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

Konstantinos Prokopidis1*, Masoud Isanejad1*, Asangaedem Akpan1,2, Maria Stefi3,7, Behnam Tajik4,5, Panagiotis Giannos6, Massimo Venturelli7 and Rajiv Sankaranarayanan3,8

1Department of Musculoskeletal Biology, Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, UK; 2Aintree University Hospital, Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK; 3Liverpool Centre for Cardiovascular Science, University of Liverpool, Liverpool, UK; 4Kuopio Musculoskeletal Research Unit, University of Eastern Finland, Kuopio, Finland; 5National Institute for Health Research Northwest Coast CRN, Liverpool, UK; 6Department of Life Sciences, Faculty of Natural Sciences, Imperial College London, London, UK; 7Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy; and 8Liverpool Heart and Chest Hospital NHS Foundation Trust, Liverpool, UK

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-a), 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

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 ≤40%, HF with mid-range or mildly reduced ejection fraction as left ventricular ejection fraction 41–49%, and HfPEF as left ventricular ejection fraction ≥ 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-
cally 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. 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) 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). 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. These observations demonstrate that people with HF have lower oxidative phosphorylation adenosine triphosphate (ATP) production rates compared with normal individuals. Additionally, magnetic resonance imaging (MRI) measurements have revealed an increased intramuscular fat concentration and a decreased muscle protein catabolism. Indeed, increased oxidative stress, myostatin, and systemic inflammation—higher levels of tumour necrosis factor-alpha (TNF-a), interleukin-6 (IL-6), interleukin-1 beta (IL-1β), 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. 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. 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, which augment the risk of anabolic resistance. There is also evidence that the prognosis of sarcopenia when complicating HF may be distinct in HFrEF in comparison with those with HFrEF. Bio-impedance analysis has shown a higher proportion of patients with low ASMI and functional impairment (low handgrip strength and slow gait speed) undergoing HFrEF compared with those with HFrEF; however, no differences in mortality rate between groups were observed. 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%. 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. 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. 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. 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). 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. Studies have demonstrated that the CFS can predict mortality independently in acute decompensated HF. 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.
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 uremic 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 HFrEF and HFP EF.\(^{35}\) The implementation of interventions targeting the

---

**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, decreased myoglobin content, 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.
bidirectional relationship of sarcopenia and HF may mitigate cardiorenal metabolic disease progression and its adverse outcomes.

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

**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 rates.

---

**Figure 2** Flowchart of the employed literature search.

- PubMed (n = 1675)
- Cochrane Library (n = 210)
- Web of Science (n = 1630)
- Scopus (n = 2981)
- Total (n = 6496)

- Duplicate records removed (n = 1657)

- Records marked as ineligible (non-systematic reviews or meta-analyses) (n = 4798)

- Reports excluded:
  - Enteral nutrition (n = 1)
  - Patients with hypogonadism (n = 1)
  - Study protocol (n = 4)

- Studies included in review (n = 35)
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 | (Standardized) Mean difference (95% CI) | $I^2$ |
|--------|----------------|---------------------|----------|-----------|----------------------------------------|------|
| Fisher 2021 | 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 pulldown (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 | 4 | 105 | HRQoL | 0.19 | –0.35 (–0.86, 0.17) | 39% |
| Ruku 2021 | 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% |
| | 2 | 105 | HRQoL | 0.61 | –0.17 (–0.80, 0.47) | 63% |
| Slimani 2018 | 2 | 71 | Leg press 1RM | 0.0001 | 0.60 (0.43, 0.77) | 83.5% |
| Giuliano 2017 | 4 | 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.
and promote type II muscle fibre hypertrophy. Endurance and resistance exercise have an antioxidant effect by increasing glutathione reductase and catalase activity and reducing glutathione peroxidase in muscle tissue. 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. 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): 0.35–1.35] and lower extremity muscle strength (SMD: 0.76, 95% CI: 0.26–1.25) (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) and quadriceps (SMD: 0.32, 95% CI: 0.03–0.61) and combined lower and upper body strength (SMD: 0.59, 95% CI: 0.22–0.96). Furthermore, previous studies have reported significant improvements in 6 min walking test (6MWTT) following resistance and concurrent training. These changes after resistance (MD: 49.94 m, 95% CI: 34.59–65.29) and concurrent training (MD: 15.86 m, 95% CI: 7.23–24.49) 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 6MWTD (MD: 33.9 m, 95% CI: 12.38–55.34; MD: 21.0 m, 95% CI: 1.57–40.4) 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 6MWTD in people with HF (MD: 46.9 m, 95% CI: 22.5–71.3), 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), the health-related quality of life (HRQoL) scores (MD: −0.84, 95% CI: −1.19 to −0.49), and the Minnesota Living with Heart Failure Questionnaire (MLFHQ) scores (MD: −3.62, 95% CI: −11.40 to −1.84), while similar findings have also been displayed previously. 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, although one study did not report any changes (SMD: 0.5 points out of 105, 95% CI: −4.4 to 5.4).

### 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 6MWTD (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). Interestingly, greater 6MWTD and quality of life have been demonstrated following oral iron supplementation and intravenous iron therapy. These findings may have been the result of improved haemoglobin resynthesis, 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. Protein sup-

### 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) | $r^2$ |
|-----------------|----------------|---------------------|-------------|---------|----------------------------------------|------|
| Fukuta 2019     | 5              | 284                 | 6MWD        | 0.002   | 33.88 m (12.38, 55.38)                  | -    |
| Pandey 2015     | 5              | 237                 | MLFHQ       | 0.003   | −9.06 (−15.04, −3.08)                   | -    |
| Chan 2016       | 5              | 202                 | 6MWD        | 0.0001  | −1.04 (−1.67, −0.41)                    | 94%  |
| Fukuta 2016     | 4              | 192                 | 6MWD        | 0.05    | 1.61 (−0.01, 3.23)                      | 90%  |
| Chan 2016       | 5              | 275                 | MLFHQ       | 0.002   | −8.98 (−14.63, −3.32)                   | -    |
| Chan 2016       | 7              | 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.
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      | 10            | 1509                | 6MWD                              | 0.0003  | 15.86 m (7.23, 24.49)                  | 74% |
| Righi 2021           | 5             | 194                 | Quadriceps muscle strength         | 0.031   | 0.32 (0.03, 0.61)                      | 0%   |
| Ye 2020              | 3             | 119                 | HRQoL                             | 0.368   | -5.34 (–10.12, –0.56)                 | 0%   |
| Long 2019            | 17            | 1995                | MLHFQ                             | <0.0001 | -7.11 (–10.49, –3.73)                 | 82%  |
| Gomes-Neto 2019      | 7             | 315                 | Knee muscle strength               | <0.0001 | 0.64 (0.41, 0.87)                     | 0%   |
| Wang 2019            | 4             | 121                 | Upper and lower body muscle strength | 0.002  | 0.59 (0.22, 0.96)                     | 0%   |
| Ciani 2018           | 21            | 4420                | HRQoL                             | <0.001  | -0.48 (–0.73, –0.24)                  | 90%  |
| Palmer 2018          | 23            | 20 244              | 6MWD                              | <0.0001 | 49.82 (26.52, 73.13)                  | 95%  |
| Chan 2010            | 13            | 1270                | MLFHQ                             | <0.0001 | 1.16 (0.76, 1.56)                     | 95%  |
| Pearson 2018         | 4             | 175                 | HRQoL                             | 0.05    | -0.42 (–0.71, –0.13)                  | 82%  |
| Zwisler 2016         | 5             | 501                 | MLFHQ                             | 0.14    | 3.24 (–7.52, 1.04)                    | 37%  |
| Dieberg 2015         | 5             | 212                 | MLFQ                              | <0.0001 | 32.13 m (17.20, 47.05)                | 83%  |
| Sagar 2015           | 12            | 1270                | MLFQ                              | <0.0001 | -6.50 (–9.47, –3.53)                  | 52%  |
| Chen 2013            | 6             | 425                 | MLFQ                              | <0.0001 | 50.05 m (28.37, 71.73)                | 42%  |
| Taylor 2012          | 4             | 155                 | MLFQ                              | <0.0001 | -7.32 (–11.38, –3.26)                 | 4%   |
| van der Meer 2012    | 10            | 2161                | 6MWD                              | 0.0005  | 47.90 m (20.92, 74.87)                | 82%  |
| Davies 2010          | 6             | 493                 | MLFQ                              | 0.004   | -10.33 (–15.89, –4.77)                | 71%  |
| Hwang 2010           | 6             | 628                 | MLFQ                              | 0.0141  | 30.41 m (6.13, 54.68)                 | 6%   |
| van Tol 2006         | 15            | 599                 | MLFQ                              | <0.0001 | 46.2 m                                | 0%   |

6MWD, 6 min walking distance; CI, confidence interval; HRQoL, health-related quality of life; IL-6, interleukin-6; MLFQ, Minnesota Living with Heart Failure Questionnaire; TNF-a, tumour necrosis factor-alpha.
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 | (Standardized) Mean difference (95% CI) | I² |
|--------|--------------|----------------|---------------------|----------------------------|---------|----------------------------------------|----|
| Habaybeh 2021 | EAA supplementation | 2 | 57 | Triceps skinfold thickness | 0.55 | $-2.14 \text{ mm} (-9.07, 4.79)$ | 85% |
| Zhou 2019 | Iron supplementation | 5 | 1079 | 6MWD | 0.0001 | $32.65 \text{ m} (4.47, 60.63)$ | 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 | CRP | 0.544 | $-19.44 (-23.44, -15.45)$ | 0% |
| | | 3 | 135 | KCCQ | 0.006 | $3.13 (-0.57, 6.83)$ | 70% |
| Zhang 2020 | Iron supplementation (intravenous iron—IV; oral iron—oral) | 3 | 789 | KCCQ | <0.0001 | $37.84 \text{ m} (24.45, 51.22)$ | IV: 31% |
| | | | | MLHFQ | 0.352 | $-19.47 (-23.36, -15.59)$ | 0% |
| | | | | 6MWD | <0.0001 | IV: 24.45 m (50.09, 98.98) | Oral: 97% |
| | | | | 6MWD | 0.52 | Oral: 24.45 m (50.09, 98.98) | Oral: 97% |
| | | | | 6MWD | 3.13 | Oral: 6MWD | Oral: 97% |
| Zhang 2019 | 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% |
| | | | | 6MWD | <0.0001 | IV: 37.84 m (24.45, 51.22) | IV: 31% |
| | | | | 6MWD | 0.52 | Oral: 24.45 m (50.09, 98.98) | Oral: 97% |
| Wang 2019 | 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 | $-23.30 (-58.31, 11.72)$ | 0% |
| Rodriguez 2018 | 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 | Vitamin D supplementation | 2 | 148 | 6MWD | 0.761 | $8.90 \text{ m} (-48.47, 66.26)$ | 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 | Intravenous iron therapy | 2 | 648 | 6MWD | <0.0001 | $30.82 \text{ m} (18.23, 43.40)$ | 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.
implementation 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. 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. 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. 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. 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 and CRP compared with controls have been demonstrated. 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.
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.
References

1. McDonagh TA, Metra M, Adamo M, Gardener RS, Baumbach A, BöhM M. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2021; 42: 3599–3726.

2. Kurmani S, Squire I. Acute heart failure: definition, classification and epidemiology. Curr Heart Fail Rep. 2017; 14: 385–392.

3. Paneroni M, Pasini E, Comini I, Vitacca M, Schena F, Scalvini S. Skeletal muscle myopathy in heart failure: the role of ejection fraction. Curr Cardiol Rep. 2018; 20: 116.

4. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. Eur J Heart Fail. 2020; 22: 1342–1356.

5. Zhang Y, Zhang J, Ni W, Yuan X, Zhang H, JI P. Sarcopenia in heart failure: a systematic review and meta-analysis. ESC Heart Failure. 2021; 8: 1007–1017.

6. Chen L-K, Woo J, Assantachai P, Auyeung T-W, Chou M-Y, Iijima K. Asian Working Group for Sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. J Am Med Dir Assoc. 2020; 21: 300–307.

7. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019; 48: 16–31.

8. Yokota T, Kinugawa S, Hirabayashi K, Yamato M, Takada S, Sugah T, Nakano I, Fukushima A, Matsushima S, Okita K, Tsutsui H. Systemic oxidative stress is associated with lower aerobic capacity and impaired skeletal muscle energy metabolism in heart failure patients. Sci Rep. 2021; 11: 2272.

9. Bhella PS, Prasad A, Heinicke K, Hastings JL, Arab-Zadeh A, Adams-Huet B, Pacini EL, Shibata S, Palmer MD, Newcomer BR, Levine BD. Abnormal haemodynamic response to exercise in heart failure with preserved ejection fraction. Eur J Heart Fail. 2011; 13: 1296–1304.

10. Kitzman DW, Nicklas B, Kraus WE, Lyles AM, Spee RF, Wijn PPF, van Loon LJG, Kemps HMC. Skeletal muscle fiber characteristics in patients with chronic heart failure: impact of disease severity and relation with muscle oxygenation during exercise. J Appl Physiol. 2018; 125: 1266–1276.

11. van Haehling S, Elmer N, Dos Santos MR, Springer J, Anker SD. Muscle wasting and cachexia in heart failure: mechanisms and therapies. Nat Rev Cardiol. 2017; 14: 323–341.

12. Markoussi-Mavrogenis G, Tromp J, Ouwerverk W, Devalaraja M, Anker SD, Cledan JG, Dickstein K, Filipatos GS, Harst P, Lang CC, Metra M, Ng LL, Ponikowski P, Samani NJ, Zannad F, Zwinderman AH, Hillege HL, Veldhuisen DJ, Kakkar R, Voors AA, Meer P. The clinical significance of interleukin-6 in heart failure: results from the BIOSAT-CHF study. Eur J Heart Fail. 2019; 21: 965–973.

13. Drews O, Taegtmeyer H. Targeting the ubiquitin-proteasome system in heart disease: the basis for new therapeutic strategies. Antioxid Redox Signal. 2014; 21: 2322–2345.

14. Jankowska EA, Biel B, Majda J, Szklarska A, Lopuszanska M, Medras M, Anker SD, Banasiak W, Poole-Wilson PA, Ponikowski P. Anabolic deficiency in men with chronic heart failure: prevalence and detrimental impact on survival. Circulation. 2006; 114: 1829–1837.

15. Liu B, Zhang T, Wright JK, Goodwin JE. The glucocorticoid receptor in cardiovascular health and disease. Cell. 2019; 8: 1227.

16. Bruno C, Silvestrini A, Calracor R, Favuzzi AM, Vergani E, Nicolazzi MA, D’abate C, Meucci E, Mordente A, Landolfi R, Mancini A. Anabolic hormones deficiencies in heart failure with preserved ejection fraction: prevalence and impact on antioxidants levels and myocardial dysfunction. Front Endocrinol. 2020; 11: 281.

17. Kirkman DL, Bohmle N, Billingsley HE, Carbonne S. Sarcopenic obesity in heart failure with preserved ejection fraction. Front Endocrinol. 2020; 11: 558271.

18. Tucker WJ, Haykowsky MJ, Seo Y, Strehling E, Forman DE. Impaired exercise tolerance in heart failure: role of skeletal muscle morphology and function. Curr Heart Fail Rep. 2018; 15: 323–331.

19. Saka K, Konishi M, Kagiyma N, Kamiya K, Saito H, Saito K, Ogasaehara Y, Maekawa E, Misumi T, Katii T, Iwata K, Saito K, Ogasahara Y, Mako N, Aka K, Kimura K, Kitamura K, Momomura SI, Matsue Y. Impact of physical performance on exercise capacity in older patients with heart failure with reduced and preserved ejection fraction. Exp Gerontol. 2021; 156: 111626.

20. Denfeld QE, Winters-Stone K, Mudd JO, Gelow JM, Kirdi S, Lee CS. The prevalence of frailty in heart failure: a systematic review and meta-analysis. Int J Cardiol. 2017; 236: 283–289.

21. Rockwood K, Theou O. Using the Clinical Frailty Scale in allocating scarce health care resources. Can Geriatr J. 2020; 23: 210–215.

22. Vitale C, Centre for Clinical and Basic Research, Department of Medical Sciences, IRCCS San Raffaele Pisana, Rome, Italy CFR, Spolleti I, Centre for Clinical and Basic Research, Department of Medical Sciences, IRCCS San Raffaele Pisana, Rome, Italy CFR, Rosano GMC, Centre for Clinical and Basic Research, Department of Medical Sciences, IRCCS San Raffaele Pisana, Rome, Italy CFR. Frailty in heart failure: implications for management. Card Fail Rev. 2018; 4: 104–106.

23. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottlieiner J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001; 56: M146–M157.

24. Juma S, Taabazuing MM, Montero-Odasso M. Clinical Frailty Scale in an acute medicine unit: a simple tool that predicts length of stay. Can Geriatr J. 2016; 19: 34–39.

25. Neet K, Sevynidis I, Latherley J, Tay J, Douglas H, Akpan A, Sankaranarayanan R. Do Rockwood frailty score and Charlson comorbidity index help to risk stratify outpatient versus inpatient management of acute decompensated heart failure? Eur Heart J. 2020; 41: e946.e1190.

26. Essa H, Broussas S, Whybrow-Huppatz I, Salmon T, Sankaranarayanan R. What is the effect of lockdown upon hospitalisation because of COVID-19 amongst patients from a heart failure registry? Int J Clin Pract. 2021; 75: e14425.

27. Adamo L, Rocha-Resende C, Prabhu SD, Mann DL. Reappraising the role of inflammation in heart failure. Nat Rev Cardiol. 2020; 17: 269–285.

28. Wohlgemuth SE, Calvani R, Marzetti E. The interplay between autophagy and mitochondrial dysfunction in oxidative stress-induced cardiac aging and pathology. J Mol Cell Cardiol. 2014; 71: 62–70.

29. Vidán MT, Blaya-Novakova V, Sánchez E, Orús J, Serra-Resach JA, Bueno H. Prevalence and prognostic impact of frailty and its components in non-dependent elderly patients with heart failure. Eur J Heart Fail. 2016; 18: 869–875.

30. Lawson CA, Seidu S, Zaccardi F, McCann G, Kadam UT, Davison MJ, Lamp C, Heerspink HL, Khunti K. Outcome trends in people with heart failure, type 2 diabetes mellitus and chronic kidney dis-
quality of life in heart failure patients: a systematic review and meta-analysis. Cardiology. 2017; 136: 79–89.
65. Guo R, Wen Y, Xu Y, Jia R, Zou S, Lu S, Liu G, Cui K. The impact of exercise training for chronic heart failure patients with cardiac resynchronization therapy: a systematic review and meta-analysis. Medicine. 2021; 100: e25128.
66. Chan E, Giallauria F, Vigorito C, Smart NA. Exercise training in heart failure patients with preserved ejection fraction: a systematic review and meta-analysis. Monaldi Arch Chest Dis. 2016; 86: 759.
67. Slimani M, Ramirez-Campillo R, Paravlic A, Hayes LD, Bragazzi NL, Sellami M. The effects of physical training on quality of life, aerobic capacity, and cardiac function in older patients with heart failure: a meta-analysis. Front Physiol. 2018; 9: 1564.
68. Pandey A, Parashar A, Kumbhani D, Agarwal S, Garg J, Kitzman D, Levine BD, Drazner M, Berry JD. Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. Circ Heart Fail. 2015; 8: 33–40.
69. Ye LF, Wang SM, Wang LH. Efficacy and safety of exercise rehabilitation for heart failure patients with cardiac resynchronization therapy: a systematic review and meta-analysis. Front Physiol. 2020; 11: 980.
70. Long L, Mordi IR, Bridges C, Sagar VA, Davies EJ, Coats AJ, Dalal H, Rees K, Singh SJ, Taylor RS. Cochrane Heart Group. Exercise-based cardiac rehabilitation for adults with heart failure. Cochrane Database Syst Rev. 2019; 1: CD003331.
71. Chien C-L, Lee C-M, Wu Y-W, Chen T-A, Wu Y-T. Home-based exercise increases exercise capacity but not quality of life in people with chronic heart failure: a systematic review. Aust J Physiother. 2008; 54: 87–93.
72. Wang T, Liu Z, Fu J, Min Z. Meta-analysis of vitamin D supplementation in the treatment of chronic heart failure. Scand Cardiovasc J. 2019; 53: 110–116.
73. Zhou X, Xu W, Xu Y, Qian Z. Iron supplementation improves cardiovascular outcomes in patients with heart failure. Am J Med. 2019; 132: 955–963.
74. Zhang J, Hu S, Jiang Y, Zhou Y. Efficacy and safety of iron therapy in patients with chronic heart failure and iron deficiency: a systematic review and meta-analysis based on 15 randomised controlled trials. Postgrad Med J. 2020; 96: 766–776.
75. Zhang S, Zhang F, Du M, Huang K, Wang C. Efficacy and safety of iron supplementation in patients with heart failure and iron deficiency: a meta-analysis. Br J Nutr. 2019; 121: 841–848.
76. Jankowska EA, Tkaczyszyn M, Suchocki T, Drozd M, von Haehling S, Doehner W, Banasiak W, Filipatos G, Anker SD, Ponikowski P. Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials. Eur J Heart Fail. 2016; 18: 786–795.
77. Avni T, Leibovici L, Gafter-Gvili A. Iron supplementation for the treatment of chronic heart failure and iron deficiency: systematic review and meta-analysis. Eur J Heart Fail. 2012; 14: 423–429.
78. Alcaide-Aldeano A, Garay A, Alcoberro L, Jiménez-Marrero S, Yun S, Tajes M, García-Romero E, Díez-López C, González-Costello J, Mateus-Porta G, Caimzos-Achirica M, Enjuanes C, Comín-Colet J, Moliner P. Iron deficiency: impact on functional capacity and quality of life in heart failure with preserved ejection fraction. J Clin Med. 2020; 9: 1199.
79. Nichols S, McGregor G, al-Mohammad A, Ali AN, Tew G, O’Doherty AF. The effect of protein and essential amino acid supplementation on muscle strength and performance in patients with chronic heart failure: a systematic review. Eur J Nutr. 2020; 59: 1785–1801.
80. Habayeh D, de Moraes MB, Slea A, Averginou C. Nutritional interventions for heart failure patients who are malnourished or at risk of malnutrition or cachexia: a systematic review and meta-analysis. Heart Fail Rev. 2021; 26: 1103–1118.
81. Castillo EC, Vazquez-Garza E, Yee-Trejo D, García-Rivas G, Torre-Amione G. What is the role of the inflammation in the pathogenesis of heart failure? Curr Cardiol Rep. 2020; 22: 139.
82. Pearson MJ, Mungovan SF, Smart NA. Effect of aerobic and resistance training on inflammatory markers in heart failure patients: systematic review and meta-analysis. Heart Fail Rev. 2018; 23: 209–223.
83. Pedersen BK. Anti-inflammatory effects of exercise: role in diabetes and cardiovascular disease. Eur J Clin Invest. 2017; 47: 600–611.
84. Rodriguez AJ, Moussa A, Ebeling PR, Scott D, de Courten B. Effects of vitamin D supplementation on inflammatory markers in heart failure: a systematic review and meta-analysis of randomized controlled trials. Sci Rep. 2018; 8: 1169.
85. Jiang WL, Gu HB, Zhang YF, Xia QQ, Qi J, Chen JC. Vitamin D supplementation in the treatment of chronic heart failure: a meta-analysis of randomized controlled trials. Clin Cardiol. 2016; 39: 56–61.
86. M.G. Meems L, van der Harst P, H. van Gilst W, A. de Boer R. Vitamin D biology in heart failure: molecular mechanisms and systematic review. Curr Drug Targets. 2011; 12: 29–41.