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Article in ESC Heart Failure · July 2022

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Exercise and nutritional interventions on sarcopenia and frailty in heart failure: a narrative review of systematic reviews and meta-analyses

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Abstract

The purpose of this review is to describe the present evidence for exercise and nutritional interventions as potential contributors in the treatment of sarcopenia and frailty (i.e. muscle mass and physical function decline) and the risk of cardiorenal metabolic comorbidity in people with heart failure (HF). Evidence primarily from cross-sectional studies suggests that the prevalence of sarcopenia in people with HF is 37% for men and 33% for women, which contributes to cardiac cachexia, frailty, lower quality of life, and increased mortality rate. We explored the impact of resistance and aerobic exercise, and nutrition on measures of sarcopenia and frailty, and quality of life following the assessment of 35 systematic reviews and meta-analyses. The majority of clinical trials have focused on resistance, aerobic, and concurrent exercise to counteract the progressive loss of muscle mass and strength in people with HF, while promising effects have also been shown via utilization of vitamin D and iron supplementation by reducing tumour necrosis factor-alpha (TNF- α), c-reactive protein (CRP), and interleukin-6 (IL-6) levels. Experimental studies combining the concomitant effect of exercise and nutrition on measures of sarcopenia and frailty in people with HF are scarce. There is a pressing need for further research and well-designed clinical trials incorporating the anabolic and anti-catabolic effects of concurrent exercise and nutrition strategies in people with HF.

Keywords Heart failure; Sarcopenia; Frailty; Exercise; Nutrition; Quality of life

Received: 8 February 2022; Revised: 16 May 2022; Accepted: 27 June 2022

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Introduction

Heart failure (HF) is a clinical condition characterized by structural and/or functional myocardial defects, leading to elevated intracardiac pressures and/or insufficient cardiac output at rest and/or during physical activity.¹ The two main phenotypes of acute or chronic HF are HF with reduced left ventricle ejection fraction (HFrEF) due to systolic dysfunction and HF with preserved ejection fraction (HFpEF) that is mainly related to diastolic dysfunction.^{2,3} HFrEF is defined as left ventricular ejection fraction at $\leq 40\%$, HF with

mid-range or mildly reduced ejection fraction as left ventricular ejection fraction at 41–49%, and HFpEF as left ventricular ejection fraction $\geq 50\%$.¹ Worldwide, it is estimated that 64.3 million people are living with HF and its 1, 2, 5, and 10 year mortality rate is approximately at 87%, 73%, 57%, and 35%, respectively.⁴ An existing complication in people with HF that may accelerate mortality rate is the loss of muscle mass and physical function, which are strongly linked to sarcopenia and frailty. The aim of this review is to highlight the prevalence, mechanistic link, and impact of sarcopenia and frailty in people with HF, espe-

cially in those with cardiorenal metabolic syndrome, and investigate the potential of exercise and nutrition interventions on physical capacity, inflammatory markers, and quality of life.

Prevalence and mechanisms of sarcopenia in heart failure

According to recent research, the prevalence of sarcopenia in people with HF is 37% for men and 33% for women, ranging between 10% and 69%, although substantial heterogeneity between studies due to the varied methods utilized for sarcopenia diagnosis has been observed.⁵ Particularly, these variations have been attributed to the different definitions utilized by the 2019 Asian Working Group guidelines [handgrip strength < 28 kg for men and < 18 kg for women; appendicular skeletal muscle index (ASMI) < 7.0 kg/m² for men and < 5.4 kg/m² for women; 6 m walk < 1.0 m/s; 5-time chair stand test ≥ 12 s; short physical performance battery score ≤ 9]⁶ and the 2019 European Working Group recommendations (handgrip strength < 27 kg for men and < 16 kg for women; ASMI < 7.0 kg/m² for men and < 5.5 kg/m² for women; gait speed ≤ 0.8 m/s; timed up-to-go test ≥ 20 s; 400 m walking test ≥ 6 min).⁷ The findings regarding the prevalence of sarcopenia in people with HF are therefore inconsistent, and thus, the use of standardized international diagnostic criteria could improve the detection rate of sarcopenia in this group.

Moreover, multiple factors have been associated with exacerbated muscle loss among people with HF, including impaired skeletal muscle mitochondrial density, function, and oxidative capacity.⁸ These observations demonstrate that people with HF have lower oxidative phosphorylation adenosine triphosphate (ATP) production rates compared with normal individuals.^{8,9} Additionally, magnetic resonance imaging (MRI) measurements have revealed an increased intramuscular fat concentration¹⁰ and a decreased muscle fibre type I to type II ratio in people with HF¹¹ that are accompanied by reduced levels of myoglobin.¹² The changes in macrostructure and microstructure of the skeletal muscle of people with HF may be explained by increased pro-inflammatory states and insulin resistance, which are responsible for mitochondrial dysfunction and elevated skeletal muscle protein catabolism. Indeed, increased oxidative stress, myostatin, and systemic inflammation—higher levels of tumour necrosis factor- α (TNF- α), interleukin-6 (IL-6), interleukin-1 beta (IL-1 β), and c-reactive protein (CRP)—may lead to elevated ubiquitin proteasome system (UPS), activating E1, E2, and E3 ligases, which are major contributors to myofibril degeneration, myocyte apoptosis, and overall muscle proteolysis.^{12,13} Particularly, the UPS is a major pathway of intracellular protein degradation that impairs cardiac cell

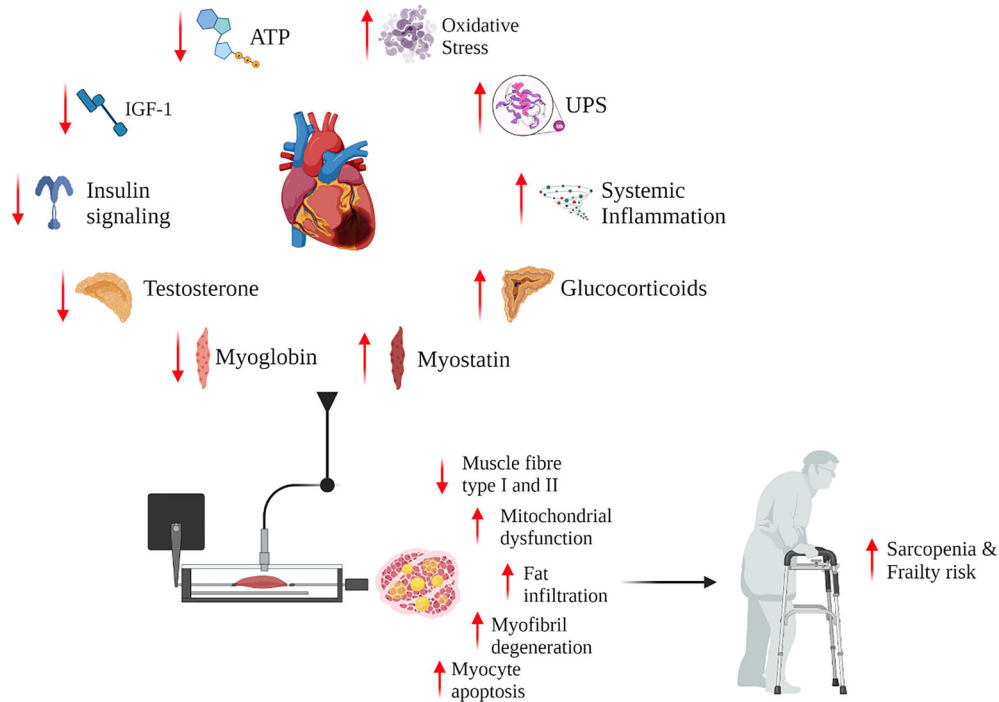
structure through activation of E3 ligase substrate proteins and Atrogin-1/MAFbx, and down-regulation of the mammalian target of rapamycin (mTOR) pathway, a regulator of hypertrophic signalling.¹⁴ HF is impacted by anabolic hormonal alterations such as impaired glucocorticoid receptor, insulin, and insulin growth factor-1 (IGF-1) signalling, and decreased endogenous testosterone,^{15,16} which augment the risk of anabolic resistance (*Figure 1*).¹⁷

There is also evidence that the prognosis of sarcopenia when complicating HF may be distinct in HFpEF in comparison with those with HFrEF.^{18,19} Bio-impedance analysis has shown a higher proportion of patients with low ASMI and functional impairment (low handgrip strength and slow gait speed) undergoing HFpEF compared with those with HFrEF; however, no differences in mortality rate between groups were observed.²⁰ Therefore, the distinction between the two HF phenotypes may be critical in the prognosis of sarcopenia and identifying risk of obesity-related complications.

Prevalence of frailty in heart failure

Numerous studies have evaluated the prevalence of frailty in people with HF, reaching approximately 45%.²¹ To date, the Clinical Frailty Scale (CFS) and Fried's phenotypic definition are the most utilized assessment tools for frailty; however, there is an ongoing debate regarding which tool is most appropriate for use in people with HF.^{22,23} The CFS is a descriptive 9-point scale that has been designed to summarize the overall fitness or frailty levels in older adults, used for both prognosis and setting care targets.²² The CFS focuses on multiple parameters of independence, including balance and overall mobility, as well as the ability of performing activities of daily living (i.e. cooking, shopping, or eating); greater CFS scores indicate a higher risk of frailty.²² Furthermore, according to Fried's phenotypic definition, frailty is defined by the presence of any three from the following characteristics—slowness (5 m gait speed), weakness (handgrip strength), low physical activity, exhaustion (as assessed by the Centre for Epidemiologic Studies Depression Scale), and shrinking (weight loss, appendicular lean mass, and serum albumin).²⁴ However, Fried's phenotypic definition is uncommonly used in routine clinical practice as it can be time intensive and impractical because it involves a combination of self-reported assessment and objective physical function tests. Therefore, the CFS has been proposed as the preferred frailty assessment tool and that is readily utilized in older populations.²⁵ Studies have demonstrated that the CFS can predict mortality independently in acute decompensated HF.^{26,27} Future studies, however, are needed to develop a standardized approach for the assessment and management of frailty specifically in people with HF, which may assist with the implementation

Figure 1 Mechanisms involved in sarcopenia and frailty during heart failure. Multiple anabolic and catabolic pathways are involved in sarcopenia during heart failure incidence. Increased oxidative stress and systemic inflammation, as well as glucocorticoid and myostatin signalling are contributors to stimulating catabolic pathways including the ubiquitin proteasome system (UPS). Additionally, these changes are accompanied by altered insulin and insulin growth factor-1 (IGF-1) responses, and lower production of adenosine triphosphate (ATP) and endogenous testosterone. These precursors of anabolic resistance may lead to mitochondrial dysfunction, myocyte apoptosis, myofibril degeneration, increased intramuscular fat, and higher muscle fibre type I to II ratio, exacerbating sarcopenia and frailty risk in people with heart failure.



of targeted treatments and ultimately lead to a better quality of life.

The biological underpinnings of frailty remain unclear, and the interaction with HF is complex. It is conceptually plausible to consider chronic inflammation as an important underlying factor, which is linked with both frailty and HF. Frailty is associated with higher levels of circulating inflammatory cytokines and incidence of sarcopenia, features that are also associated with HF.^{28,29} Finally, other potential mechanisms that may underpin frailty causing HF are DNA damage, impaired autophagy, and mitochondrial dysfunction, which are biological processes that occur in both aging and HF.

Prevalence of cardiorenal metabolic syndrome in heart failure and impact upon sarcopenia

Cardiorenal metabolic syndrome refers to the concomitant presence of heart disease, type 2 diabetes mellitus (T2DM), and chronic kidney disease (CKD) through a crosslinked organ-induced dysregulation that has emerged

via biochemical, inflammatory, and immunological pathways.³⁰ There is a bidirectional interaction between CKD and HF, whereby renal failure may lead to ureamic cardiomyopathy, characterized by left ventricular hypertrophy and diastolic dysfunction, and is associated with electrophysiological changes, while the resulting cardiac insufficiency exacerbates renal impairment through hypoperfusion.³¹ Observational research has shown that CKD and T2DM have a 40% and 12% prevalence in people with HF, respectively.³¹ CKD is associated with low-grade inflammation and elevated myostatin levels and consequently an increased risk of muscle loss.³² Furthermore, CKD is accompanied by increased rates of hypogonadism that further exacerbate the risk of muscle mass and strength reduction.³³ Therefore, CKD combined with HF may amplify the loss of muscle mass, muscle strength, and worsen physical performance, compared with HF alone. Additionally, insulin resistance in individuals with T2DM may stimulate proteolytic cell systems, including UPS, calpain, and caspase pathways.³⁴ Hence, the coexistence of HF, diabetes, and CKD may aggravate the risk of muscle loss and sarcopenia via accelerating mitochondrial dysfunction and muscle fibre type I and II atrophy in both HF_{rEF} and HF_{pEF}.³⁵ The implementation of interventions targeting the

bidirectional relationship of sarcopenia and HF may mitigate cardiorenal metabolic disease progression and its adverse outcomes.

influence outcome measures (i.e. cancer, muscular dystrophies, and inflammatory conditions such as arthritis); and (iv) received enteral nutrition.

Search strategy

The protocol of this narrative review search was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD: 42021266773).

Three independent reviewers (KP, MS, and BT) searched PubMed, Scopus, Web of Science, and Cochrane library from inception until 30 August 2021. A search strategy involving the following terms was used: 'heart failure' OR 'preserved ejection fraction' OR 'reduced left ventricle ejection fraction' AND 'resistance exercise' OR 'resistance training' OR 'strength training' OR 'concurrent' OR 'aerobic' OR 'nutrition*' OR 'diet*' OR 'protein supplementation' OR 'whey protein' OR 'soy protein' OR 'casein' OR 'iron' OR 'vitamin D' OR 'polyphenols' OR 'omega-3' AND 'sarcopenia' OR 'frailty' OR 'quality of life' OR 'muscle mass' OR 'musc* strength' OR 'physical performance' OR 'systemic inflammation' OR 'cytokines'. Discrepancies in the literature search process were resolved by a third investigator (MI). Studies were included based on the following criteria: (i) must be a randomized controlled trial (RCT) and (ii) included patients with HF aged 18 years and over. Studies were excluded if they (i) were non-RCTs; (ii) included patients with HF aged <18 years; (iii) included patients with disease pathologies that could

Search results

The initial literature search yielded 6496 publications. After exclusion of 1657 duplicates, 4839 publications were identified. Following screening of titles and abstracts, 4798 publications with irrelevant study design were excluded and 41 systematic reviews and meta-analyses were assessed for eligibility. Of these, four studies were study protocols, one study provided enteral nutrition, and one study had incompatible study population (i.e. patients with hypogonadism). In total, 35 studies were included in this narrative review (Figure 2).

Impact of exercise on muscle loss, physical capacity, and quality of life in heart failure

Resistance and endurance exercise interventions have been widely used to promote skeletal muscle anabolism and enhance physical capacity. Resistance exercise is considered the most valuable tool against age-related muscle loss, as it is known to improve the muscle protein synthetic rates³⁶

Figure 2 Flowchart of the employed literature search.

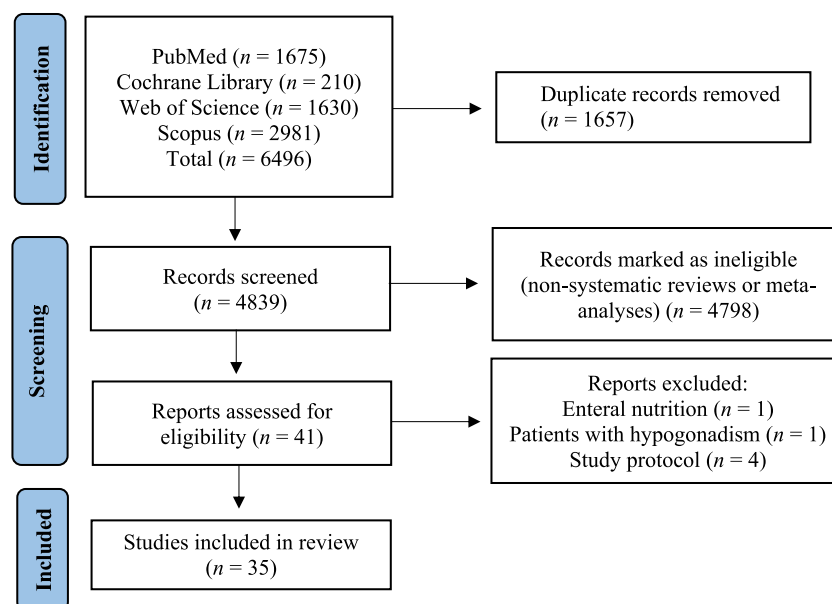


Table 1 Effects of resistance exercise only on physical capacity and quality of life in patients with heart failure based on previous meta-analyses

Author	No. of studies	No. of participants	Outcomes	P value	Mean difference (95% CI)	I ²
Fisher 2021 ³⁹	4	81	Leg strength—1RM (leg press)	0.003	0.76 (0.26, 1.25)	0%
	4	78	Knee extensors—1RM (leg extension)	0.001	1.41 (0.57, 2.25)	60%
	2	36	Knee flexors—1RM (leg curl)	0.08	1.16 (−0.12, 2.43)	57%
	3	86	Isokinetic peak torque (knee extensors 60°/s Nm)	0.05	0.42 (−0.01, 0.85)	0%
	2	54	Isokinetic peak torque (knee extensors 180°/s Nm)	0.18	0.37 (−0.17, 0.91)	0%
	3	63	Maximal isometric strength (knee extensors)	0.08	0.74 (−0.10, 1.58)	60%
	4	71	1RM upper body (pectoralis)	0.0009	0.85 (0.35, 1.35)	0%
	2	39	1RM lateral pull-down (latissimus dorsi)	0.01	0.84 (0.17, 1.51)	0%
	3	74	Combined muscle strength	0.0008	0.83 (0.34, 1.31)	0%
	6	140	6MWD	<0.0001	49.94 m (34.59, 65.29)	0%
	5	108	HRQoL	<0.0001	−8.25 (−11.51, −4.99)	0%
Dallas 2021 ⁵⁴	4	105	HRQoL	0.19	−0.35 (−0.86, 0.17)	39%
Ruku 2021 ⁴²	8	288	Lower extremity strength	0.0002	1.02 (0.48, 1.57)	77%
	5	144	Upper extremity strength	0.0007	0.58 (0.24, 0.92)	12%
Slimani 2018 ⁶⁷	2	105	HRQoL	0.61	−0.17 (−0.80, 0.47)	63%
Giuliano 2017 ⁴¹	4	71	Leg press 1RM	0.0001	0.60 (0.43, 0.77)	83.5%
		118	Isokinetic peak torque 60°/s	0.782	6.84 Nm (−0.75, 14.43)	0%
		54	Isokinetic peak torque 180°/s	0.986	5.02 Nm (−7.07, 17.12)	0%
			HRQoL	0.624	−5.71 (−9.85, −1.56)	0%

1RM, one-repetition maximum; 6MWD, 6 min walking distance; CI, confidence interval; HRQoL, health-related quality of life.

Table 2 Effects of aerobic exercise only on physical capacity, quality of life, and inflammatory markers in patients with heart failure based on previous meta-analyses

Author	No. of studies	No. of participants	Outcomes	P value	(Standardized) Mean difference (95% CI)	I ²
Fukuta 2019 ⁵¹	5	284	6MWD	0.002	33.88 m (12.38, 55.38)	-
	7	372	MLFHQ	0.003	-9.06 (-15.04, -3.08)	-
Slimani 2018 ⁶⁷	6	283	HRQoL	0.001	-1.04 (-1.67, -0.41)	94%
Pearson 2018 ⁸²	3	97	CRP	0.05	1.61 (-0.01, 3.23)	90%
Fukuta 2016 ⁶³	4	192	6MWD	0.02	30.28 m (4.32, 56.23)	-
	5	217	MLFHQ	0.002	-8.98 (-14.63, -3.32)	-
Chan 2016 ⁶⁶	5	202	6MWD	<0.0001	32.13 m (17.20, 47.05)	83%
	7	275	MLFHQ	<0.0001	-6.77 (-9.70, -3.84)	48%
Pandey 2015 ⁶⁸	5	237	MLFHQ	0.02	-3.97 (-7.21, -0.72)	0%

6MWD, 6 min walking distance; CI, confidence interval; CRP, c-reactive protein; HRQoL, health-related quality of life; MLFHQ, Minnesota Living with Heart Failure Questionnaire.

and promote type II muscle fibre hypertrophy.³⁷ Endurance and resistance exercise have an antioxidant effect by increasing glutathione reductase and catalase activity and reducing glutathione peroxidase in muscle tissue.³⁸ Resistance training sessions lasting 40–60 min, consisting of 1–2 sets/exercise, 10–15 repetitions each, performed 2–3 times/week have shown to effectively improve the lower and upper extremity muscle strength, peak torque, and maximum leg press strength in people with HFrEF and HFpEF.^{39–43} Most trials included in recent meta-analyses have utilized a 12 week exercise regime that demonstrated significant improvements in both upper [standardized mean difference (SMD): 0.85, 95% confidence interval (CI): 0.35–1.35³⁹; SMD: 0.46, 95% CI: 0.05–0.87]⁴² and lower extremity muscle strength (SMD: 0.76, 95% CI: 0.26–1.25³⁹; SMD: 1.46, 95% CI: 0.41–2.50)⁴² (Table 1). Additionally, concurrent training (endurance and resistance exercise combined) has also been shown to lead to positive outcomes on isokinetic knee extensor (SMD: 0.7, 95% CI: 0.3–1.0),⁴³ quadriceps (SMD: 0.32, 95% CI: 0.03–0.61),⁴⁴ and combined lower and upper body strength (SMD: 0.59, 95% CI: 0.22–0.96).⁴⁵ Furthermore, previous studies have reported significant improvements in 6 min walking test (6MWT) following resistance^{46,47} and concurrent training.^{45,47–49} These changes after resistance (MD: 49.94 m, 95% CI: 34.59–65.29)³⁹ and concurrent training (MD: 15.86 m, 95% CI: 7.23–24.49)⁵⁰ may potentially be attributed to increased lower limb strength.

Moreover, endurance exercise alone for 20–40 min, 3 times/week, at 60–70% VO₂max for 12–24 weeks, has been associated with an improved 6MWT (MD: 33.9 m, 95% CI: 12.38–55.34⁵¹; MD: 21.0 m, 95% CI: 1.57–40.4)⁴⁸ due to enhanced peak oxygen capacity. Similarly, functional electrical stimulation performed 5 times/week, each session lasting 60 min, for 5 weeks, has been shown to improve 6MWT in people with HF (MD: 46.9 m, 95% CI: 22.5–71.3),⁵² suggesting that endurance exercise at appropriately adjusted duration and intensity may also improve muscle strength and physical performance in people with HF.

The effect of exercise interventions on quality of life has been extensively studied (Tables 1–4). Recent meta-analyses

have revealed that concurrent exercise may improve the Kansas City Cardiomyopathy Questionnaire (KCCQ) scores at 6 months of follow-up (MD: 1.94, 95% CI: 0.35–3.56),⁵³ the health-related quality of life (HRQoL) scores (MD: -0.84, 95% CI: -1.19 to -0.49),⁵⁴ and the Minnesota Living with Heart Failure Questionnaire (MLFHQ) scores (MD: -6.62, 95% CI: -11.40 to -1.84),⁵ while similar findings have also been displayed previously.^{55–62} Conventional, continuous, and high-intensity endurance training may all significantly improve quality of life, which has been also shown to be correlated with peak oxygen uptake,^{51,54,63–70} although one study did not report any changes (SMD: 0.5 points out of 105, 95% CI: -4.4 to 5.4).⁷¹

Effect of nutrition interventions on muscle loss and physical capacity in heart failure

Only a few systematic reviews and meta-analyses have explored the effects of nutrition interventions on sarcopenia measures in people with HF. Vitamin D supplementation utilizing normal (2000–4000 IU/day) and large infusions (50 000 IU/week) for 3–12 months have not exhibited greater 6MWT (MD: -23.30 m, 95% CI: -58.31 to 11.72), although improvements in quality of life were observed (MD: 6.75, 95% CI: 2.87–10.64).⁷² Interestingly, greater 6MWT and quality of life have been demonstrated following oral iron supplementation^{73–75} and intravenous iron therapy.^{76,77} These findings may have been the result of improved haemoglobin resynthesis,⁷⁸ considering that the beneficial effects observed were more pronounced in iron-deficient people with HF. Nevertheless, meta-analyses assessing the impact of nutrition interventions are scarce due to paucity of experimental data. Accordingly, only one systematic review has investigated the effects of protein and essential amino acid (EAA) supplementation (duration: 6 weeks to 6 months; dose: 8 g/day EAA) on muscle strength, revealing no significant changes compared with controls.⁷⁹ Protein sup-

Table 3 Effects of resistance and aerobic (concurrent) exercise combined on physical capacity, quality of life, and inflammatory markers in patients with heart failure based on previous meta-analyses

Author	No. of studies	No. of participants	Outcomes	P value	(Standardized) Mean difference (95% CI)	I ²
Cavalheiro 2021 ⁵⁰	10	1509	6MWD	0.0003	15.86 m (7.23, 24.49)	74%
Righi 2021 ⁴⁴	10	1459	MLHFQ	0.007	-6.62 (-11.40, -1.84)	99%
Ye 2020 ⁶⁹	5	194	Quadriceps muscle strength	0.031	0.32 (0.03, 0.61)	0%
Long 2019 ⁷⁰	3	119	HRQoL	0.368	-5.34 (-10.12, -0.56)	0%
Gomes-Neto 2019 ⁴³	17	1995	MLHFQ	<0.0001	-7.11 (-10.49, -3.73)	82%
	7	315	Knee muscle strength	<0.0001	0.64 (0.41, 0.87)	0%
Wang 2019 ⁴⁵	8	524	HRQoL	0.0003	-9.83 (-15.15, -4.51)	83%
	4	121	Upper and lower body muscle strength	0.002	0.59 (0.22, 0.96)	0%
	6	320	6MWD	<0.0001	46.36 m (28.41, 64.31)	0%
	7	523	HRQoL	0.005	-9.22 (-15.64, -2.79)	73%
Ciani 2018 ⁶¹	21	4420	HRQoL	<0.001	-0.48 (-0.73, -0.24)	90%
Palmer 2018 ⁴⁹	9	1239	6MWD	<0.0001	41.15 m (16.68, 65.63)	85%
	23	20 244	6MWD	<0.0001	49.82 (26.52, 73.13)	95%
	30	1254	MLFHQ	<0.0001	1.16 (0.76, 1.56)	95%
Chan 2016 ⁶⁶	13	1270	HRQoL	0.05	-0.42 (-0.71, -0.13)	82%
Pearson 2018 ⁸²	4	175	IL-6	0.01	0.41 (0.09, 0.72)	0%
	6	244	TNF-α	0.002	0.42 (0.15, 0.68)	0%
Zwisler 2016 ⁵⁵	5	501	MLFHQ	0.14	-3.24 (-7.52, 1.04)	37%
Dieberg 2015 ⁵⁶	5	212	6MWD	<0.0001	32.13 m (17.20, 47.05)	83%
	6	216	MLFHQ	<0.0001	-6.50 (-9.47, -3.53)	52%
Sagar 2015 ⁵⁷	12	1270	MLFHQ	0.0007	-5.83 (-9.21, -2.44)	70%
Chen 2013 ⁵⁸	6	425	6MWD	<0.0001	50.05 m (28.37, 71.73)	42%
	5	401	HRQoL	0.30	-0.22 (-0.64, 0.19)	73%
Taylor 2012 ⁵⁹	4	155	MLFHQ	<0.0001	-7.32 (-11.38, -3.26)	4%
van der Meer 2012 ⁶⁰	10	2161	6MWD	0.0005	47.90 m (20.92, 74.87)	82%
	9	699	MLFHQ	0.0008	-6.89 (-10.92, -2.86)	57%
Davies 2010 ⁶²	6	493	MLFHQ	0.004	-10.33 (-15.89, -4.77)	71%
Hwang 2010 ⁴⁶	6	628	6MWD	0.0141	30.41 m (6.13, 54.68)	-
van Tol 2006 ⁴⁷	15	599	6MWD	<0.0001	46.2 m	-
	9	463	MLFHQ	<0.0001	-9.7	-

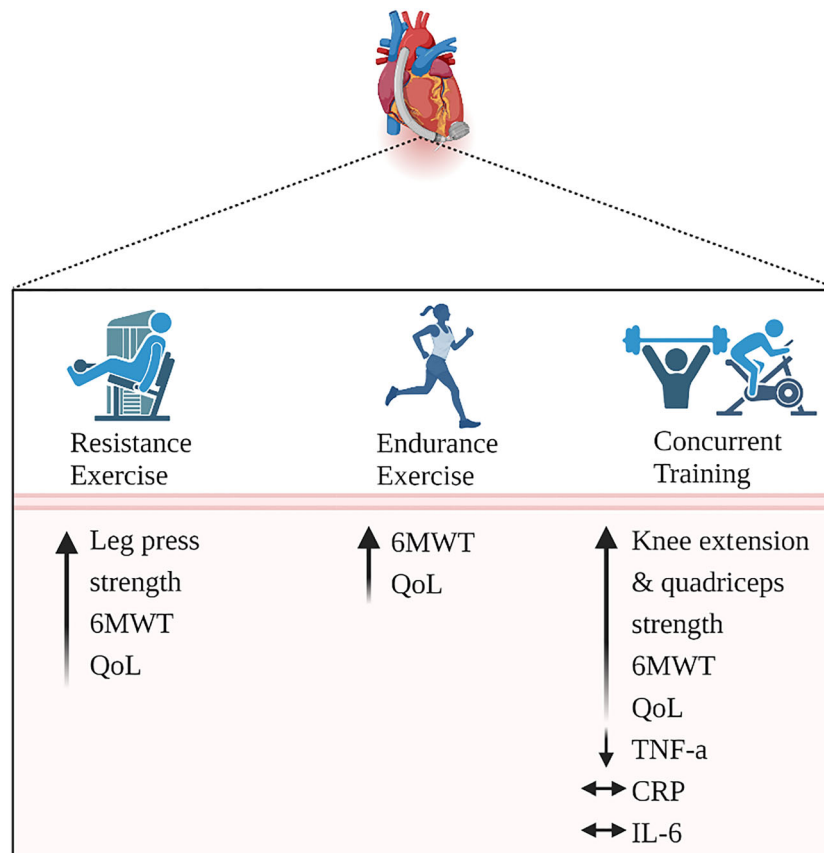
6MWD, 6 min walking distance; CI, confidence interval; HRQoL, health-related quality of life; IL-6, interleukin-6; MLFHQ, Minnesota Living with Heart Failure Questionnaire; TNF-α, tumour necrosis factor-α.

Table 4 Effects of nutrition interventions on physical capacity, quality of life, and inflammatory markers in patients with heart failure based on previous meta-analyses

Author	Intervention	No. of studies	No. of participants	Outcomes	P value	Mean difference (Standardized) (95% CI)	I ²
Habaybeh 2021 ⁶⁰	EAA supplementation	2	57	Triceps skinfold thickness	0.55	-2.14 mm (-9.07, 4.79)	85%
Zhou 2019 ⁷³	Iron supplementation	5	1079	6MWD	0.0001	32.65 m (4.47, 60.63)	89%
		3	135	CRP	0.544	-4.64 (-6.12, -3.17)	0%
		4	1020	KCCQ	0.061	4.09 (0.61, 7.56)	59%
		2	75	MLHFQ	0.353	-19.44 (-23.44, -15.45)	0%
Zhang 2020 ⁷⁴	Iron supplementation	6	2412	KCCQ	0.006	3.13 (-0.57, 6.83)	70%
		2	75	MLHFQ	0.352	-19.47 (-23.36, -15.59)	0%
Zhang 2019 ⁷⁵	Iron supplementation (intravenous iron—IV; oral iron—oral)	3	789	6MWD	IV: <0.0001 Oral: 0.52	IV: 37.84 m (24.47, 51.22) Oral: 24.45 m (-50.09, 98.98)	IV: 31% Oral: 97%
Wang 2019 ⁷²	Vitamin D supplementation	3	180	CRP	0.007	-0.41 (-0.71, -0.11)	0%
		3	198	HRQoL	0.0007	6.75 (2.87, 10.64)	43%
		4	344	6MWD	0.19	-23.30 m (-58.31, 11.72)	0%
Rodriguez 2018 ⁶⁴	Vitamin D supplementation	3	231	CRP	0.66	-0.08 (-0.46, 0.30)	53%
		2	154	IL-6	0.28	-2.00 (-5.65, 1.65)	99%
		5	380	TNF-a	0.04	-0.21 (-0.41, -0.01)	0%
Jiang 2016 ⁸⁵	Vitamin D supplementation	2	148	6MWD	0.761	8.90 m (-48.47, 66.26)	0%
		2	157	CRP	0.045	-0.72 (-1.42, -0.02)	47%
		3	257	TNF-a	0.01	-2.42 (-4.26, -0.57)	96%
Jankowska 2016 ⁷⁶	Intravenous iron therapy	2	648	6MWD	<0.0001	30.82 m (18.23, 43.40)	0%
		2	651	KCCQ	<0.0001	5.52 (2.75, 8.29)	0%
		2	70	MLHFQ	<0.0001	-19.47 (-23.36, -15.59)	0%

6MWD, 6 min walking distance; CI, confidence interval; CRP, c-reactive protein; EAA, essential amino acids; HRQoL, health-related quality of life; IL-6, interleukin-6; KCCQ, Kansas City Cardiomyopathy Questionnaire; MLHFQ, Minnesota Living with Heart Failure Questionnaire; TNF-a, tumour necrosis factor-alpha.

Figure 3 Exercise interventions with potentially beneficial effects on measures of sarcopenia and quality of life in patients with heart failure. 6MWT, 6 min walking test; CRP, c-reactive protein; IL-6, interleukin-6; QoL, quality of life; TNF- α , tumour necrosis factor- α .



plementation may exert beneficial effects on muscle mass; however, an analysis conducted by Habaybeh *et al.* identified two studies that did not reveal a significant benefit for triceps skinfold thickness, which was used as a surrogate marker of muscle mass.⁸⁰ To conclude, there is currently no sufficient evidence to support the use of nutrition interventions as a means of mitigating the risk of sarcopenia and frailty in people with HF. More trials examining the impact of isolated or combined nutritional sources on measures of muscle mass and physical capacity in people with HF are warranted.

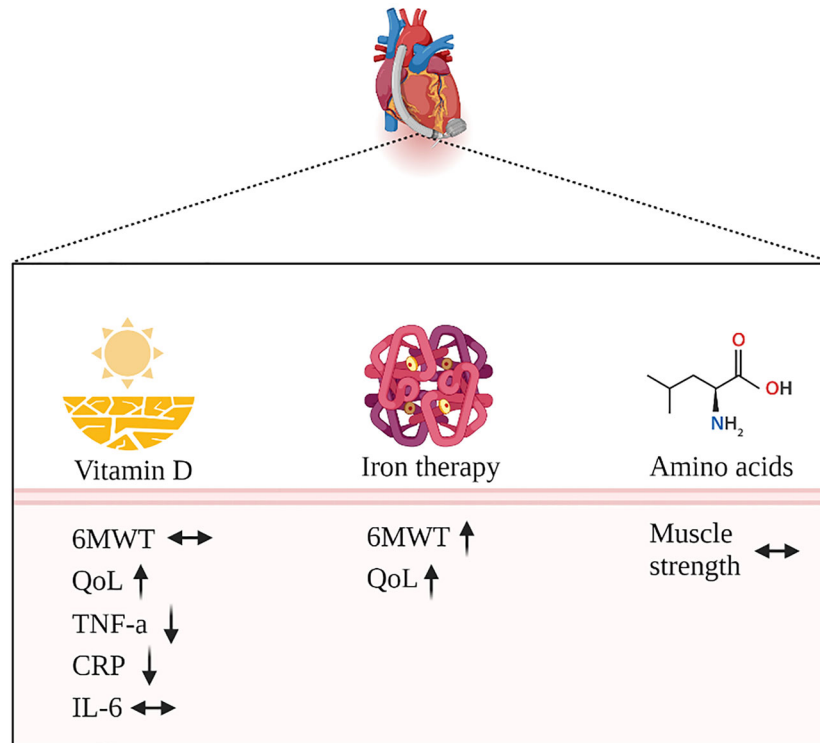
Impact of exercise and nutrition interventions on inflammatory markers in people with heart failure

Acute and systemic inflammation has been described as a prominent feature in people with HF.⁸¹ Only one meta-analysis has examined the effect of exercise on inflammatory cytokines in people with HF, demonstrating a significant reduction in circulating TNF- α levels (SMD: 0.42,

95% CI: 0.15–0.68) following concurrent training. However, no reductions in IL-6, CRP, fibrinogen, soluble intercellular adhesion molecule-1 (sICAM-1), or soluble vascular adhesion molecule-1 (sVCAM-1) were observed.⁸² It is worth noting that exercise leads to an acute elevation of anti-inflammatory myokines such as IL-6 and IL-10, which in turn may trigger the release of IL-1Ra, inhibiting TNF- α stimulation.⁸³ Furthermore, we did not identify any systematic reviews or meta-analyses examining the independent effects of resistance or endurance exercise on inflammatory responses in HF. The impact of exercise on measures of sarcopenia, inflammation, and quality of life in patients with HF is presented in *Figure 3*.

Additionally, no differences in serum IL-6 levels following vitamin D supplementation in people with HF have been reported, although lower concentrations of circulating TNF- α ⁸⁴ and CRP compared with controls have been demonstrated.⁸⁵ Particularly, vitamin D may potentiate cardioprotective properties in the context of HF, considering that vitamin D is a negative regulator of the hormone renin and is therefore thought to prevent hypertension and adverse cardiac remodelling due to renin-angiotensin system dysfunction.⁸⁶

Figure 4 Nutrition interventions with potentially beneficial effects on measures of sarcopenia and quality of life in patients with heart failure. 6MWT, 6 min walking test; CRP, c-reactive protein; IL-6, interleukin-6; QoL, quality of life; TNF- α , tumour necrosis factor- α .



Overall, the potential effects of nutrition interventions in patients with HF are illustrated in *Figure 4*.

Conclusions

In this review of systematic reviews and meta-analyses, we highlighted the current knowledge on physical activity and nutrition interventions aiming to improve physical capacity, muscle mass, and quality of life among people with HF. Current evidence suggests that resistance and concurrent training may promote beneficial effects on 6MWT, lower limb strength, and quality of life in people with HF, while nutrition interventions such as vitamin D supplementation may elicit an anti-catabolic effect by mitigating inflammatory markers responsible in enhancing muscle proteolytic pathways. Nevertheless, data on the impact of vitamin D supplementation on muscle mass and strength, and quality of life in people with HF are currently lacking. To date, there are a limited number of trials assessing the impact of protein and amino acid supplementation on physical capacity and quality of life in people with HF. In addition, this review did not identify any studies looking at the combined effect of exercise and

nutrition interventions on reducing the risk of sarcopenia and frailty in people with HF. Therefore, it is imperative that future studies investigate the concomitant anabolic and anti-catabolic role of combined exercise and nutrition strategies in this patient group.

Acknowledgements

Figures were created using Biorender.com.

Conflict of interest

The authors declare no competing interests.

Funding

This manuscript received no external funding.

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