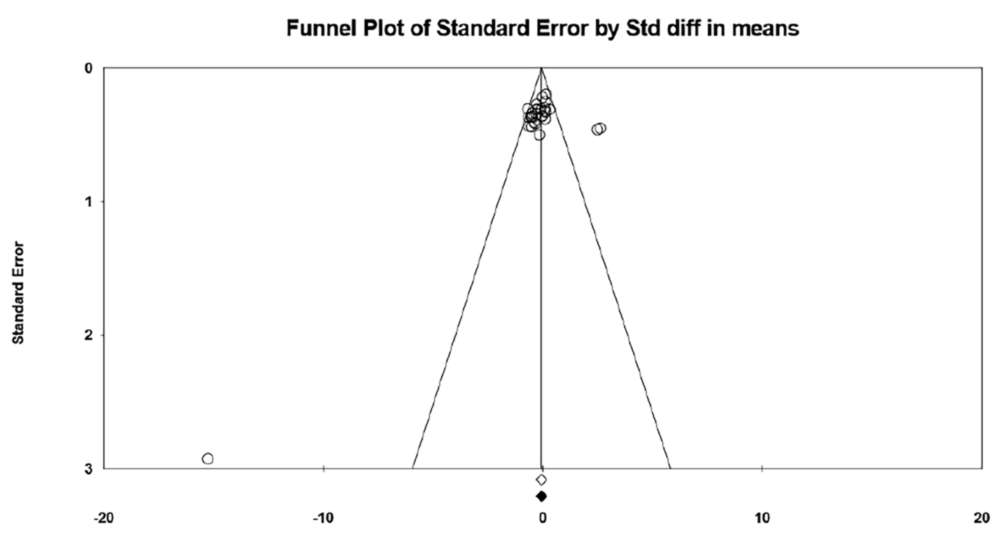

Fig. 7. Funnel plot for TNF-alpha marker.

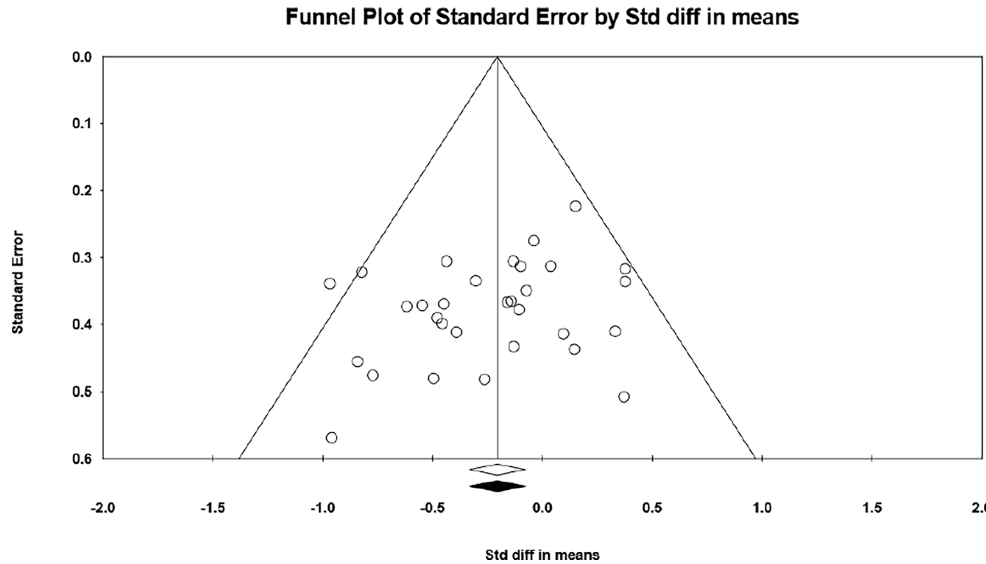

Fig. 8. Funnel plot for IL-6 marker.

2.353, p = 0.637], respectively. Subgroup by exercise intensity showed a significant reduction in TNF-α marker for high intensity compared to the control group [SMD −0.243 and 95% CI: −0.413 to −0.072, p = 0.005], whereas subgroup for low and moderate intensities, duration of follow-up, BMI, HFpEF, and LVEF with unknown status did not show significant changes (P greater than 0.05).

4.2. IL-6

According to 31 exercise intervention arms compared to the control group, exercise training intervention significantly reduced IL-6 values [SMD −0.205 and 95% CI: −0.332 to −0.078, p = 0.002] (Fig. 3). There was no significant heterogeneity, thereby I-squared was less than 50% (I-squared = 8.84%, P = 0.326). Analysis of subgroup by age, BMI and type of exercise revealed that there was a significant reduction in IL-6 marker for middle aged [SMD −0.284 and 95% CI: −0.486 to −0.083, p = 0.006], overweight status [SMD −0.359 and 95% CI: −0.550 to −0.167, p = 0.001] and aerobic exercise [SMD −0.258 and 95% CI: −0.411 to −0.105, p = 0.001] compared to control group, whereas resistance and concurrent exercise interventions did not show significant changes for IL-6 [SMD 0.251 and 95% CI: −0.682 to 0.179, p = 0.253] and [SMD −0.030 95% CI: −0.296 to 0.236, p = 0.826], respectively. Subgroup by exercise intensity showed a significant reduction in IL-6 marker for high intensity [SMD −0.185 and 95% CI: −0.359 to −0.012, p = 0.037] and moderate intensity [SMD −0.210 and 95% CI: −0.405 to −0.015), p = 0.034] compared to the control group. Subgroup by duration of follow-up showed a significant reduction in IL-6 marker for short-term duration [SMD −0.301 and 95% CI: −0.469 to −0.131, p = 0.001] compared to the control group, whereas subgroup for long-term duration did not show significant changes [SMD −0.084 and 95% CI: −0.276 to 0.109, p = 0.394].

Subgroup by mean LVEF showed a significant reduction in IL-6 marker for heart failure with preserved ejection fraction (HFpEF) compared to the control group, whereas other mean LVEF subgroups did not show significant changes [HFmrEF (p = 0.847), HFrEF (p = 0.081), and unknown (p = 0.058)].

4.3. IL-1-beta

According to seven exercise intervention arms compared to the

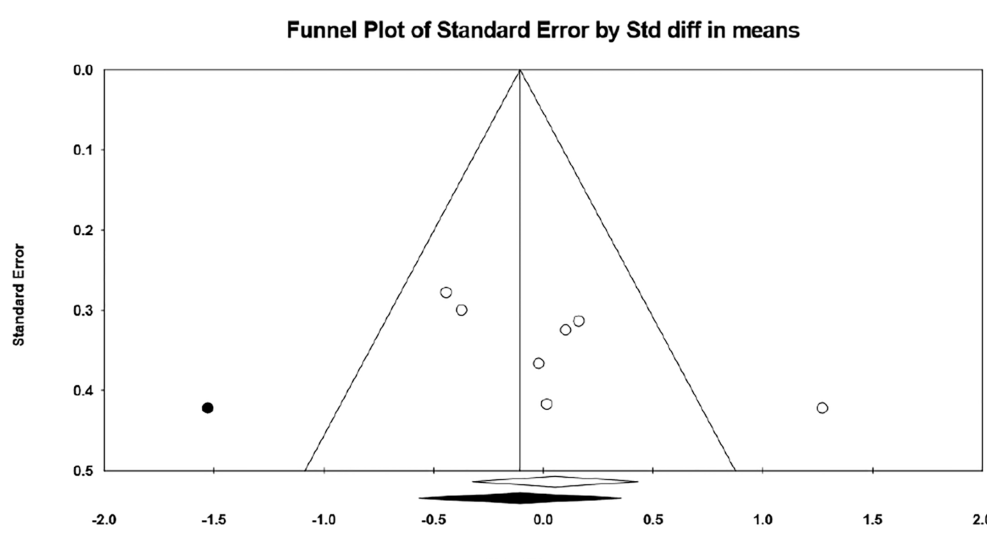

Fig. 9. Funnel plot for IL-1 beta marker.

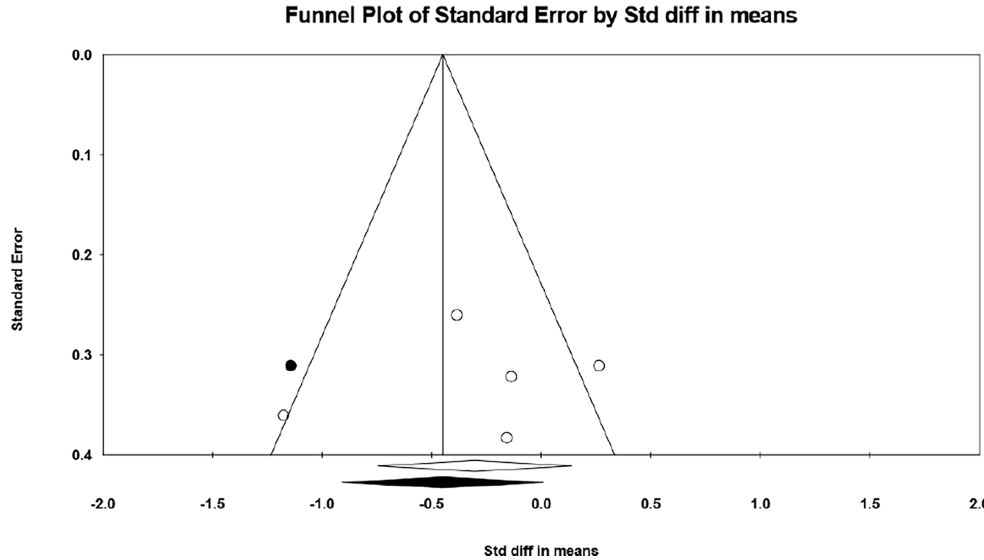

Fig. 10. Funnel plot for IL-8 marker.

control group, exercise intervention did not significantly change IL-1-beta values [SMD 0.054 and 95% CI: −0.324 to 0.431, p = 0.780] (Fig. 4). Heterogeneity analysis showed that there was a significant heterogeneity, thereby I-squared was more than 50% (I-squared = 55.542%, P = 0.036). Subgroup by type of exercise revealed that there was no significant difference in IL-1-beta for aerobic exercise compared to the control [SMD 0.113 and 95% CI: −0.165 to 0.392, p = 0.425]. In addition, subgroup by age, BMI, exercise intensity, duration of follow-up as well as mean LVEF did not show significant changes (P greater than 0.05).

4.4. IL-8

According to five exercise intervention arms compared to the control group, aerobic exercise did not significantly change IL-8 values [SMD −0.304 and 95% CI: −0.745 to 0.137, p = 0.177] (Fig. 5). Heterogeneity analysis showed that there was a significant heterogeneity, thereby I-squared was more than 50% (I-squared = 58.640%, P = 0.046). Subgroup analysis by age, BMI, type, intensity, duration of exercise and mean LVEF did not show significant changes for IL-8 (P greater than 0.05).

4.5. hs-CRP

According to 33 exercise intervention arms compared to the control group, exercise intervention significantly reduced hs-CRP [SMD −0.379 and 95% CI: −0.556 to −0.202, p = 0.001] (Fig. 6). Heterogeneity analysis showed that there was a significant heterogeneity, thereby I-squared was more than 50% (I-squared = 73.638%, P = 0.001). Analysis of subgroup by age, BMI, type of exercise and mean LVEF revealed that there was a significant reduction in hs-CRP for middle aged [SMD −0.455 and 95% CI: −0.762 to −0.149, p = 0.004], elderly-age [SMD −0.342 and 95% CI: −0.576 to −0.108, p = 0.001], overweight [SMD −0.464 and 95% CI: −0.681 to −0.247, p = 0.001], aerobic exercise [SMD −0.341 and 95% CI: −0.528 to −0.154, p = 0.001] and concurrent training [SMD −0.659 and 95% CI: −1.259 to −0.059, p = 0.031] compared to the control. Subgroup by exercise intensity showed a significant reduction in hs-CRP for both high [SMD −0.460 and 95% CI: −0.837 to −0.084, p = 0.017] and moderate intensities compared to the control group [SMD −0.275 and 95% CI: −0.439 to −0.112, p = 0.001].

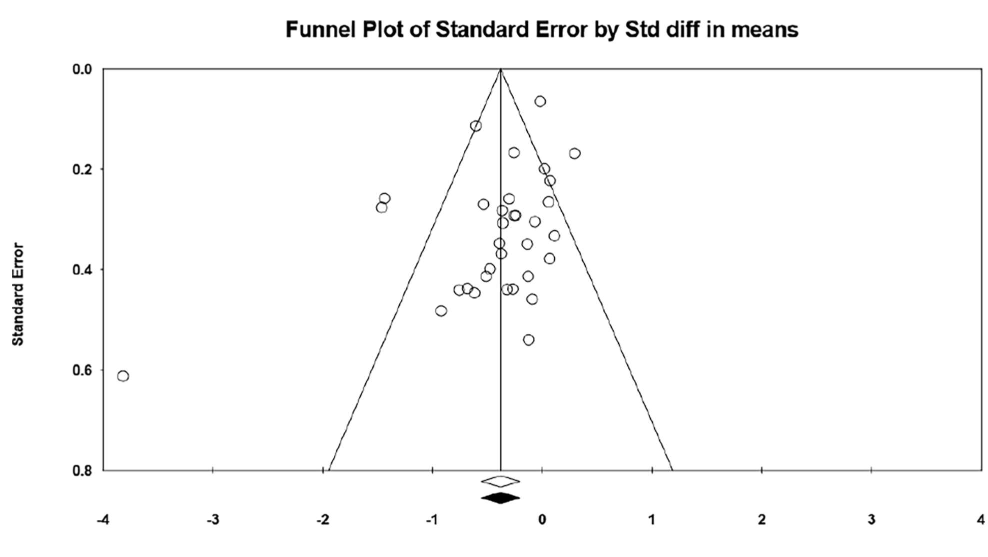

Fig. 11. Funnel plot for hs-CRP marker.

Subgroup by duration of follow-up showed a significant reduction in hs-CRP for three durations of short-term [SMD −0.125 and 95% CI: −0.222 to −0.029, $p = 0.011$], long-term [SMD −0.535 and 95% CI: −1.068 to −0.001, $p = 0.049$] and very long-term [SMD −0.555 and 95% CI: −1.005 to −0.104, $p = 0.016$] compared to the control group. Subgroup by mean LVEF showed a significant reduction in hs-CRP for heart failure with reduced ejection fraction (HFrEF) [SMD −0.389 and 95% CI: −0.645 to −0.134, $p = 0.003$] and heart failure with mildly reduced ejection fraction (HFmrEF) [SMD −0.450 and 95% CI: −0.896 to −0.003, $p = 0.048$] compared to the control group.

4.6. Quality assessment and publication bias

The quality assessment of included studies for Pedro scores ranged 7–15 with maximum 15 scores (high risk of bias = Pedro score of less than 5; excluded articles) is illustrated in Table 1. The visual interpretation of funnel plot and Egger's test were used to assess the publication bias. The visual interpretation of funnel plot showed a symmetric distribution (i.e., publication bias was not present) for TNF-α (Fig. 7), which Egger's test was also carried out to confirm this symmetry at a non-significance level ($p = 0.201$). The visual interpretation of funnel plot showed an asymmetric distribution (i.e., publication bias was present) for IL-6 (Fig. 8), which Egger's test was also carried out to confirm this asymmetry at a significance level ($p = 0.085$). The visual interpretation of funnel plot showed an asymmetric distribution (i.e., publication bias was present) for IL-1-beta (Fig. 9), which Egger's test was also carried out to confirm this asymmetry at a significance level ($p = 0.058$). The visual interpretation of funnel plot showed symmetry (i.e., publication bias was not present) for IL-8 (Fig. 10), which Egger's test was also carried out to confirm this symmetry at a non-significance level ($p = 0.750$). The visual interpretation in the funnel plot of hc-CRP showed asymmetry, suggesting that there was a significant publication bias for hs-CRP (Fig. 11). Egger's test for hs-CRP was carried out to confirm this asymmetry, which was confirmed to be significant ($p = 0.028$).

5. Discussion

The effects of aerobic, resistance and concurrent exercises vs. the control group on inflammaging markers in patients with HF were the aims of our systematic review and *meta*-analysis. Our results indicated that exercises of 3-week to 24-month, exercise frequency of 2–7 day/week, intensity ranges 60–80% HRmax, and duration per session 30–60 min significantly reduced hs-CRP, IL-6, and TNF-α values in patients with HF aged 49–77 yrs and overweight status. In other words, our results showed that middle aged, concurrent training and high intensity for reducing TNF-α showed small sized effects ($d = 0.421$, $d = 0.288$ and $d = 0.243$) in patients with HF, respectively. Middle aged, overweight status, aerobic exercise, moderate intensity and short-term duration have small sized effects ($d = 0.284$, $d = 0.359$, $d = 0.258$, $d = 0.210$ and $d = 0.301$) for reducing IL-6 values in patients with HF, respectively. Furthermore, middle aged ($d = 0.455$), elderly aged ($d = 0.342$), overweight status ($d = 0.464$), aerobic training ($d = 0.341$) moderate and high exercise intensities ($d = 0.275$ and $d = 0.460$) have small sized effects and concurrent exercise has a medium ($d = 0.659$) effect size for reducing hs-CRP. Both long-term and very long-term durations have medium ($d = 0.535$ and $d = 0.555$) sized effects for reducing hs-CRP in patients with HF. Therefore, the results of our systematic review and *meta*-analysis confirmed that concurrent and aerobic exercises based on the type, intensity and duration were effective non-pharmacological interventions to improve inflammaging markers including TNF-α, IL-6 and hs-CRP in patients with HF, whereas resistance training only was not an effective exercise intervention. However, our results indicated that exercise interventions were not effective for IL-1-beta and IL-8 markers in overweight or obese patients with HF.

Since cardiomyocytes are an important source of inflammatory markers in heart damage, an increase in cardiac cytokines can reduce cardiac function, especially in patients with HF.[62] The pathophysiology of HF is associated with an increase in pro-inflammatory cytokines, inflammaging and endothelial dysfunction.[62,63] In contrast, exercise is an effective non-pharmacological prescription that can reduce the inflammaging process, and is certainly important in terms of clinical exercise physiology, given that inflammation process plays a major role in the development of many metabolic disorders.[6] These findings suggest that cardiomyocytes-related inflammatory cytokines play important roles in the pathologic and physiologic responses of the heart, especially clinical HF. It is possible that an optimal reduction in inflammation process following exercise intervention resulted in the restore endothelial function, improved neo-angiogenesis, reduced production of inflammatory cytokines, reactive oxygen species, peripheral vascular resistance, and improved cardiac hemodynamic and physiologic responses in HF.[8,64] In other words, a decrease in TNF-α, IL-6 and hs-CRP values following exercise has an anti-inflammaging role in overweight patients with HF, which was observed after aerobic and concurrent interventions in our *meta*-analysis.

Our findings were consistent with the results of Pearson et al.[65], Monteiro-Junior et al.[66], and Hayashino et al.[18] reported that exercise training decreased TNF-α, CRP and IL-6 values in HF, type 2 diabetes mellitus (T2DM) and older persons. In addition, Alizaei-Yousefabadi et al.[67] reported that exercise was effective at lowering CRP and TNF-α values in metabolic syndrome patients. Xing et al.[68] reported that combined exercise had a significant reduction in CRP, IL-6 and TNF-α values in middle aged and older adults with T2DM compared to the control. Huang et al.[69] demonstrated that aerobic exercise has a significant reduction in IL-6 and TNF-α markers in patients with dementia. In contrast, *meta*-analysis studies reported that there was no significant effect between groups (HIIT or exercise training vs. control) in IL-6 and CRP in patients with metabolic disorders,[19] IL-6 and TNF-α in healthy adults.[70] In addition, a *meta*-analysis[71] reported that resistance training was effective in reducing CRP, IL-6 and TNF-α in elderly adults, which differ with the results of our *meta*-analysis. In this regards, the difference in the type of exercise including resistance training in the Kim & Yeun study[71] and healthy participants in the Rose et al. study[70], could explain the inconsistencies reasons with the findings of our *meta*-analysis.

After cardiac dysfunction, the adaptive immune system-induced inflammatory response upregulates cytoprotective responses, and provides the heart with a short-term adaptation to elevated stress and physiological inflammation. However, this acute inflammatory response can become dysregulated inflammatory response and chronic inflammation.[64,72] Chronic inflammation as a main factor of aging process is associated with aging-related pathologic condition.[73] The aging process and pro-inflammatory cytokines are associated with serum insulin,[74] BMI,[6,75] waist circumference,[75] overweight and obesity,[6,74,75] fat-free mass or lean mass[6,76], and visceral fat.[77] The cellular senescence, genetic susceptibility, microbiota composition changes, autophagy dysfunction, oxidative stress, and mitochondrial dysfunction are potential mechanisms of inflammaging process, which lead to the development of metabolic disorders and HF.[78] It seems that the effects of pathologic and physiologic conditions on circulating inflammatory levels and/or inflammaging are contradictory. In other words, acute exercise results showed that circulating levels of inflammatory markers significantly increase immediately after exercise, a reduction on the following day, and return to baseline values within 72-hour.[72] However, the physiologic and pathologic mechanisms of exercise-induced inflammaging responses remain unclear.

The positive physiological adaptations and decreased inflammatory cytokines were reported by concurrent and resistance exercises in HF.[12–14] Since the exercise, especially aerobic and concurrent exercises play important roles in improving myocardial stretch markers, regulated cardiac function and optimal reduced inflammatory cytokines,[74] it is possible that exercise interventions can be considered non-pharmacological interventions in HF, as the results of our *meta*-

analysis were confirmed a reduction in inflammaging markers of TNF-α, IL-6, and hs-CRP in patients with HF. It has been reported that inflammatory cytokines are secreted by cardiomyocytes, adipose tissue, lung epithelial cells, skeletal muscle mass, and obesity. The results of studies demonstrated that exercise interventions lead to a reduction in adipose tissue by decreased expression of toll like receptors (TLRs) on macrophages and monocytes,[6,79] an increase in blood flow to the respiratory and skeletal muscles and improved pulmonary function, maximal oxygen uptake (VO2max) and muscle mass,[9] improved left ventricular ejection fraction and mitochondrial function in HF.[4,9] It is possible that these positive physiological adaptations by aerobic and concurrent training are associated with a reduction in production of pro-inflammatory cytokines such as IL-6, TNF-α, and liver-induced CRP in patients with HF, as demonstrated in our *meta*-analysis. In addition, reduced hs-CRP, IL-6, and TNF-α by aerobic and concurrent interventions with moderate and high exercise intensities as well as short, long and very long-term follow-ups may down-regulate the inflammaging process in both cardiomyocytes and fibroblasts in HF.[65,80] The down-regulation of inflammatory markers of hs-CRP, IL-6, and TNF-α and inflammaging is evidence of the anti-inflammatory properties of aerobic and concurrent interventions in patients with HF.[4,6,80] Based on the exercise protocol, optimal protocol and intensity, frequency and duration of exercise interventions are related to the release of cardiac inflammatory markers and/or inflammaging[4,72] although differential effects of exercise interventions on inflammatory responses as well as inflammaging process in patients with HF are not fully understood.

5.1. Limitations and strengths

The lack of association between resistance training and IL-1β and IL-8 markers or concurrent training and IL-8, low number of included original articles based on subgroup by obesity status and type of exercise, and heterogeneity & publication bias according to the data were limitations in this *meta*-analysis. In contrast, strengths of our *meta*-analysis are as follow: subgroup *meta*-analyses of age, BMI, type of exercise, exercise intensity, follow-up of exercise and mean LVEF in patients with HF.

6. Conclusions

In conclusion, our *meta*-analysis confirmed that exercise training, especially aerobic and concurrent interventions (based on the type, intensity and duration of exercise) in middle aged, elderly aged and overweight status were effective to reduce (improve) inflammaging markers of TNF-α, IL-6, and hs-CRP, which these exercise-related anti-inflammaging responses were observed across ages (middle-aged and elderly-aged), exercise intensities, duration follow-ups, and mean LVEFs (HFrEF, HFmrEF and HFpEF) in overweight patients with HF.

Our *meta*-analysis have significant clinical implications for patients with HF. The association of specific exercise protocols in patients with HF appear to modify the inflammaging process through reduced inflammatory markers of TNF-α, IL-6, and hs-CRP in the published clinical studies. Future work should explore how exercise interventions, aging, and BMI modify inflammaging process and inflammation in humans. Exercise intervention comes in various forms, therefore knowing the principle of exercise provides a more optimized exercise prescription for patients with HF through down-regulation of the inflammaging process and inflammation. Therefore, exercise prescription has an anti-inflammaging effect, which these exercise-related anti-inflammaging properties as clinical benefits in general and exercise-based cardiac rehabilitation, in a more specific format, improve clinical evolution and survival in patients with HF of different etiologies.[81].

Funding

None. This systematic review and *meta*-analysis did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors are grateful to the corresponding authors et al. included original articles in our systematic review & meta-analysis.

References

[1] C. Franceschi, P. Garagnani, P. Parini, C. Giuliani, A. Santoro, Inflammaging: a new immune-metabolic viewpoint for age-related diseases, Nat. Rev. Endocrinol. 14 (10) (2018) 576–590, https://doi.org/10.1038/s41574-018-0059-4.
[2] L. Ferrucci, E. Fabbri, Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty, Nat. Rev. Cardiol. 15 (9) (2018) 505–522, https://doi.org/10.1038/s41569-018-0064-2.
[3] S.P., Murphy, R. Kakkar, C.P. McCarthy, J.L. Januzzi Jr., Inflammation in heart failure:JACC state-of-the-art review. J. Am. Coll. Cardiol. 75 (2020) (11):1324-1340. doi:10.1016/j.jacc.2020.01.014.
[4] A. Malandish, N. Ghadamyari, A. Karimi, M. Naderi, The role of exercise training on cardiovascular peptides in patients with heart failure: A systematic review and meta-analysis, Curr. Res. Physiol. 2022 (5) (2022) 270–286, https://doi.org/10.1016/j.crphys.2022.06.004.
[5] J. Niebauer, A.L. Clark, K.M. Webb-Peploe, A.J. Coats, Exercise training in chronic heart failure: effects on pro-inflammatory markers, Eur. J Heart Fail. 7 (2) (2005) 189–193, https://doi.org/10.1016/j.ejheart.2004.07.012.
[6] M. Khalafi, A. Malandish, S.K. Rosenkranz, The impact of exercise training on inflammatory markers in postmenopausal women: A systemic review and meta-analysis, Exp. Gerontol. 150 (2021) 111398.
[7] M.F. Piepoli, S. Binno, A.J.S. Coats, A. Cohen-Solal, U. Corrà, C.H. Davos, T. Jaarsma, L. Lund, D. Niederseer, F. Orso, G.Q. Villani, P. Agostoni, M. Volterrani, P. Seferovic, A.J.S. Coats, et al., Committee on exercise physiology & training of the heart failure association of the European society of cardiology.Regional differences in exercise training implementation in heart failure:findings from the exercise training in heart failure(ExTraHF)survey, Eur. J. Heart Fail. 21 (9) (2019) 1142–1148, https://doi.org/10.1002/ejhf.1538.
[8] E. Crimi, L.J. Ignarro, F. Cacciatore, C. Napoli, Mechanisms by which exercise training benefits patients with heart failure, Nat. Rev. Cardiol. 6 (4) (2009) 292–300, https://doi.org/10.1038/nrcardio.2009.8.
[9] A. Santoso, R. Maulana, F. Alzahra, H.S. Prameswari, A.M. Ambari, A.B. Hartopo, I. A. Arso, B. Radi, The effects of aerobic exercise on N-terminal Pro-B-type natriuretic peptide and cardiopulmonary function in patients with heart failure: A meta-analysis of randomised clinical trials, Heart Lung Circ. 29 (12) (2020) 1790–1798, https://doi.org/10.1016/j.hlc.2020.05.098.
[10] S. Abolahrari-Shirazi, J. Kojuri, Z. Bagheri, Z. Rojhani-Shirazi, Efficacy of combined endurance-resistance training versus endurance training in patients with heart failure after percutaneous coronary intervention: A randomized controlled trial, J. Res. Med. Sci. 23 (2018) 12, https://doi.org/10.4103/jrms.JRMS_743_17.
[11] B. Butts, J. Butler, S.B. Dunbar, E. Corwin, R.A. Gary, Effects of exercise on ASC methylation and IL-1 cytokines in heart failure, Med. Sci. Sports Exerc. 50 (9) (2018) 1757–1766, https://doi.org/10.1249/MSS.0000000000001641.
[12] A.I. Karavidas, K.G. Raisakis, J.T. Parissis, D.K. Tsekoura, S. Adamopoulos, D. A. Korres, D. Farmakis, A. Zacharoulis, I. Fotiadis, E. Matsakas, A. Zacharoulis, Functional electrical stimulation improves endothelial function and reduces peripheral immune responses in patients with chronic heart failure, Eur. J. Cardiovasc. Prev. Rehabil. 13 (4) (2006) 592–597, https://doi.org/10.1097/01.hjr.0000219111.02544.ff.
[13] S. Adamopoulos, J.-P. Schmid, P. Dendale, D. Poerschke, D. Hansen, A. Dritsas, A. Kouloubinis, T. Alders, A. Gkouziouta, I. Reyckers, V. Vartela, N. Plessas, C. Doulaptsis, H. Saner, I.D. Laoutaris, Combined aerobic/inspiratory muscle training vs. aerobic training in patients with chronic heart failure: The Vent-HeFT trial:a European prospective multicentre randomized trial, Eur. J. Heart Fail. 16 (5) (2014) 574–582, https://doi.org/10.1002/ejhf.70.
[14] L.R.d. Meirelles, C. Matsuura, A.d.C. Resende, Â.A. Salgado, N.R. Pereira, P. G. Coscarelli, A.C. Mendes-Ribeiro, T.MC. Brunini, Chronic exercise leads to antiaggregant, antioxidant and anti-inflammatory effects in heart failure patients, Eur. J. Prev Cardiol. 21 (10) (2014) 1225–1232, https://doi.org/10.1177/2047487313491662.
[15] V.M. Conraads, P. Beckers, J. Bosmans, et al., Combined endurance/resistance training reduces plasma TNF-alpha receptor levels in patients with chronic heart failure and coronary artery disease, Eur. Heart J. 23 (23) (2002) 1854–1860, https://doi.org/10.1053/euhj.2002.3239.
[16] E. Marco, A.L. Ramírez-Sarmiento, A. Coloma, M. Sartor, J. Comin-Colet, J. Vila, C. Enjuanes, J. Bruguera, F. Escalada, J. Gea, M. Orozco-Levi, High-intensity vs. sham inspiratory muscle training in patients with chronic heart failure:a

prospective randomized trial, Eur. J. Heart Fail. 15 (8) (2013) 892–901, https://doi.org/10.1093/eurjhf/hft035.
[17] L.S. Redwine, M.A. Pung, K. Wilson, K.J. Bangen, L. Delano-Wood, B. Hurwitz, An exploratory randomized sub-study of light-to-moderate intensity exercise on cognitive function, depression symptoms and inflammation in older adults with heart failure, J. Psychosom. Res. 128 (2020), 109883, https://doi.org/10.1016/j.jpsychores.2019.109883.
[18] Y. Hayashino, J.L. Jackson, T. Hirata, N. Fukumori, F. Nakamura, S. Fukuhara, S. Tsujii, H. Ishii, Effects of exercise on C-reactive protein, inflammatory cytokine and adipokine in patients with type-2 diabetes:a meta-analysis of randomized controlled trials, Metabolism 63 (3) (2014) 431–440, https://doi.org/10.1016/j.metabol.2013.08.018.
[19] M. Khalafi, M.E. Symonds, The impact of high-intensity interval training on inflammatory markers in metabolic disorders: A meta-analysis, Scand. J. Med. Sci. Sports. 30 (11) (2020) 2020–2036, https://doi.org/10.1111/sms.13754.
[20] M.J., Page, J.E. McKenzie, P.M. Bossuyt, et al., The PRISMA 2020 statement:an updated guideline for reporting systematic reviews, BMJ 2021,372:n71. doi: 10.1136/bmj.n71.
[21] X. Wan, W. Wang, J. Liu, T. Tong, Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range, BMC Med. Res. Methodol. 14 (2014) 135, https://doi.org/10.1186/1471-2288-14-135.
[22] J.P.T. Higgins, J. Thomas, J. Chandler, et al., Cochrane handbook for systematic reviews of interventions, John Wiley & Sons, 2019.
[23] J. Cohen, Statistical power analysis for the behavioral sciences, Academic press, 2013.
[24] M. Egger, G.D. Smith, M. Schneider, C. Minder, Bias in meta-analysis detected by a simple, graphical test, BMJ 315 (7109) (1997) 629–634, https://doi.org/10.1136/bmj.315.7109.629.
[25] T.-C. Fu, C.-H. Wang, P.-S. Lin, C.-C. Hsu, W.-J. Cherng, S.-C. Huang, M.-H. Liu, C.-L. Chiang, J.-S. Wang, Aerobic interval training improves oxygen uptake efficiency by enhancing cerebral and muscular hemodynamics in patients with heart failure, Int. J. Cardiol. 167 (1) (2013) 41–50, https://doi.org/10.1016/j.ijcard.2011.11.086.
[26] S. Gielen, M. Sandri, I. Kozarez, J. Kratzsch, D. Teupser, J. Thiery, S. Erbs, N. Mangner, K. Lenk, R. Hambrecht, G. Schuler, V. Adams, Exercise training attenuates MuRF-1 expression in the skeletal muscle of patients with chronic heart failure independent of age:the randomized Leipzig exercise intervention in chronic heart failure and aging catabolism study, Circulation 125 (22) (2012) 2716–2727, https://doi.org/10.1161/CIRCULATIONAHA.111.047381.
[27] P. Feiereisen, M. Vaillant, G. Gilson, C. Delagardelle, Effects of different training modalities on circulating anabolic/catabolic markers in chronic heart failure, J. Cardiopulm. Rehabil. Prev. 33 (5) (2013) 303–308, https://doi.org/10.1097/HCR.0b013e3182a1e4e5.
[28] V. Racca, A. Torri, P. Grati, C. Panzarino, I. Marventano, M. Saresella, P. Castiglioni, Inflammatory cytokines during cardiac rehabilitation after heart surgery and their association to postoperative atrial fibrillation, Sci. Rep. 10 (1) (2020), https://doi.org/10.1038/s41598-020-65581-1.
[29] S. Aksoy, G. Findikoglu, F. Ardic, S. Rota, D. Dursunoglu, Effect of 10-week supervised moderate-intensity-intermittent vs. continuous-aerobic-exercise programs on vascular adhesion molecules in patients with heart failure, Am. J. Phys. Med. Rehabil. 94 (10S) (2015) 898–911, https://doi.org/10.1097/PHM.0000000000000306.
[30] Y.-O. Shin, J.-S. Bae, J.-B. Lee, J.-K. Kim, Y.-J. Kim, C. Kim, J.-K. Ahn, I.-K. Bang, B.-K. Lee, T. Othman, Y.-K. Min, H.-M. Yang, Effect of cardiac rehabilitation and statin treatment on anti-HSP antibody titers in patients with coronary artery disease after percutaneous coronary intervention, Int. Heart J. 47 (5) (2006) 671–682, https://doi.org/10.1536/ihj.47.671.
[31] G.L. Pierce, R.S. Schofield, D.P. Casey, S.A. Hamlin, J.A. Hill, R.W. Braith, Effects of exercise training on forearm and calf vasodilation and proinflammatory markers in recent heart transplant recipients:a pilot study, Eur. J. Cardiovasc. Prev. Rehabil. 15 (1) (2008) 10–18, https://doi.org/10.1097/HJR.0b013e3282f0b63b.
[32] T. Ahmad, M. Fiuzat, D.B. Mark, B. Neely, M. Neely, W.E. Kraus, D.W. Kitzman, D. J. Whellan, M. Donahue, F. Zannad, I.L. Piña, K. Adams, C.M. O'Connor, G. M. Felker, The effects of exercise on cardiovascular biomarkers in patients with chronic heart failure, Am. Heart J. 167 (2) (2014) 193–202.e1, https://doi.org/10.1016/j.ahj.2013.10.018.
[33] M.M. Fernandes-Silva, G.V. Guimarães, V.OC. Rigaud, M.S. Lofrano-Alves, R. E. Castro, L.G. de Barros Cruz, E.A. Bocchi, F. Bacal, Inflammatory biomarkers and effect of exercise on functional capacity in patients with heart failure: Insights from a randomized clinical trial, Eur. J. Prev. Cardiol. 24 (8) (2017) 808–817, https://doi.org/10.1177/2047487317690458.
[34] E. Eleuteri, A. Mezzani, A. Di Stefano, D. Vallese, I. Gnemmi, L. Delle Donne, A. Taddeo, S. Della Bella, P. Giannuzzi, Aerobic training and angiogenesis activation in patients with stable chronic heart failure:a preliminary report, Biomarkers 18 (5) (2013) 418–424, https://doi.org/10.3109/1354750X.2013.805342.
[35] S. Erbs, R. Höllriegel, A. Linke, E.B. Beck, V. Adams, S. Gielen, S. Möbius-Winkler, M. Sandri, N. Kränkel, R. Hambrecht, G. Schuler, Exercise training in patients with advanced chronic heart failure(NYHA-IIIb)promotes restoration of peripheral vasomotor function, induction of endogenous regeneration, and improvement of left ventricular function, Circ. Heart Fail. 3 (4) (2010) 486–494, https://doi.org/10.1161/CIRCHEARTFAILURE.109.868992.
[36] K. Isaksen, B. Halvorsen, P.S. Munk, P. Aukrust, A.I. Larsen, Effects of interval training on inflammatory biomarkers in patients with ischemic heart failure, Scand. Cardiovasc. J. 53 (4) (2019) 213–219, https://doi.org/10.1080/14017431.2019.1629004.
[37] A.I. Larsen, P. Aukrust, T. Aarsland, K. Dickstein, Effect of aerobic exercise training on plasma levels of tumor necrosis factor alpha in patients with heart failure, Am J Cardiol. 88 (7) (2001) 805–808, https://doi.org/10.1016/s0002-9149(01)01859-8.
[38] A. Linke, V. Adams, P.C. Schulze, S. Erbs, S. Gielen, E. Fiehn, S. Mőbius-Winkler, A. Schubert, G. Schuler, R. Hambrecht, Antioxidative effects of exercise training in patients with chronic heart failure:increase in radical scavenger enzyme activity in skeletal muscle, Circulation 111 (14) (2005) 1763–1770, https://doi.org/10.1161/01.CIR.0000165503.08661.E5.
[39] C. Walther, S. Möbius-Winkler, A. Linke, M. Bruegel, J. Thiery, G. Schuler, R. Halbrecht, Regular exercise training compared with percutaneous intervention leads to a reduction of inflammatory markers and cardiovascular events in patients with coronary artery disease, Eur J Cardiovasc Prev Rehabil. 15 (1) (2008) 107–112, https://doi.org/10.1097/HJR.0b013e3282f29aa6.
[40] S. Adamopoulos, J. Parissis, D. Karatzas, C. Kroupis, M. Georgiadis, G. Karavolias, J. Paraskevaidis, K. Koniavitou, A.J.S. Coats, D.T. Kremastinos, Physical training modulates proinflammatory cytokines and the soluble Fas/soluble Fas ligand system in patients with chronic heart failure, J Am Coll Cardiol. 39 (4) (2002) 653–663, https://doi.org/10.1016/s0735-1097(01)01795-8.
[41] J.N. Myers, J.J. White, B. Narasimhan, R.L. Dalman, Effects of exercise training in patients with abdominal aortic aneurysm: preliminary results from a randomized trial, J Cardiopulm Rehabil Prev. 30 (6) (2010) 374–383, https://doi.org/10.1097/HCR.0b013e3181ebf2db.
[42] E. Prescott, R. Hjardem-Hansen, F. Dela, B. Ørkild, A.S. Teisner, H. Nielsen, Effects of a 14-month low-cost maintenance training program in patients with chronic systolic heart failure: a randomized study, Eur J Cardiovasc Prev Rehabil. 16 (4) (2009) 430–437, https://doi.org/10.1097/HJR.0b013e32831e94f8.
[43] S. Balen, N. Vukelić-Damijani, V. Persić, et al., Anti-inflammatory effects of exercise training in the early period after myocardial infarction, Coll Antropol. 32 (1) (2008) 285–291. PMID:18494215.
[44] R. Byrkjeland, B.B. Nilsson, A.S. Westheim, H. Arnesen, I. Seljeflot, Inflammatory markers as related to disease severity in patients with chronic heart failure: limited effects of exercise training, Scand J Clin Lab Invest. 71 (7) (2011) 598–605, https://doi.org/10.3109/00365513.2011.598943.
[45] F. Giallauria, P. Cirillo, M. D'agostino, G. Petrillo, A. Vitelli, M. Pacileo, V. Angri, M. Chiariello, C. Vigorito, Effects of exercise training on high-mobility group box-1 levels after acute myocardial infarction, J Card Fail. 17 (2) (2011) 108–114, https://doi.org/10.1016/j.cardfail.2010.09.001.
[46] Y.-J. Kim, Y.-O. Shin, J.-S. Bae, J.-B. Lee, J.-H. Ham, Y.-J. Son, J.-K. Kim, C. Kim, B.-K. Lee, J.-K. Oh, T. Othman, Y.-K. Min, H.-M. Yang, Beneficial effects of cardiac rehabilitation and exercise after percutaneous coronary intervention on hsCRP and inflammatory cytokines in CAD patients, Pflugers Arch. 455 (6) (2008) 1081–1088, https://doi.org/10.1007/s00424-007-0356-6.
[47] C. Kim, D.Y. Kim, C.J. Moon, Prognostic influences of cardiac rehabilitation in korean acute myocardial infarction patients.Ann Rehabil, Med. 35 (3) (2011) 375–380, https://doi.org/10.5535/arm.2011.35.3.375.
[48] N. Kobayashi, Y. Tsuruya, T. Iwasawa, N. Ikeda, S. Hashimoto, T. Yasu, H. Ueba, N. Kubo, M. Fujii, M. Kawakami, M. Saito, Exercise training in patients with chronic heart failure improves endothelial function predominantly in the trained extremities, Circ J. 67 (6) (2003) 505–510, https://doi.org/10.1253/circj.67.505.
[49] J. Lara Fernandes, C.V. Serrano, F. Toledo, M.F. Hunziker, A. Zamperini, F.H. Teo, R.T. Oliveira, M.H. Blotta, M.U. Rondon, C.E. Negrão, Acute and chronic effects of exercise on inflammatory markers and B-type natriuretic peptide in patients with coronary artery disease, Clin Res Cardiol. 100 (1) (2011) 77–84, https://doi.org/10.1007/s00392-010-0215-x.
[50] R.M. MastersonCreber, C.S. Lee, K. Margulies, B. Riegel, Identifying biomarker patterns and predictors of inflammation and myocardial stress, J Card Fail. 21 (6) (2015) 439–445, https://doi.org/10.1016/j.cardfail.2015.02.006.
[51] M.M. McDermott, S. Tiukinhoy, P. Greenland, K. Liu, W.H. Pearce, J.M. Guralnik, S. Unterreiner, T.J. Gluckman, M.H. Criqui, L. Ferrucci, A pilot exercise intervention to improve lower extremity functioning in peripheral arterial disease unaccompanied by intermittent claudication, J Cardiopulm Rehabil. 24 (3) (2004) 187–196, https://doi.org/10.1097/00008483-200405000-00010.
[52] X. Melo, A. Abreu, V. Santos, P. Cunha, M. Oliveira, R. Pinto, M. Carmo, B. o. Fernhall, H. Santa-Clara, A Post hoc analysis on rhythm and high intensity interval training in cardiac resynchronization therapy, Scand Cardiovasc J. 53 (4) (2019) 197–205, https://doi.org/10.1080/14017431.2019.1630747.
[53] R.V. Milani, C.J. Lavie, M.R. Mehra, Reduction in C-reactive protein through cardiac rehabilitation and exercise training, J Am Coll Cardiol. 43 (6) (2004) 1056–1061, https://doi.org/10.1016/j.jacc.2003.10.041.
[54] P.S. Munk, U.M. Breland, P. Aukrust, T. Ueland, J.T. Kvaløy, A.I. Larsen, High intensity interval training reduces systemic inflammation in post-PCI patients, Eur J Cardiovasc Prev Rehabil. 18 (6) (2011) 850–857, https://doi.org/10.1177/1741826710397600.
[55] G. Parrinello, D. Torres, S. Paterna, P. DiPasquale, C. Trapanese, G. Licata, Short-term walking physical training and changes in body hydration status, B-type natriuretic peptide and C-reactive protein levels in compensated congestive heart failure.Int, J Cardiol. 144 (1) (2010) 97–100, https://doi.org/10.1016/j.ijcard.2008.12.130.
[56] P.R. Pullen, S.H. Nagamia, P.K. Mehta, W.R. Thompson, D. Benardot, R. Hammoud, J.M. Parrott, S. Sola, B.V. Khan, Effects of yoga on inflammation and exercise capacity in patients with chronic heart failure, J Card Fail. 14 (5) (2008) 407–413, https://doi.org/10.1016/j.cardfail.2007.12.007.
[57] G. Ranković, B. Milicić, T. Savić, B. Dindić, Z. Mancev, G. Pesić, Effects of physical exercise on inflammatory parameters and risk for repeated acute coronary

syndrome in patients with ischemic heart disease, Vojnosanit Pregl. 66 (1) (2009) 44–48, https://doi.org/10.2298/vsp0901044r.
[58] P.V. Tisi, M. Hulse, A. Chulakadabba, P. Gosling, C.P. Shearman, Exercise training for intermittent claudication: does it adversely affect biochemical markers of the exercise-induced inflammatory response?Eur, J Vasc Endovasc Surg. 14 (5) (1997) 344–350, https://doi.org/10.1016/s1078-5884(97)80283-3.
[59] K. Tsarouhas, C. Tsitsimpikou, A. Haliassos, et al., Study of insulin resistance, TNF-α, total antioxidant capacity and lipid profile in patients with chronic heart failure under exercise, In Vivo 25 (6) (2011) 1031–1037. PMID:22021702.
[60] G.Y. Yeh, E.P. McCarthy, P.M. Wayne, L.W. Stevenson, M.J. Wood, D. Forman, R. B. Davis, R.S. Phillips, Taichi exercise in patients with chronic heart failure: a randomized clinical trial.Arch, Intern Med. 171 (8) (2011), https://doi.org/10.1001/archinternmed.2011.150.
[61] T.D. Trippel, V. Holzendorf, M. Halle, G. Gelbrich, K. Nolte, A. Duvinage, S. Schwarz, T. Rutscher, J. Wiora, R. Wachter, C. Herrmann-Lingen, H.-D. Duengen, G. Hasenfuß, B. Pieske, F. Edelmann, Ghrelin and hormonal markers under exercise training in patients with heart failure with preserved ejection fraction: results from the Ex-DHF pilot study.ESC, Heart Fail. 4 (1) (2017) 56–65, https://doi.org/10.1002/ehf2.12109.
[62] Aoyagi T,Matsui T.The cardiomyocyte as a source of cytokines in cardiac injury.J Cell Sci Ther.2011;2012(S5):003. doi:10.4172/2157-7013.s5-003.
[63] R.B. Patel, L.A. Colangelo, S.J. Bielinski, N.B. Larson, J. Ding, N.B. Allen, E. D. Michos, S.J. Shah, D.M. Lloyd-Jones, Circulating Vascular Cell Adhesion Molecule-1 and Incident Heart Failure: The Multi-Ethnic Study of Atherosclerosis (MESA), Circulating vascular cell adhesion molecule-1 and incident heart failure: the multi-ethnic study of atherosclerosis(MESA).J Am Heart Assoc. 9 (22) (2020) e019390, https://doi.org/10.1161/JAHA.120.019390.
[64] L. Adamo, C. Rocha-Resende, S.D. Prabhu, D.L. Mann, Reappraising the role of inflammation in heart failure, Nat Rev Cardiol. 17 (5) (2020) 269–285, https://doi.org/10.1038/s41569-019-0315-x.
[65] M.J. Pearson, N. King, N.A. Smart, Effect of exercise therapy on established and emerging circulating biomarkers in patients with heart failure:a systematic review and meta-analysis.Open, Heart 5 (2) (2018) e000819.
[66] R.S. Monteiro-Junior, P. de Tarso Maciel-Pinheiro, E. da Matta Mello Portugal, L. F. da Silva Figueiredo, R. Terra, L.S.F. Carneiro, V.D. Rodrigues, O.J. M. Nascimento, A.C. Deslandes, J. Laks, Effect of exercise on inflammatory profile of older persons:systematic review and meta-analyses, J Phys Act Health. 15 (1) (2018) 64–71, https://doi.org/10.1123/jpah.2016-0735.
[67] H. AlizaeiYousefabadi, A. Niyazi, S. Alaee, M. Fathi, G.R. MohammadRahimi, Anti-inflammatory effects of exercise on metabolic syndrome patients: A systematic review and meta-analysis, Biol Res Nurs. 23 (2) (2021) 280–292, https://doi.org/10.1177/1099800420958068.
[68] H. Xing, J. Lu, S.Q. Yoong, Y.Q. Tan, J. Kusuyama, X.V. Wu, Effect of aerobic and resistant exercise intervention on inflammaging of type-2 diabetes mellitus in middle-mged and older adults: A systematic review and meta-analysis, J Am Med Dir Assoc. 23 (5) (2022) 823–830.e13, https://doi.org/10.1016/j.jamda.2022.01.055.
[69] X. Huang, X. Zhao, B. Li, Y. Cai, S. Zhang, F. Yu, Q. Wan, Biomarkers for evaluating the effects of exercise interventions in patients with MCI or dementia: A systematic review and meta-analysis, Exp Gerontol. 151 (2021) 111424.
[70] G.L. Rose, T.L. Skinner, G.I. Mielke, M.A. Schaumberg, The effect of exercise intensity on chronic inflammation: A systematic review and meta-analysis, J Sci Med Sport. 24 (4) (2021) 345–351, https://doi.org/10.1016/j.jsams.2020.10.004.
[71] S.-D. Kim, Y.-R. Yeun, Effects of resistance training on C-reactive protein and inflammatory cytokines in elderly adults: A systematic review and meta-analysis of randomized controlled trials, Int J Environ Res Public Health. 19 (6) (2022) 3434.
[72] H. Hamasaki, The Effects of Exercise on Natriuretic Peptides in Individuals without Heart Failure, Sports 4 (2) (2016) 32, https://doi.org/10.3390/sports4020032.
[73] D.R. Seals, V.E. Brunt, M.J. Rossman, Keynote lecture: strategies for optimal cardiovascular aging, Am J Physiol Heart Circ Physiol. 315 (2) (2018) H183–H188, https://doi.org/10.1152/ajpheart.00734.2017.
[74] G.G. Biondi-Zoccai, A. Abbate, G. Liuzzo, L.M. Biasucci, Atherothrombosis, inflammation, and diabetes, J. Am. Coll. Cardiol. 41 (7) (2003) 1071–1077, https://doi.org/10.1016/s0735-1097(03)00088-3.
[75] P. Ziccardi, F. Nappo, G. Giugliano, K. Esposito, R. Marfella, M. Cioffi, F. D'Andrea, A.M. Molinari, D. Giugliano, Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year, Circulation 105 (7) (2002) 804–809, https://doi.org/10.1161/hc0702.104279.
[76] A.V. Sardeli, C.M. Tomeleri, E.S. Cyrino, B. Fernhall, C.R. Cavaglieri, M.P. T. Chacon-Mikahil, Effect of resistance training on inflammatory markers of older adults: A meta-analysis, Exp. Gerontol. 111 (2018) 188–196, https://doi.org/10.1016/j.exger.2018.07.021.
[77] M. Khalafi, A. Malandish, S.K. Rosenkranz, A.A. Ravasi, Effect of resistance training with and without caloric restriction on visceral fat: A systemic review and meta-analysis, Obes. Rev. 22 (9) (2021) e13275.
[78] H. Li, M.H. Hastings, J. Rhee, L.E. Trager, J.D. Roh, A. Rosenzweig, Targeting age-related pathways in heart failure, Circ. Res. 126 (4) (2020) 533–551, https://doi.org/10.1161/CIRCRESAHA.119.315889.
[79] M. Gleeson, B. McFarlin, M. Flynn, Exercise and toll-like receptors, Exerc. Immunol. Rev. 12 (2006) 34-53. PMID:17201071.
[80] H. Keshavarz-Bahaghighat, A.M. Darwesh, D.K. Sosnowski, J.M. Seubert, Mitochondrial dysfunction and inflammaging in heart failure: novel roles of CYP-derived epoxylipids, Cells. 9 (7) (2020) 1565, https://doi.org/10.3390/cells9071565.
[81] A. Malandish, A. Karimi, M. Naderi, N. Ghadamyari, M. Gulati, Impacts of exercise interventions on inflammatory markers and vascular adhesion molecules in patients with heart failure: a meta-analysis of RCTs, CJC Open 5 (2023) 429–453, https://doi.org/10.1016/j.cjco.2023.02.009.