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The role of exercise training on cardiovascular peptides in patients with heart failure: A systematic review and meta-analysis

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ABSTRACT

Background: The purpose of this systematic review & meta-analysis was to determine the roles of aerobic, resistance or concurrent exercises vs. control (CON) group on B-type natriuretic peptide (BNP) and N-terminal-pro hormone BNP (NT-proBNP) in patients with heart failure.
Methods: The electronic databases of PubMed, Scopus, Web of Science, and Google Scholar were searched up to May 2022 for aerobic vs. CON, resistance vs. CON, and concurrent vs. CON studies on circulating (serum or plasma) levels of BNP and NT-proBNP in patients with heart failure. Non-randomized or randomized controlled trial studies were included. Standardized mean difference (SMD) and 95% confidence intervals (95% CIs) were calculated. This systematic review & meta-analysis was registered in PROSPERO at the University of York with the registration number [CRD42021271632].
Results: A total of 28 articles (37 intervention arms), 26 aerobic intervention arms, 3 resistance intervention arms, and 8 concurrent intervention arms were included. A total of 2563 participants (exercise groups = 1350 and CON groups = 1213) were included. Exercise training significantly decreased NT-proBNP marker [-0.229 (SMD and 95% CI: 0.386 to −0.071), p = 0.005], irrespective of overweight/obesity status. Analysis of subgroup by type of exercise training revealed that there was a significant reduction in the NT-proBNP marker for aerobic exercise group compared to the CON group [-0.336 (SMD and 95% CI: 0.555 to −0.105), p = 0.004], whereas concurrent exercise did not show significant changes in the NT-proBNP marker [-0.134 (SMD and 95% CI: 0.350 to 0.083), p = 0.227]. In addition, exercise training did not significantly change the BNP marker [-0.122 (SMD and 95% CI: 0.322 to 0.079), p = 0.235].
Conclusions: The results suggested that exercise training, especially aerobic exercise can be improved the NT-proBNP concentrations in patients with HF (irrespective of overweight/obesity status), which may be a sign of positive physiological adaptations to aerobic exercise.

1. Introduction

Heart failure (HF) is a heterogeneous syndrome, causing significant mortality and morbidity worldwide (Metra and Teerlink, 2017; Groenewegen et al., 2020). Recently, the results of clinical studies have shown that B-type natriuretic peptide (BNP) and N-terminal-pro hormone BNP (NT-proBNP), as myocardial stretch markers (Chow et al., 2017; Pearson et al., 2018), are recognized as the gold standard circulating markers for the prognostic, diagnostic, prevention, management, and assessment of HF disease (Chow et al., 2017). BNP or ventricular/brain natriuretic peptide is a 32-amino acid hormone/polypeptide (Xu-Cai and Wu, 2010; Hall, 2004) secreted by cardiomyocytes in response to an increase in left ventricular stretching and wall stress (Topf et al., 2020). NT-proBNP is a 76-amino acid prohormone that is cleaved from the molecule to release the BNP (Hall, 2004). A number of studies demonstrated that serum levels of BNP and NT-proBNP increase significantly in response to pathophysiological conditions such as acute HF, chronic HF, ventricular hypertrophy, cardiac ischemia, atrial fibrillation, hypertension, hypoxia, diabetes mellitus, and infection (Topf et al., 2020; Xu-Cai and Wu, 2010). The primary and secondary prevention of cardiovascular diseases (CVDs),

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Abbreviations

HF	Heart failure
BNP	B-type natriuretic peptide
NT-proBNP	N-terminal-pro hormone BNP
CVDs	Cardiovascular diseases
AHA	American Heart Association
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
HFrEF	Heart failure with reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
NSAIDs	Nonsteroidal anti-inflammatory drugs
CCBs	Calcium channel blockers
BMI	Body mass index
CMA	Comprehensive meta-analysis
CIs	Confidence intervals
1RM	One-repetition maximum
ESC	European society cardiology
LVEF	Left ventricular ejection fraction

pharmacological interventions and medications, lifestyle changes, physical activity and exercise training and/or cardiac rehabilitation are important approaches to the HF (Piepoli et al., 2019). The American Heart Association (AHA) guidelines have demonstrated that exercise training (as a non-pharmacological intervention) or cardiac rehabilitation is now a class 1 recommendation in patients with HF (Pearson et al., 2018; Piña et al., 2003; Piepoli et al., 2019).

In general, exercise training is an important non-pharmacological intervention that is effective and safe (Malandish et al., 2020a, 2020b; Khalafi et al., 2021a; Khalafi et al., 2021b), and is often recommended as a class 1 treatment of CVDs, especially for the HF patients (Pearson et al., 2018; Piña et al., 2003; Piepoli et al., 2019). Regular physical activity also improves cardiac function (Adamopoulos et al., 2014; Aksoy et al., 2015; Pearson et al., 2018), VO2max (Conraads et al., 2004), and quality of life (Adamopoulos et al., 2014; Kawauchi et al., 2017) in patients with HF, and thus may be an effective non-pharmacological intervention to improve myocardial stretch function and cardio-metabolic risk factors in HF patients. It seems that an optimal reduction in serum levels of BNP and NT-proBNP may contribute to the beneficial role of exercise intervention on myocardial stretch function and cardio-metabolic risks in patients with HF (Abolahrari-Shirazi et al., 2018; Adamopoulos et al., 2014; Conraads et al., 2004; Giallauria et al., 2006-a; Giallauria et al., 2008; Maria-Sarullo et al., 2006; Masterson-Creber et al., 2015; Wisløff et al., 2007; Fu et al., 2013; Yeh et al., 2004), irrespective of overweight/obese status. A number of studies have reported that aerobic exercise intervention (Fu et al., 2013; Yeh et al., 2004; Abolahrari-Shirazi et al., 2018; Giallauria et al., 2006-a; Giallauria et al., 2008; Maria-Sarullo et al., 2006; Masterson-Creber et al., 2015; Melo et al., 2019; Wisløff et al., 2007) and as well as concurrent or combined aerobic and resistance interventions (Abolahrari-Shirazi et al., 2018; Adamopoulos et al., 2014; Conraads et al., 2004) can reduce serum levels of BNP and NT-proBNP in patients with HF compared to the control group, while other studies have reported no change (Karavidas et al., 2008; Kawauchi et al., 2017; Kobayashi et al., 2003; Yeh et al., 2011; Ahmad et al., 2014; Aksoy et al., 2015; Eleuteri et al., 2013; Giallauria et al., 2006-b; Marco et al., 2013; Nilsson et al., 2010; Prescott et al., 2009; Sandri et al., 2012; Van Berendoncks et al., 2010). In this regard, there is the systematic review and meta-analysis-based evidence supporting a favorable effect in serum levels of BNP (Smart and Steele, 2010; Smart et al., 2012) and NT-proBNP (Smart and Steele, 2010; Smart et al., 2012; Pearson et al., 2018) in patients with HF. It seems that the roles of aerobic (Fu et al., 2013; Yeh et al., 2004; Abolahrari-Shirazi et al., 2018; Giallauria et al., 2006-a; Giallauria et al., 2008; Maria-Sarullo et al., 2006; Masterson-Creber et al., 2015; Wisløff et al., 2007), resistance (Karavidas et al., 2008) and/or concurrent (Abolahrari-Shirazi et al., 2018; Adamopoulos et al., 2014; Conraads et al., 2004) interventions on serum levels of BNP and NT-proBNP have contradictory results in HF patients compared to the control group. Therefore, the purpose of this systematic review and meta-analysis was to clarify the roles of aerobic, resistance, and concurrent exercise interventions vs. control group on cardiovascular peptides including BNP and NT-proBNP in patients with HF.

2. Methods

2.1. Search strategy

The international prospective registration of our systematic review and meta-analysis protocol was registered in PROSPERO at the University of York [*CRD42021271632*]. This systematic review and meta-analysis was designed based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement guidelines (Page et al., 2021) and the Cochrane Handbook for Systematic Reviews of Interventions. The electronic databases of PubMed, Scopus, Web of Science, and Google Scholar were searched to identify original published articles up to May 2022 by four independent researchers (A M, N Gh, A K, and M N). The search strategy for exercise training interventions, BNP and NT-proBNP markers, and HF patients included the keywords as follows: [(((((concurrent OR combined OR combination OR Circuit) AND (resistance OR strength)) AND (aerobic OR endurance OR HIIT/high intensity interval training OR SIT/sprint interval training OR Continuous)) AND (training OR exercise OR exercise training OR physical activity OR cardiac rehabilitation)) AND ((“BNP” OR ″B-type natriuretic peptide” OR “brain natriuretic peptide” OR “ventricular natriuretic peptide” OR “NT-proBNP” OR ″N-terminal-pro hormone B-type natriuretic peptide")) 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")]. The keywords were combined by using the Boolean operator “OR”. The five different sets of keywords were combined by using “AND”. The keywords used could be found in the main title, abstract, different sections of the abstract, and/or in the keywords of each original article. In addition, systematic reviews and meta-analyses, and reference lists of all extracted articles were scrutinized for eligibility and to ensure that no relevant articles have been missed. The titles and abstracts of all articles were screened after removing duplicate publications and then full-text of articles were assessed for eligibility. All extracted articles were scrutinized independently by four reviewers (A M, N Gh, A K, and M N).

2.2. Study selection

Non-randomized and randomized controlled trials of exercise training interventions and/or cardiac rehabilitation programmes were considered for eligibility of inclusion criteria as follows: (a) only English language and peer-reviewed original articles, (b) original research with human participants (males and females), (c) patients with HF aged 18 yrs or older, (d) HF patients with maintaining routine medications or usual care such as chronic HF, acute HF, left ventricular dysfunction after myocardial infarction, chronic systolic HF, moderate systolic dysfunction after myocardial infarction, HF with reduced ejection fraction (HFrEF), HF with preserved ejection fraction (HFpEF), and compensated congestive HF, (e) measuring serum levels of BNP and NT-proBNP at baseline and after intervention, (f) duration of exercise training $\geq$2 weeks, (g) having at least one exercise training group (aerobic, resistance or concurrent) with HF vs. control group with HF or healthy control group, (h) usual care or routine medications for control group with and without exercise prescription and/or home-based exercise training intervention. The modality of exercise training in this systematic review and meta-analysis included aerobic ('aerobic training; endurance training; exercise-based cardiac rehabilitation; cardiac rehabilitation programme; low and moderate-intensity inspiratory; physical training; aerobic interval training; HIIT; Tai Chi'), resistance ('resistance training; functional electrical stimulation; inspiratory muscle training; peripheral resistance training'), concurrent ('concurrent training', combined training'). It should be noted that there were no restrictions on the duration of exercise training or used training protocols in the 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 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 was performed by four independent reviewers (A M, N Gh, A K, and M N) and any disagreement was resolved by discussion among all teamwork reviewers (A M, N Gh, A K, and M N). The characteristics of the data for each study were extracted as follows: (a) study design, (b) participant characteristics including age, sex, body mass index (BMI) and sample size, (c) exercise training characteristics including mode, duration and frequency, (d) outcome markers including circulating BNP and NT-proBNP markers. The pre- and post-test values (mean and standard deviation) or mean differences and associated standard deviations were entered into the meta-analysis in order to generate forest plots. If means and standard deviations were not reported, they were calculated from standard errors, median, range and/or interquartile range (Wan et al., 2014; Higgins et al., 2019). The Getdata Graph Digitizer software was used for the data extraction from figures. If studies had multiple arms of exercise interventions, data for the aerobic vs. control group, resistance vs. control group and concurrent vs. control group were included. In addition, for the studies with more than one evaluated post-test intervention period, only the last period of post-test intervention was considered. When insufficient information was available from the published articles and/or additional information was required, the corresponding author was contacted.

2.4. Quality assessment and sensitivity analysis

The PEDro scale was used to assess the risk of bias (Higgins et al., 2019), which included as follows: (1) eligibility criteria specified, (2) random allocation of participants, (3) allocation concealed, (4) groups similar at baseline, (5) assessors blinded, (6) outcome measures assessed in 85% of participants, (7) intention to treat analysis, (8) comparing between-groups for statistical differences, (9) point measures and measures of variability reported for main effects, (10) activity monitoring in control group, (11) relative exercise intensity reviewed (12) non-supervised or supervised (Table 1). To evaluate the robustness of the results was used of sensitivity analysis.

2.5. Statistical analysis

The comprehensive meta-analysis (CMA) software was used for data analysis and as well as calculating the standardized mean difference and 95% confidence intervals (CIs) by fixed and random-effects models. Significance level was considered at a $P < 0.05$. The effect size was calculated to compare the effects of exercise training interventions (aerobic, resistance and concurrent) vs. control group on circulating BNP and NT-proBNP markers. The Cochrane guidelines for interpreting effect sizes were considered as follows: small effect size (0.2–0.49), medium effect size (0.5–0.79), and large effect size (more than 0.8) (Cohen, 2013). Heterogeneity was assessed by using the I^2 statistic. Furthermore, the Cochrane guidelines in the interpretation of the I^2 statistic were considered as follows: low heterogeneity (25%), medium heterogeneity (50%), and high heterogeneity (75%). The visual interpretation of funnel plots was considered to identify publication bias. In addition, Egger's test was used as a secondary determinant test; significant publication bias was considered apparent if $P < 0.1$ (Egger et al., 1997).

3. Results

3.1. Included studies

The initial search in the electronic databases of PubMed, Scopus, Web of Science, and Google Scholar identified 1550, 235, 228, and 1285 articles, respectively. After removing duplicates and screening articles based on the title/abstract, 84 full-text papers were included for final screening based on the inclusion and exclusion criteria. Of those 84 papers, 28 full-text articles met the inclusion criteria and 56 full-text articles were excluded with reasons as follows: (1) three articles with "letters to the editor", (2) sixteen articles without control group, (3) four articles with hormone therapy in exercise group, (4) two articles with combined dietary supplementation plus exercise interventions in HF patients, (5) two articles were measured serum levels of BNP and NT-proBNP in obese hypertension patients and athletes, (6) six articles with measured serum levels of BNP and NT-proBNP at baseline, (7) ten articles without reporting BNP and NT-proBNP values in HF patients, (8) four articles without any exercise training interventions in HF patients, (9) seven article with acute exercise training interventions in HF patients, and (10) two articles did not have specific and enough information in exercise training intervention and BNP and NT-proBNP values in patients with HF, and no additional information was provided after contacting the corresponding author. Nine articles included two arms of exercise training intervention (Abolahrari-Shirazi et al., 2018; Aksoy et al., 2015; Delagardelle et al., 2008; Giallauria et al., 2006-a; Fu et al., 2013; Kawauchi et al., 2017; Melo et al., 2019; Sandri et al., 2012; Wisløff et al., 2007). A total of 28 articles (37 intervention arms), 26 aerobic intervention arms, 3 resistance intervention arms, and 8 concurrent intervention arms were included. A total of 2563 participants (exercise groups = 1350 and CON groups = 1213) were included. The flowchart of study selection is shown in Fig. 1.

3.2. Participant characteristics

The participant characteristics of included articles are presented in Table 2. As mentioned above, total sample sizes including 2563 participants (1350 participants in exercise groups and 1213 participants in control groups) were included in our meta-analysis. The sample size, mean age, and mean BMI for each article ranged between 8 and 477 participants (Conraads et al., 2007; Ahmad et al., 2014), 49 ± 19.36 and 76.5 ± 9 yrs (Sandri et al., 2012; Wisløff et al., 2007), and between 24.5 ± 3 and 30 ± 11.61 kg/m^2 (Wisløff et al., 2007; Sandri et al., 2012), respectively. A total of 28 included articles, 27 articles were included both male and female genders, and one article was included only male gender (Eleuteri et al., 2013).

3.3. Characteristics of interventions in exercise and control groups

The characteristics of exercise training interventions and control group-related interventions are illustrated in Table 3. Types of exercise interventions including aerobic (Abolahrari-Shirazi et al., 2018; Ahmad et al., 2014; Aksoy et al., 2015; Conraads et al., 2007; Eleuteri et al., 2013; Fu et al., 2013; Giallauria et al., 2006-a; Giallauria et al., 2006-b; Giallauria et al., 2008; Kobayashi et al., 2003; Maria-Sarullo et al., 2006; Masterson-Creber et al., 2015; Melo et al., 2019; Nilsson et al., 2010; Passino et al., 2006; Radi et al., 2017; Sandri et al., 2012; Wisløff et al.,

Table 1
Risk of bias assessment.

Authors et al. (yrs)	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
Abolahrari-Shirazi et al., 2018	✓	✓	✓	✓	✓	✓✓✓	✓	✓✓	✓	✓	✓	✓	15
Adamopoulos et al. (2014)	✓	✓	✓	✓	–	✓✓	–	✓✓	✓	✓	✓	✓	12
Ahmad et al. (2014)	✓	✓	✓	✓	✓	✓✓	–	✓✓	✓	–	✓	✓	12
Aksoy et al. (2015)	✓	✓	–	✓	–	–	–	✓✓	✓	–	–	✓	7
Conraads et al. (2004)	✓	✓	–	✓	–	✓	–	✓✓	✓	–	–	✓	8
Conraads et al. (2007)	✓	✓	✓	✓	–	✓✓	–	✓✓	✓	–	✓	✓	11
Delagardelle et al. (2008)	✓	✓	✓	✓	–	✓✓	✓	✓✓	✓	–	–	✓	11
Eleuteri et al. (2013)	✓	✓	✓	✓	-	✓✓✓	✓	✓✓	✓	–	✓	✓	13
Fu et al. (2013)	✓	✓	–	✓	-	✓✓	–	✓✓	✓	–	✓	✓	10
Giallauria et al., 2006-a	✓	–	–	✓	✓	✓✓✓	✓	✓✓	✓	–	✓	✓	12
Giallauria et al., 2006-b	✓	✓	✓	✓	✓	✓✓✓	–	✓✓	✓	–	✓	✓	13
Giallauria et al. (2008)	✓	✓	✓	✓	✓	✓✓✓	–	✓✓	✓	–	✓	✓	13
Karavidas et al. (2008)	✓	✓	✓	✓	✓	✓✓	✓	✓✓	✓	–	–	✓	12
Kawauchi et al. (2017)	✓	✓	✓	✓	–	✓	–	✓✓	✓	–	–	✓	9
Kobayashi et al. (2003)	✓	✓	–	✓	–	✓✓✓	✓	✓✓	✓	–	–	✓	11
Marco et al. (2013)	✓	✓	✓	✓	✓	✓✓	✓	✓✓	✓	–	–	✓	12
Maria-Sarullo et al. (2006)	✓	✓	✓	✓	✓	✓✓✓	–	✓✓	✓	–	–	✓	12
Masterson-Creber et al. (2015)	✓	✓	✓	✓	–	✓✓	–	✓✓	✓	–	✓	✓	11
Melo et al. (2019)	✓	✓	✓	✓	–	✓	✓	✓✓	✓	–	✓	✓	11
Nilsson et al. (2010)	✓	✓	–	✓	–	✓✓	–	✓	✓	–	–	✓	8
Passino et al. (2006)	✓	✓	–	✓	–	✓	–	✓✓	✓	–	✓	✓	9
Prescott et al. (2009)	✓	✓	–	✓	–	✓✓	–	✓✓	✓	–	✓	✓	10
Radi et al. (2017)	✓	✓	–	✓	–	✓✓	–	✓✓	✓	–	–	✓	9
Sandri et al. (2012)	✓	✓	–	✓	–	✓✓✓	✓	✓✓	✓	–	–	✓	11
Van Berendoncks et al. (2010)	✓	✓	–	✓	✓	✓	–	✓✓	✓	–	–	✓	9
Wisløff et al. (2007)	✓	✓	✓	✓	–	✓✓✓	–	✓✓	✓	–	✓	✓	13
Yeh et al. (2004)	✓	✓	✓	✓	–	✓✓	✓	✓✓	✓	✓	–	✓	12
Yeh et al. (2011)	✓	✓	–	✓	–	✓✓	✓	✓✓	✓	–	–	✓	10

Note: Total PEDRO score out of 15 points; (✓) = one point; (–) = not reported or unclear; *Three points possible—one point if adherence >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.

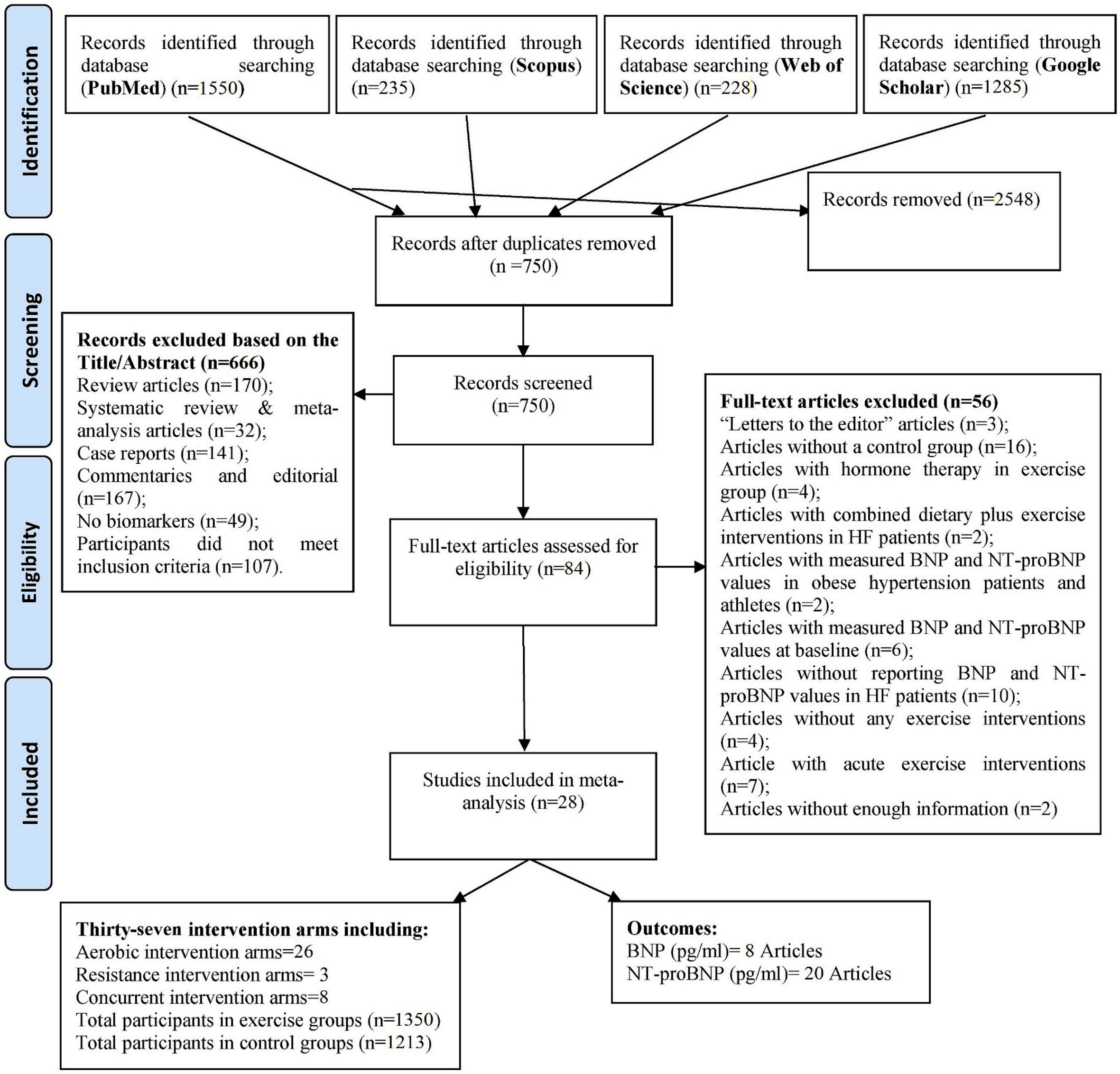

Fig. 1. Flowchart of study selection.
Note. HF= Heart failure; BNP= B-type natriuretic peptide; NT-proBNP = N-terminal-pro hormone B-type natriuretic peptide.

2007; Yeh et al., 2004; Yeh et al., 2011), resistance (Karavidas et al., 2008; Kawauchi et al., 2017), and concurrent (Abolahrari-Shirazi et al., 2018; Adamopoulos et al., 2014; Conraads et al., 2004; Delagardelle et al., 2008; Marco et al., 2013; Prescott et al., 2009; Van Berendoncks et al., 2010) were studies included in our meta-analysis. The intensity ranges for the aerobic exercise interventions were performed from 40% VO2peak (Abolahrari-Shirazi et al., 2018), 60% HRmax reserve (Ahmad et al., 2014; Masterson-Creber et al., 2015), increased heart rate up to 20 bpm above resting (Radi et al., 2017) and 15–18 on the Borg scale (Nilsson et al., 2010) to 70% HRmax reserve (Masterson-Creber et al., 2015), 80% VO2peak (Fu et al., 2013; Prescott et al., 2009), 90% of the ventilator threshold level (Conraads et al., 2004; Conraads et al., 2007; Eleuteri et al., 2013; Kobayashi et al., 2003; van Berendoncks et al., 2010) and as well as 90–95% HRmax (Melo et al., 2019; Wisløff et al., 2007), with the most common exercise intensity 60–75% VO2peak (Delagardelle et al., 2008; Fu et al., 2013; Giallauria et al., 2006a,b; Giallauria et al., 2008; Maria-Sarullo et al., 2006; Passino et al., 2006; Sandri et al., 2012) or 60–70% HRmax reserve (Ahmad et al., 2014; Masterson-Creber et al., 2015). The intensity ranges for the resistance training interventions were performed from 50% of 1RM/one-repetition maximum (Conraads et al., 2004; Kawauchi et al., 2017; van Berendoncks et al., 2010) and 4–5 on the modified Borg scale (Prescott et al., 2009) to 60% of 1RM (Abolahrari-Shirazi et al., 2018; Conraads et al., 2004; Delagardelle et al., 2008; van Berendoncks et al., 2010), 60% of individual sustained maximal inspiratory pressure (Adamopoulos et al., 2014), functional electrical stimulation 25 Hz (Karavidas et al., 2008), 70% of 1RM (Delagardelle et al., 2008) and 100% of 10RM (Marco et al., 2013), with the most common exercise intensity 50–60% of 1RM (Conraads et al., 2004; van Berendoncks et al., 2010). The duration of exercise intervention protocols was varied from 1 month (4 weeks) (Marco et al., 2013; Radi et al., 2017) to 12 months (Masterson-Creber et al., 2015), with the most common period of 3 months (12 weeks) (Adamopoulos et al., 2014; Ahmad et al., 2014; Eleuteri et al., 2013; Fu et al., 2013; Giallauria et al., 2006-a; Giallauria et al., 2006-b; Kobayashi et al., 2003; Maria-Sarullo et al., 2006; Wisløff et al., 2007; Yeh et al., 2004; Yeh et al., 2011). The duration of 6 weeks (Karavidas et al., 2008), 7 weeks (Abolahrari-Shirazi et al., 2018), 8 weeks (Kawauchi et al., 2017; Prescott et al., 2009), 10 weeks (Aksoy et al., 2015), 4 months (Conraads et al., 2004; Delagardelle et al., 2008; Nilsson et al., 2010; Sandri et al., 2012; Van Berendoncks et al., 2010), 5 months (Conraads et al., 2007), 6 months (Giallauria et al., 2008; Melo et al., 2019), and 9 months (Passino et al., 2006) were used in other

Table 2
The participant characteristics included articles at baseline.

Source, yrs	Country	Exercise + Control = Total sample size (Baseline)	Sex	Participant characteristics	Groups	Age (yrs) (Baseline) Mean ± SD	BMI (kg/m^2) (Baseline) Mean ± SD	BNP or NT-proBNP
Abolahrari-Shirazi et al., 2018	Iran	25(Concurrent) + 25 (Aerobic) + 25(Control) = 75	Male/Female	Patients with heart failure	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	NT-proBNP
Adamopoulos et al. (2014)	Belgium	21 + 22 = 43	Male/Female	Patients with chronic heart failure	Concurrent Control	Concurrent: 57.8 ± 11.7 Control: 58.3 ± 13.2	Concurrent: 28.6 ± 6.7 Control: 27.2 ± 2.9	NT-proBNP
Ahmad et al. (2014)	England	477 + 451 = 928	Male/Female	Patients with chronic heart failure	Aerobic Control	Aerobic: 59.0 (51.2, 67.9) Control: 59.0 (50.7, 68.0)	Unknown	NT-proBNP
Aksoy et al. (2015)	Turkey	15(Continuous) + 15(Intermittent) + 15(Control) = 45	Male/Female	patients with chronic heart failure	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	NT-proBNP
Conraads et al. (2004)	Belgium	27 + 22 = 49	Male/Female	Patients with chronic heart failure	Concurrent Control	Concurrent 59 ± 2 Control: 59 ± 2	Unknown	NT-proBNP
Conraads et al. (2007)	Belgium	8 + 9 = 17	Male/Female	Patients with chronic heart failure	Aerobic Control	Aerobic: 57 ± 2 Control: 61 ± 4	Unknown	NT-proBNP
Delagardelle et al. (2008)	Luxembourg	45 + 15 = 60	Male/Female	Patients with and without ischemic chronic heart failure	Concurrent Control	Concurrent 59.3 ± 5.9 Control: 55.5 ± 7.5	Concurrent 28.56 ± 4.9 Control: 28.2 ± 4.8	NT-proBNP
Eleuteri et al. (2013)	Italy	11 + 10 = 21	Male	Patients with chronic heart failure	Aerobic Control	Aerobic: 66 ± 2 Control: 63 ± 2	Unknown	NT-proBNP
Fu et al. (2013)	Taiwan	15 (Aerobic interval) + 15 (Aerobic continuous) + 15(Control) = 45	Male/Female	Patients with heart failure	Aerobic Interval Continuous Control	Aerobic: Interval 67.5 ± 1.8 Continuous 66.3 ± 2.1 Control: 67.8 ± 2.5	Unknown	BNP
Giallauria et al., 2006-a	Italy	22 + 22 = 44	Male/Female	Patients with left ventricular dysfunction after myocardial infarction	Aerobic Control	Aerobic: 55 ± 2 Control: 54 ± 3	Unknown	NT-proBNP
Giallauria et al., 2006-b	Italy	20 + 20 = 40	Male/Female	Patients after acute myocardial infarction	Aerobic Control	Aerobic: 68.6 ± 2.3 Control: 68.2 ± 2.6	Unknown	NT-proBNP
Giallauria et al. (2008)	Italy	30 + 31 = 61	Male/Female	Patients with moderate systolic dysfunction after myocardial infarction	Aerobic Control	Aerobic: 55.9 ± 3.1 Control: 55.1 ± 3.7	Aerobic: 25.6 ± 2.4 Control: 25.3 ± 2.9	NT-proBNP
Karavidas et al. (2008)	Greece	20 + 10 = 30	Male/Female	Patients with chronic heart failure	Resistance/Functional electrical stimulation Control	Resistance: 62 ± 12 Control: 64 ± 8	Resistance: 27 ± 5 Control: 28 ± 4	BNP
Kawauchi et al. (2017)	Brazil	13 + 9 = 22	Male/Female	Patients with heart failure	Resistance Control	Low resistance: 54 ± 10 Moderate resistance: 56 ± 7 Control: 56 ± 7	Low resistance: 28 ± 6 Moderate resistance: 28 ± 5 Control: 25 ± 4	BNP
Kobayashi et al. (2003)	Japan	14 + 14 = 28	Male/Female	Patients with chronic heart failure	Aerobic Control	Aerobic: 55 ± 7.48	Unknown	BNP

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Table 2 (*continued*)

Source, yrs	Country	Exercise + Control = Total sample size (Baseline)	Sex	Participant characteristics	Groups	Age (yrs) (Baseline) Mean ± SD	BMI (kg/m^2) (Baseline) Mean ± SD	BNP or NT-proBNP
						Control: 62 ± 7.48		
Marco et al. (2013)	Spain	11 + 11 = 22	Male/ Female	patients with chronic heart failure	Concurrent Control	Concurrent: 68.5 ± 8.88 Control: 70.1 ± 10.75	Concurrent: 28.4 ± 3.64 Control: 26.3 ± 2.4	NT-proBNP
Maria-Sarullo et al. (2006)	Italy	30 + 30 = 60	Male/ Female	Patients with chronic heart failure	Aerobic Control	Aerobic: 53.1 ± 6.1 Control: 52.9 ± 4.9	Unknown	NT-proBNP
Masterson-Creber et al. (2015)	USA	163 + 157 = 320	Male/ Female	Patients with chronic heart failure	Aerobic Control	58.66 ± 11.91	Unknown	NT-proBNP
Melo et al., 2019-a	Portugal	7 + 9 = 16	Male/ Female	Patients with chronic heart failure (atrial fibrillation)	Aerobic Control	69.4 ± 7.2	28.2 ± 4.8	BNP
Melo et al., 2019-b	Portugal	11 + 10 = 21	Male/ Female	Patients with chronic heart failure (sinus rhythm)	Aerobic Control	66.2 ± 14.57	26.7 ± 4.58	BNP
Nilsson et al. (2010)	Norway	39 + 39 = 78	Male/ Female	Patients with chronic heart failure	Aerobic Control	Aerobic: 68.9 ± 7.9 Control: 71.5 ± 7.9	Unknown	NT-proBNP
Passino et al. (2006)	Italy	44 + 41 = 85	Male/ Female	Patients with heart failure	Aerobic Control	Aerobic: 60 ± 13.26 Control: 61 ± 12.80	Aerobic: 25.8 ± 1.98 Control: 25.1 ± 5.12	NT-proBNP, BNP
Prescott et al. (2009)	Denmark	20 + 23 = 43	Male/ Female	Patients with chronic systolic heart failure	Concurrent Control	Concurrent: 68 ± 11 Control: 66.9 ± 12.5	Concurrent: 27.7 ± 4.12 Control: 27.7 ± 5.92	NT-proBNP
Radi et al. (2017)	Indonesia	48 + 65 = 113	Male/ Female	Patients with heart failure	Aerobic Control	Aerobic: 51.8 (49.3–54.4) Control: 51.7 (49.6–53.7)	Unknown	NT-proBNP
Sandri et al. (2012)	Germany	15 (Aerobic) + 15(Control) + 15 (Aerobic) + 15(Control) = 60	Male/ Female	Patients with chronic heart failure ≤55 years Patients with chronic heart failure ≥65 years	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	NT-proBNP
Van Berendoncks et al. (2010)	Belgium	46 + 34 = 80	Male/ Female	Patients with chronic heart failure	Concurrent Control	Concurrent: 57.5 ± 10.8 Control: 61.1 ± 11.6	Concurrent: 25.1 ± 4.4 Control: 25.1 ± 4.3	NT-proBNP
Wisløff et al. (2007)	Norway	9 (Aerobic/moderate continuous) + 9 (Aerobic/interval) + 9(Control) = 27	Male/ Female	Patients with heart failure	Aerobic Control	Aerobic moderate: 74.4 ± 12 interval: 76.5 ± 9 Control: 75.5 ± 13	Aerobic: moderate: 24.7 ± 3 interval: 24.5 ± 3 Control: 25.5 ± 2	NT-proBNP
Yeh et al. (2004)	USA	15 + 15 = 30	Male/ Female	Patients with chronic heart failure	Aerobic Control	Aerobic: 66 ± 12 Control: 61 ± 14	Unknown	BNP
Yeh et al. (2011)	USA	50 + 50 = 100	Male/ Female	Patients with chronic heart failure	Aerobic Control	Aerobic: 68.1 ± 11.9 Control: 66.6 ± 12.1	Unknown	BNP

Note: B-type natriuretic peptide (BNP), N-terminal pro B-type natriuretic peptide (NT-proBNP).

studies. The exercise frequency was performed from 2 (Melo et al., 2019; Nilsson et al., 2010; Prescott et al., 2009; Yeh et al., 2004, 2011) to 7 (Kawauchi et al., 2017; Marco et al., 2013) day/week, with the most common exercise frequency of 3 day/week (Abolahrari-Shirazi et al., 2018; Adamopoulos et al., 2014; Ahmad et al., 2014; Aksoy et al., 2015; Conraads et al., 2004; Conraads et al., 2007; Delagardelle et al., 2008; Fu et al., 2013; Giallauria et al., 2006-a; Giallauria et al., 2006-b; Giallauria et al., 2008; Kobayashi et al., 2003; Maria-Sarullo et al., 2006; Masterson-Creber et al., 2015; Passino et al., 2006; Radi et al., 2017; van Berendoncks et al., 2010; Wisløff et al., 2007). In addition, the exercise frequency of 4 day/week (Sandri et al., 2012) and as well as 5 day/week (Eleuteri et al., 2013; Karavidas et al., 2008) was performed in other studies. The session duration per session for the aerobic exercise interventions was consisted of 15 min (Ahmad et al., 2014; Kobayashi

Table 3
Characteristics of exercise intervention and control group in patients with heart failure.

Source, yr	Exercise intervention					
	Type	Frequency (days/week)	Follow-up (Duration)	Mode	Supervised or Unsupervised	Control group
Abolahrari-Shirazi et al., 2018-a	Combined (cycle + weight training)	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; 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.	Supervised	Control group (patients) 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 (patients) 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. (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 s. After the sixth level, the rest period was kept at 5 s. The duration of training was 30 min.	Supervised	Patients in control group underwent aerobic + resistance trainings similar to the concurrent group. However, control group was exercised at 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 15–30 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	Control group (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 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.	Supervised	Control group (patients) was on optimal medical therapy without any particular regular physical activity before.
Conraads et al. (2004)	Combined (cycling & jogging + weight training)	3	4 months	Combined group was performed endurance/resistance exercise programme in the hospital for 60 min. Endurance = at 90% of the ventilator threshold including 20–30 min of cycling and/or jogging. Resistance =	Supervised	Control group was patients with the untrained heart failure and unchanged medication during 4 months.

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Table 3 (*continued*)

Source, yr	Exercise intervention					
	Type	Frequency (days/week)	Follow-up (Duration)	Mode	Supervised or Unsupervised	Control group
				resistive weight training at 50%–60% of 1-RM, two sets for 30 min. Per station, 1 set, consisting of 10 repetitions, was performed with a gradual increase (15 repetitions after 1 month, 2 sets of 10 repetitions after 2 months, 2 sets of 15 repetitions after 3 months). Nine muscle groups of the lower and the upper limbs and torso: (leg extension: quadriceps; pullover: latissimus dorsi; chest press: pectoralis, serratus anterior, anterior deltoids and triceps; pectoral fly: pectoralis and anterior deltoids; arm curl: biceps; triceps extension: triceps; shoulder press: deltoids and trapezius; rowing: latissimus dorsi, rhomboidei and posterior deltoids; lat pulldown: latissimus dorsi),		
Conraads et al. (2007)	Aerobic (cycle & waking)	3	5 months	Patients attended an ambulatory exercise programme consisting of 3 sessions/week, 90% of the ventilatory threshold, and each lasting for 1 h. Each session started with a 5 min warming-up and stretching period, followed by endurance training (cycling, walking) and a period of 5 min cooling-down	Supervised	Control group (patients) undergo standard therapy only.
Delagardelle et al. (2008)	Concurrent (cycle & treadmill + strength training)	3	3–4 months	The concurrent group was performed an intensive ambulatory training program of 40 sessions, 3 times per week, and at 60–75% VO2 peak during 3–4 months. Every training session consisted of 45 min of exercise, with 5 min of warm-up and 40 min of training. Resistance training was set at 60% of 1-RM during the 20 first sessions and then increased to 70% of 1-RM, ensuring that one series of ten repetitions lasted exactly 1 min for a total work time of 40 min.	Supervised	Control group (patients) was not able to participate in the ambulatory training program because of geographic constraints.
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.	Supervised	Control group (patients) was continued their optimal medical therapy without exercise intervention.
Fu et al. (2013)	Aerobic (cycle)	3	12 weeks	Aerobic training including 2 groups: Aerobic interval training group warmed up for 3 min at 30% of VO2peak [≈30% heart rate reserve (HRR); ≈30. (HRpeak−HRrest) +HRrest] before exercise five 3-min intervals at 80% of VO2peak (≈80% HRR). Each interval was separated by 3-min exercise at 40% of VO2peak (≈40% HRR). The exercise session was terminated by 3-min cool-down at 30% of VO2peak. Moderate-continuous training 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 (patients) only engaged in general home-based health care.
Giallauria et al., 2006-a	Aerobic (cycle)	3	3 months	Aerobic training was performed for 30 min on a bicycle ergometer at 70% of the VO2peak achieved at the initial symptom-limited cardiopulmonary exercise test, which was preceded by a 5-min warming-up and followed by a 5-min cooling-down.	Supervised	Patients in control group were discharged with routine instructions to continue physical activity and maintain a correct lifestyle.
	Aerobic (cycle)	3	3 months		Supervised	

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Table 3 (*continued*)

Source, yr	Exercise intervention					Control group
	Type	Frequency (days/week)	Follow-up (Duration)	Mode	Supervised or Unsupervised	
Giallauria et al., 2006-b				Training sessions, preceded by a 5-min warming-up and followed by a 5-min cooling-down, were performed by pedalling for 30 min on a bicycle ergometer at 60% of the VO2peak achieved at the initial symptom-limited cardiopulmonary exercise test.		Patients in control group were discharged with routine instructions to continue physical activity and maintain a correct lifestyle.
Giallauria et al. (2008)	Aerobic (cycle)	3	6 months	Training sessions were preceded by a 5-min warming-up and followed by a 5-min cooling-down. Exercise was performed for 30 min on a bicycle ergometer with the target of 60–70% of VO2peak achieved at the initial symptom-limited cardiopulmonary exercise test.	Supervised	Control group patients were discharged with generic instructions to maintaining physical activity and a correct Lifestyle.
Karavidas et al. (2008)	Resistance (functional electrical stimulation)	5	6 weeks	Resistance 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 ankle joints. When the muscles of the right leg were contracted, the muscles of the left leg were relaxing and vice versa.	Supervised	Control group (patients) was exposed to the same regimen as the functional electrical stimulation group, using a lower intensity of stimulation (5 Hz) that did not lead to visible or palpable contractions, as judged objectively or subjectively.
Kawauchi et al. (2017)	Resistance (inspiratory and peripheral resistance training)	7	8 weeks	combined training = moderate-intensity inspiratory and peripheral resistance training group (MIPRT) Low-intensity inspiratory and peripheral resistance training group (LIPRT): performed a combination of IMT at 15% of the maximum inspiratory pressure (MIP) and peripheral muscle training with 0.5 kg for 30 min. Moderate-intensity inspiratory and peripheral resistance training group (MIPRT): trained their inspiratory muscles at 30% of the MIP combined with peripheral muscle training at 50% of one maximum repetition (1RM) for 30 min.	Supervised	Control patients maintained daily medication use and self-controlled salt/fluid ingestion during the 8-week.
Kobayashi et al. (2003)	Aerobic (cycle)	2–3	3 months	Aerobic group was performed cycle ergometer training that exercise speed was adjusted to maintain the heart rate equivalent to the ventilator threshold level for 15 min.	Supervised	Control group (patients) was continued their optimal medical therapy without exercise intervention for the same time period.
Marco et al. (2013)	Concurrent (inspiratory muscle endurance & strength)	7	4 weeks	Concurrent group performed high-intensity inspiratory muscle training 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 at a 15–20 breaths/min.	Supervised	Control group (patients) received sham- inspiratory muscle training at an initial workload of 10 cmH2O which was increased 2.5 cmH2O every week.
Maria-Sarullo et al. (2006)	Aerobic (cycle)	3	3 months	Aerobic group underwent using a bicycle ergometer for 30 min at 60–70% of their VO2 peak.	Supervised	Control group (patients) did not change their optimal medical therapy and previous physical activity.
Masterson-Creber et al. (2015)	Aerobic (walking & cycling)	3	12 months	Aerobic group performed walking or cycling at a 60–70% HRmax reserve for 30–35 min.	Supervised	Control group patients in the usual care group were not provided with a formal exercise prescription.
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	Supervised	Control group patients received usual care.

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Table 3 (*continued*)

Source, yr	Exercise intervention					
	Type	Frequency (days/week)	Follow-up (Duration)	Mode	Supervised or Unsupervised	Control group
				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.		
Nilsson et al. (2010)	Aerobic (cycle)	2	4 months	Aerobic group was performed group-based simple aerobic exercises, including three intervals of high intensity (15–18 on the Borg scale). The total duration of the exercise program was 50 min.	Supervised	Control group (patients) was referred to follow-up care by their primary care physician and was not discouraged from regular physical activity.
Passino et al. (2006)	Aerobic (cycle)	3	9 months	Aerobic group was performed cycling on a bike for a minimum of 3 days per week, 30 min per day. Patients were instructed to exercise at 60 rpm, keeping heart rate constantly monitored at 65% of peak VO2 heart rate, by a wearable device.	Supervised	Control group (patients) underwent follow-up visits at the third and ninth month to exclude changes in their usual lifestyle and physical activity
Prescott et al. (2009)	Concurrent (walking, cycling, step machine, and step board)	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 patients with usual care were encouraged to keep on training at home but were not offered group sessions or to keep diaries
Radi et al. (2017)	Aerobic (cycle, walking or treadmill)	3	1 month	Aerobic group was trained personnel's, three sessions per week for 20–40 min per session; the exercise consisted of warming up, low to moderate intensity of endurance training (leg ergocycle and walking or treadmill), with electrocardiogram telemetry when necessary, the exercise program was expected to increase the heart rate up to 20 bpm above resting, and was completed after cooling down.	Supervised	Control group patients continued the standard care without early exercise program.
Sandri et al. (2012)	Aerobic (cycle)	4	4 months	Aerobic group was performed per weekday each for 20 min (excluding 5 min of warming-up and cooling-down) using a bicycle ergometer interrupted by recreation intervals of at least 60 min after each session. Workloads were adjusted to heart rate so that 70% of the symptom-limited maximum oxygen uptake was reached.	Supervised	Control group patients received usual clinical care by their physicians.
van Berendoncks et al., 2010	Concurrent (treadmill, cycle, stair or step, arm-cycling, half recumbent or reclined cycling + weight training)	3	4 months	Concurrent group was performed aerobic and resistance trainings. Aerobic training THR (target heart rate) was calculated as 90% of the heart rate achieved at the anaerobic threshold. The initial resistance training intensity was set at 50% of 1RM (1 repetitive maximum) (for the nine different muscle groups), with an increase to 60% after 2 months. Repetitions were slowly increased from 1 × 10, 1 × 15, 2 × 10 to 2 × 15 repetitions. Between each series of repetitions, rest for 1 min was allowed. Aerobic group trained for 8 min on five different training devices (treadmill, bicycle, stair or step, arm-cycling, half recumbent or reclined cycling). When changing from one device to another, 2 min of recuperation time was introduced. During the first 2 months,	Supervised	Control group or untrained patients maintained their optimal medical therapy.

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Table 3 (*continued*)

Source, yr	Exercise intervention					Control group
	Type	Frequency (days/week)	Follow-up (Duration)	Mode	Supervised or Unsupervised	
				patients assigned to the concurrent group trained for almost 40 min on the fitness equipment, whereas only 10 min were spent on aerobic. The next 2 months, resistance training was reduced to 30 min (nine muscle groups, 2 × 15 repetitions each) and ET was increased to 2 × 8 min.		
Wisløff et al. (2007)	Aerobic (treadmill walking)	3	12 weeks	Aerobic interval training group warmed up for 10 min at 50%–60% of Vo2peak (≈60%–70% of peak heart rate) before walking four 4-min intervals at 90%–95% of peak heart rate. Each interval was separated by 3-min active pauses, walking at 50%–70% of peak heart rate. The training session was terminated by a 3-min cool-down at 50%–70% of peak heart rate. Performed four 4-min intervals with an exercise intensity that made them breathe heavily without becoming too stiff in their legs once a week. Moderate continues training group walked continuously at 70%–75% of peak heart rate for 47 min each session to make sure the training protocols were isocaloric. Walked continuously for 47 min without breathing heavily once a week	Supervised	Control group was told to follow advice from their family doctor with regard to physical activity; in addition, they met for 47 min of continuous treadmill walking at 70% of peak heart rate every 3 weeks.
Yeh et al. (2004)	Aerobic (Tai Chi)	2	12 weeks	Aerobic group was performed 1-h of tai chi trainings twice weekly for 12 weeks. A standard protocol of meditative warm-up exercises followed by five simplified tai chi movements (adapted from Master Cheng Man-Ch'ing's Yang-style short form). Traditional warm-up exercises included weight shifting, arm swinging, visualization techniques, and gentle stretches of the neck, shoulders, spine, arms, and legs. Each class was supervised by a physician, 35-min instructional videotape outlining the warm-up exercises and tai chi movements. Patients were encouraged to practice at home at least three times per week.	Supervised	Control group patients received usual care.
Yeh et al. (2011)	Aerobic (Tai Chi)	2	12 weeks	Aerobic group was performed 1-h 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.

et al., 2003) to 60 min (Conraads et al., 2007; Melo et al., 2019; Sandri et al., 2012; Yeh et al., 2011), with the most common session duration of 30–45 min (Abolahrari-Shirazi et al., 2018; Ahmad et al., 2014; Aksoy et al., 2015; Conraads et al., 2004; Eleuteri et al., 2013; Fu et al., 2013; Giallauria et al., 2006a,b; Giallauria et al., 2008; Maria-Sarullo et al., 2006; Masterson-Creber et al., 2015; Passino et al., 2006; Radi et al., 2017; Wisløff et al., 2007; Yeh et al., 2004). The session duration per session for the resistance training interventions was consisted of 30 min (Adamopoulos et al., 2014; Conraads et al., 2004; Karavidas et al., 2008; Kawauchi et al., 2017) to 45 min (Abolahrari-Shirazi et al., 2018), with the most common session duration of 30 min. The session duration per session for the concurrent interventions was consisted of 20 min (Marco et al., 2013) to 90 min (Prescott et al., 2009), with the most common session duration of 60 min (Conraads et al., 2004; Delagardelle et al., 2008). The exercise sessions and participants were supervised in all included studies.

The characteristics of control group-related interventions were used of without exercise interventions (Aksoy et al., 2015; Conraads et al., 2004; Delagardelle et al., 2008; Eleuteri et al., 2013; Giallauria et al., 2006-a; Giallauria et al., 2006-b; Giallauria et al., 2008; Kobayashi et al., 2003; Maria-Sarullo et al., 2006; van Berendoncks et al., 2010; Passino et al., 2006), optimal medical or standard therapy (Aksoy et al., 2015; Conraads et al., 2004; Conraads et al., 2007; Kawauchi et al., 2017; Radi et al., 2017), general home-based health care (Fu et al., 2013), usual care (Ahmad et al., 2014; Masterson-Creber et al., 2015; Melo et al., 2019; Nilsson et al., 2010; Prescott et al., 2009; Sandri et al., 2012-a; Yeh et al., 2004), time-matched education (Yeh et al., 2011), pamphlet for daily exercising at home (Abolahrari-Shirazi et al., 2018-a; Abolahrari-Shirazi et al., 2018-b), aerobic + resistance trainings similar to the exercise group at only 10% of their sustained maximal inspiratory pressure (Adamopoulos et al., 2014), functional electrical stimulation using a lower intensity of stimulation (5 Hz) (Karavidas et al., 2008), sham-inspiratory muscle training at an initial workload of 10 cmH2O (Marco et al., 2013), and advice from their family doctor with regard to physical activity (Wisløff et al., 2007).

3.4. BNP and NT-proBNP markers

In this systematic review and meta-analysis, the gold standard circulating markers of HF disease including serum/plasma BNP and NT-proBNP levels were measured in eight (Fu et al., 2013; Karavidas et al., 2008; Kawauchi et al., 2017; Kobayashi et al., 2003; Melo et al., 2019; Passino et al., 2006; Yeh et al., 2004, 2011) and 20 (Abolahrari-Shirazi et al., 2018; Adamopoulos et al., 2014; Ahmad et al., 2014; Aksoy et al., 2015; Conraads et al., 2004; Conraads et al., 2007; Delagardelle et al., 2008; Eleuteri et al., 2013; Giallauria et al., 2006a,b; Giallauria et al., 2008; Marco et al., 2013; Maria-Sarullo et al., 2006; Masterson-Creber et al., 2015; Nilsson et al., 2010; Passino et al., 2006; Prescott et al., 2009; Radi et al., 2017; Sandri et al., 2012; Van Berendoncks et al., 2010; Wisløff et al., 2007) articles, respectively.

3.5. Meta-analysis

3.5.1. BNP

According to eight exercise intervention arms compared to the control group, exercise training intervention did not significantly change the BNP marker [−0.122 (SMD and 95% CI: 0.322 to 0.079), p = 0.235] (Fig. 2). Heterogeneity analysis showed that there was no significant heterogeneity, thereby I-squared was less than 50% (I-squared = 001, P = 0.581). Analysis of subgroup by type of exercise training intervention did not show significant changes for both aerobic [−0.136 (SMD and 95% CI: 0.352 to 0.081), p = 0.220] and resistance [−0.036 (SMD and 95% CI: 0.574 to 0.501), p = 0.895] exercise interventions compared to the control group (Fig. 2).

3.5.2. NT-proBNP

According to 21 exercise intervention arms compared to the control group, exercise training intervention significantly decreased NT-proBNP marker [−0.229 (SMD and 95% CI: 0.386 to −0.071), p = 0.005] (Fig. 3), irrespective of overweight/obesity status. Heterogeneity analysis showed that I-squared was more than 50% (I-squared = 64.68, P = 0.001) and therefore heterogeneity was significant. Analysis of subgroup by type of exercise training revealed that there was a significant reduction in the NT-proBNP marker for aerobic exercise compared to the control group [−0.336 (SMD and 95% CI: 0.555 to −0.105), p = 0.004], whereas concurrent exercise did not show significant changes in the NT-proBNP marker [−0.134 (SMD and 95% CI: 0.350 to 0.083), p = 0.227], (Fig. 3).

3.5.3. Quality assessment and publication bias

The quality assessment of included studies (Pedro scores ranged between 15 and 7 with maximum 15 scores) is illustrated in Table 1. The visual interpretation of funnel plot was used to assess the publication bias. In addition, the Egger's test was used as another technique for assessing publication bias. Assessment of visual interpretation in the funnel plot showed symmetry, suggesting that there was no significant publication bias for BNP (Fig. 4). Egger's test for BNP was carried out to confirm this symmetry, which was confirmed to be non-significant (p = 0.752). In contrast, the visual interpretation of funnel plot showed asymmetry (no significant publication bias) for NT-proBNP (Fig. 5), which Egger's test was also carried out to confirm this asymmetry at a significance level (p = 0.041).

4. Discussion

The results of our systematic review and meta-analysis showed that exercise training improved NT-proBNP marker in patients with HF aged 49 ± 19.36 to 76.5 ± 9 yrs, irrespective of overweight/obesity status. In other words, our results indicated that aerobic exercise intervention has a small sized effect for reducing NT-proBNP marker in patients with HF. Therefore, the results of our study confirmed that aerobic exercise intervention was effective in improving NT-proBNP marker in patients with HF, whereas concurrent exercise intervention was no effective for NT-proBNP marker. In addition, our results indicated that exercise training interventions such as aerobic and resistance exercises were no effective for the BNP marker in patients with HF.

Recent investigations reported that endogenous peptide markers such as BNP and NT-proBNP are secreted mainly from heart tissue. The endogenous peptides have numerous beneficial effects on cardiovascular system such as vasodilation and natriuresis (Maeder et al., 2008). The results of studies showed that myocardial BNP release is inversely associated with peak VO2 in healthy humans (Maeder et al., 2018), which may be due to non-cardiac and cardiac mechanisms. The mechanism of beneficial effects of endogenous peptides would counteract the adverse adaptations of the activation of renin-angiotensin-aldosterone and sympathetic nervous systems (Maeder et al., 2018). In contrast, recent clinical studies on the BNP and NT-proBNP markers report a pathophysiological role in response to an increase in left ventricular stretching and wall stress and as well as myocardial stretch in patients with HF (Chow et al., 2017; Pearson et al., 2018; Topf et al., 2020). Recently, European society cardiology (ESC) guidelines revealed that BNP ≥100 and NT-proBNP ≥ 300 pg/ml values for confirmed acute HF and BNP ≥35 and NT-proBNP ≥ 125 pg/ml values for suspected HF are pathologic and diagnostic conditions for HF (McDonagh et al., 2021). These findings suggest that endogenous peptides, especially BNP and NT-proBNP play important roles in the pathologic and physiologic responses of the heart. It is possible that an optimal increase in BNP and NT-proBNP following exercise training intervention resulted in the regulation of cardiac function, increased physiological adaptations in left ventricular function, vasodilation and natriuresis in healthy humans

Model	Study name	Subgroup (type of exercise)	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Fu et al., 2013-a	Aerobic	-0.705	0.397	0.158	-1.483	0.073	-1.777	0.076
	Fu et al., 2013-b	Aerobic	-0.605	0.401	0.161	-1.391	0.181	-1.508	0.132
	Kobayashi et al., 2003	Aerobic	0.027	0.378	0.143	-0.714	0.768	0.071	0.943
	Melo et al., 2019-a	Aerobic	0.009	0.504	0.254	-0.979	0.996	0.017	0.986
	Melo et al., 2019-b	Aerobic	0.204	0.438	0.192	-0.655	1.063	0.466	0.641
	Passino et al., 2006	Aerobic	-0.334	0.219	0.048	-0.762	0.095	-1.527	0.127
	Yeh et al., 2001	Aerobic	0.193	0.200	0.040	-0.200	0.585	0.961	0.337
	Yeh et al., 2004	Aerobic	-0.264	0.367	0.134	-0.983	0.455	-0.720	0.472
Fixed Aerobic			-0.136	0.110	0.012	-0.352	0.081	-1.227	0.220
	Karavidas et al., 2008	Resistance	-0.211	0.388	0.151	-0.972	0.550	-0.542	0.588
	Kawauchi et al., 2017-a	Resistance	0.045	0.547	0.299	-1.027	1.117	0.083	0.934
	Kawauchi et al., 2017-b	Resistance	0.230	0.548	0.301	-0.845	1.304	0.419	0.675
Fixed Resistance			-0.036	0.274	0.075	-0.574	0.501	-0.132	0.895
Fixed Overall			-0.122	0.102	0.010	-0.322	0.079	-1.187	0.235

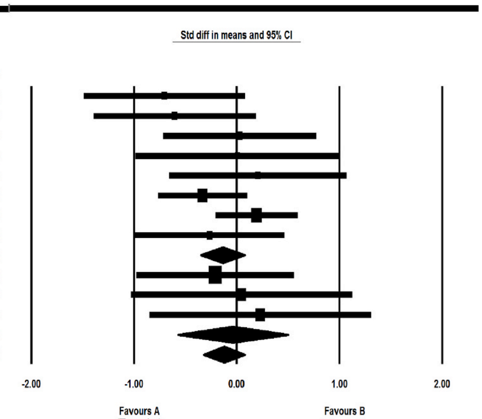

Fig. 2. Forest plot of the effects of exercise training on BNP. Data are standardized mean difference (SMD) (95% confidence intervals).

Model	Study name	Subgroup (Type of exercise)	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Abolahrari-Shirazi et al., 2018-b	Aerobic	−0.478	0.287	0.082	−1.040	0.085	−1.665	0.096
	Ahmad et al., 2014	Aerobic	0.008	0.066	0.004	−0.121	0.136	0.118	0.906
	Aksoy et al., 2015-a	Aerobic	0.030	0.365	0.133	−0.686	0.746	0.082	0.935
	Aksoy et al., 2015-b	Aerobic	0.224	0.366	0.134	−0.494	0.941	0.610	0.542
	Conraads et al., 2007	Aerobic	−0.031	0.486	0.236	−0.983	0.922	−0.063	0.950
	Eleuteri et al., 2013	Aerobic	0.119	0.437	0.191	−0.738	0.976	0.273	0.785
	Giallauria et al., 2006-a	Aerobic	−1.960	0.367	0.135	−2.679	−1.241	−5.343	0.000
	Giallauria et al., 2006-b	Aerobic	−1.668	0.367	0.135	−2.388	−0.949	−4.544	0.000
	Giallauria et al., 2008	Aerobic	−0.934	0.270	0.073	−1.463	−0.406	−3.464	0.001
	Maria-Sarullo et al., 2006	Aerobic	−0.419	0.261	0.068	−0.931	0.092	−1.606	0.108
	Masterson-Creber et al., 2015	Aerobic	−0.051	0.112	0.013	−0.271	0.168	−0.460	0.645
	Nilsson et al., 2010	Aerobic	0.420	0.229	0.052	−0.029	0.869	1.835	0.067
	Passino et al., 2006	Aerobic	−0.243	0.218	0.047	−0.670	0.184	−1.116	0.264
	Radi et al., 2017	Aerobic	−0.078	0.190	0.036	−0.451	0.295	−0.411	0.681
	Sandri et al., 2012-a	Aerobic	−0.589	0.373	0.139	−1.320	0.142	−1.579	0.114
	Sandri et al., 2012-b	Aerobic	−0.407	0.369	0.136	−1.130	0.316	−1.102	0.270
	Wisloff et al., 2007-a	Aerobic	−0.047	0.577	0.333	−1.178	1.085	−0.081	0.936
	Wisloff et al., 2007-b	Aerobic	−0.506	0.566	0.320	−1.615	0.603	−0.895	0.371
Random Aerobic			−0.336	0.117	0.014	−0.566	−0.105	−2.858	0.004
	Abolahrari-Shirazi et al., 2018-a	Concurrent	−0.183	0.283	0.080	−0.739	0.372	−0.647	0.518
	Adamopoulos et al., 2014	Concurrent	−0.376	0.308	0.095	−0.979	0.228	−1.221	0.222
	Conraads et al., 2004	Concurrent	−0.218	0.288	0.083	−0.783	0.346	−0.757	0.449
	Delagardelle et al., 2008-a	Concurrent	0.116	0.396	0.157	−0.660	0.892	0.293	0.770
	Delagardelle et al., 2008-b	Concurrent	0.079	0.459	0.210	−0.820	0.977	0.171	0.864
	Marco et al., 2013	Concurrent	0.046	0.426	0.182	−0.790	0.882	0.108	0.914
	Prescott et al., 2009	Concurrent	−0.223	0.307	0.094	−0.825	0.378	−0.729	0.466
	van-Berendoncks et al., 2010	Concurrent	−0.054	0.226	0.051	−0.497	0.389	−0.239	0.811
Random Concurrent			−0.134	0.111	0.012	−0.350	0.083	−1.209	0.227
Random Overall			−0.229	0.080	0.006	−0.386	−0.071	−2.839	0.005

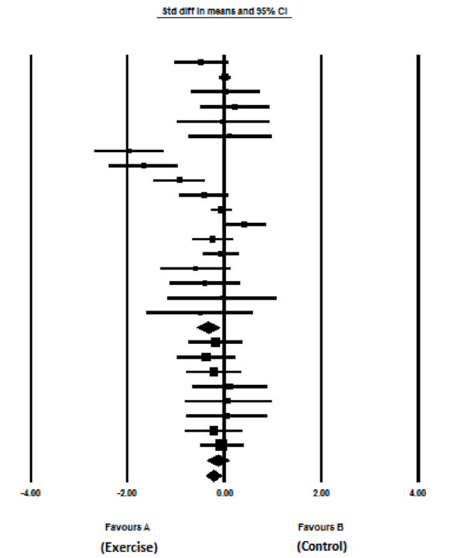

Fig. 3. Forest plot of the effects of exercise training on NT-proBNP. Data are standardized mean difference (SMD) (95% confidence intervals).

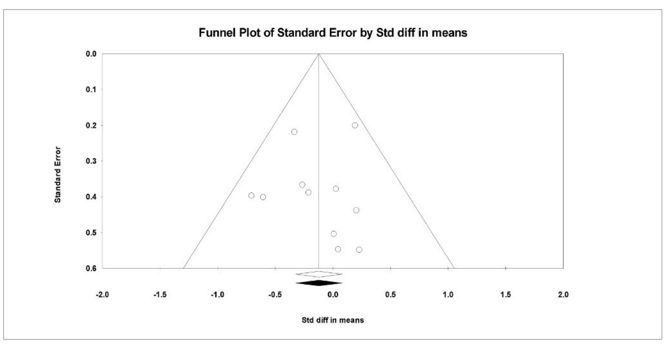

Fig. 4. Funnel plot for BNP marker.

(Maeder et al., 2008). However, a decrease in BNP and NT-proBNP values following exercise training has a positive adaptation on CVS in HF patients (McDonagh et al., 2021; Santoso et al., 2020; Pearson et al., 2018), which was observed after aerobic exercise training for NT-proBNP marker, irrespective of overweight/obese status, in our systematic review and meta-analysis. The findings of our systematic review and meta-analysis were consistent with the results of previous systematic review and meta-analysis studies (Santoso et al., 2020; Pearson et al., 2018; Cipriano et al., 2014; Smart et al., 2012; Smart and Steele, 2010) and were inconsistent with others (Pearson et al., 2018; Smart et al., 2012; Smart and Steele, 2010).

The findings of our study were consistent with the results of Santoso et al. that aerobic exercise training was significant in lowering NT-proBNP values compared to the control group (Santoso et al., 2020). In addition, Pearson et al. reported that conventional exercise training (exercises that incorporate an individual body part with single or mutli-joint movements such as presses, rows, fly, squats, etc.) has a significant improvement in NT-proBNP biomarker in HF patients (Pearson et al., 2018). Cipriano et al. demonstrated that aerobic exercise training was effective at improving NT-proBNP values in systolic HF patients (Cipriano et al., 2014). Smart et al. showed that aerobic and resistance exercise trainings had favorable roles on NT-proBNP marker in HF (Smart et al., 2012). Moreover, Smart and Steele reported that resistance and aerobic exercises were effective in lowering NT-proBNP values in patients with HF (Smart and Steele, 2010). In contrast, Pearson et al. demonstrated that exercise training was significant in improving BNP values in patients with HF (Pearson et al., 2018). Smart et al. reported that resistance and aerobic exercise interventions were

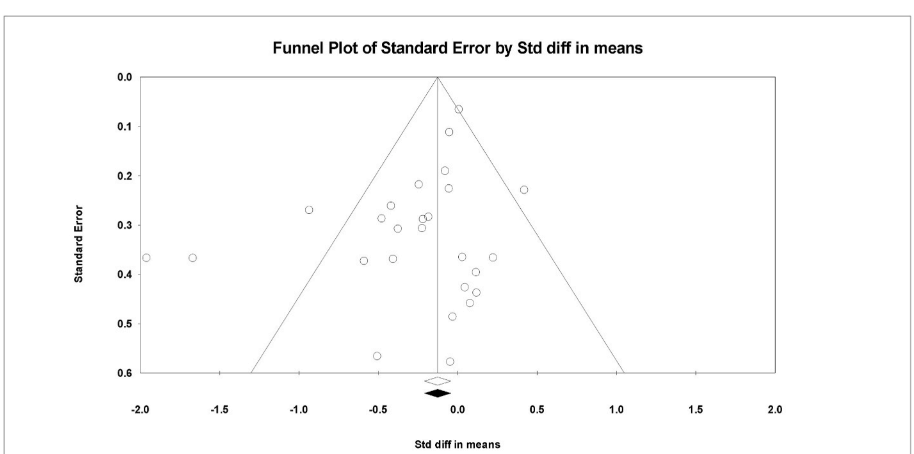

Fig. 5. Funnel plot for NT-proBNP marker.

significant in lowering BNP in HF patients (Smart et al., 2012). In addition, Smart and Steele indicated that resistance and aerobic exercises were significant at improving BNP marker in HF patients (Smart and Steele, 2010), which were inconsistent with the results of our systematic review and meta-analysis.

The results of studies indicate that higher concentrations of BNP and NT-proBNP markers are associated with a higher risk of morbidity and mortality from any cause, pump failure and cardiac sudden death and as well as HF (Rørth et al., 2020). In addition, circulating BNP and NT-proBNP levels are inversely associated with serum insulin (Neeland et al., 2013; Mehra et al., 2004; Hamasaki, 2016), visceral fat (Neeland et al., 2013; Hamasaki, 2016), body mass index (BMI) (Neeland et al., 2013; Hamasaki, 2016), waist circumference (Hamasaki, 2016) and as well as overweight/obesity status (Neeland et al., 2013; Mehra et al., 2004; Hamasaki, 2016). It seems that the effects of pathologic and physiologic conditions on circulating BNP and NT-proBNP values are contradictory. In other words, the results of acute exercise showed that circulating BNP and NT-proBNP levels significantly increase immediately after exercise training, a reduction on the following day, and return to baseline values after one week (Hamasaki, 2016). It is possible that an increase in circulating BNP and NT-proBNP levels is related to the exercise-induced physiological endocrine responses in response to an increase in the myocardial stress (Hamasaki, 2016), suggesting that BNP and NT-proBNP releases during and after exercise training are related to the cytoprotective and growth-regulating responses as well as physiological reaction of cardiomyocytes, but not myocardial damage (D'Souza et al., 2003; Hamasaki, 2016). However, the physiological mechanism of exercise training-induced BNP and NT-proBNP releases remain unclear.

The results of systematic review and meta-analysis studies indicated that a reduction in NT-proBNP by aerobic exercise is associated with improved cardiopulmonary function, increased peak VO2, improved workload and increased left ventricular ejection fraction (LVEF) in patients with HF (Santoso et al., 2020), which was consistent with the results of our systematic review and meta-analysis. Since the exercise training, especially aerobic exercise plays an important role in improving myocardial stretch markers such as BNP and NT-proBNP, it is possible that aerobic exercise training as a non-pharmacological intervention can be considered as a cardiac rehabilitation programme (a class 1 recommendation) in HF patients. It has been reported that BNP and NT-proBNP values did not change after resistance training in elderly subjects (Beltran Valls et al., 2014). However, some studies demonstrated that muscle mass inversely related to the BNP levels (Yamashita et al., 2014). It is possible that the changes in BNP and NT-proBNP concentrations by resistance training are not related to the myocardial stress-induced NP secretion (Hamasaki, 2016). Based on the science of training in exercise physiology, optimal protocol and intensity, frequency and duration of exercise trainings are related to the release of cardiac biomarkers and as well as BNP and NT-proBNP markers (Hamasaki, 2016) although differential effects of exercise interventions on NPs secretions in HF and/or healthy subjects are not fully understood.

4.1. Strengths and limitations

The mean age 49–76.5 yrs, BMI 24.5–30 kg/m^2, the most common period of 3 months (12 weeks), a focus on HF patients, subgroup analysis based on type of exercise and as well as lack of reports of morbidity and mortality associated with the supervised exercise training programmes in HF patients were strengths of our meta-analysis. However, the current systematic review and meta-analysis had some limitations. The lack of concurrent exercise for BNP marker, lack of resistance training for NT-proBNP marker, low number of included studies based on subgroup by type of exercise training, and as well as heterogeneity and publication bias according to the data were limitations of this meta-analysis.

5. Conclusions

In conclusion, exercise training, especially aerobic exercise was useful in improving (lowering) circulating NT-proBNP concentrations in patients with HF, irrespective of overweight/obesity status, although the BNP marker remained unchanged.

The main clinical implications of our systematic review and meta-analysis were a reduction in circulating NT-proBNP levels after exercise training, especially aerobic exercise training in HF patients. Therefore, exercise training, especially aerobic training as a non-pharmacological intervention and as well as a cardiac rehabilitation programme (a class 1 recommendation) can be used at improving NT-proBNP marker for the prevention, management, and assessment of HF, irrespective of overweight/obesity status.

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CRediT authorship contribution statement

Abbas Malandish: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Roles, Writing – original draft, Writing – review & editing. **Niloufar Ghadamyari:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Roles, Writing – original draft, Writing – review & editing. **Asma Karimi:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Roles, Writing – original draft, draft, Writing – review & editing. **Mahdi Naderi:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Roles, Writing – original draft, Writing – review & editing.

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.

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