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Fatigue in Persons with Heart Failure: A Systematic Literature Review and Meta-Synthesis Using the Biopsychosocial Model of Health

Noelle V. Pavlovic, RN, MSN[*,1], **Nisha A. Gilotra, MD**[2], **Christopher S. Lee, PhD, RN**[4,5], **Chiadi Ndumele, MD, PhD**[2], **Dimitra Mammos, BA**[1], **Cheryl Dennison Himmelfarb, PhD, RN**[1,2,3], **Martha Abshire Saylor, PhD, RN**[1]

[1]Johns Hopkins School of Nursing

[2]Johns Hopkins School of Medicine

[3]Johns Hopkins Bloomberg School of Public Health

[4]Boston College William F. Connell School of Nursing

[5]Mary MacKillop Institute for Health Research, Australian Catholic University

Abstract

Background: Fatigue is a common and distressing symptom of heart failure and has important implications for patient-reported and clinical outcomes. Despite being a common and bothersome symptom, fatigue has been understudied in heart failure.

Objective: To synthesize existing literature on fatigue in heart failure through a systematic literature review guided by the biopsychosocial model of health.

Methods: A systematic search of the literature was performed on March 18th, 2020, using Pubmed, Embase, and CINAHL. Full-text, primary research articles, written in English, in which fatigue was a primary symptom of interest in adults with a diagnosis of heart failure were included.

Results: The search yielded 1138 articles; 33 articles that met inclusion criteria were selected for extraction and synthesis. Biological and psychological factors associated with fatigue were New York Heart Association functional class, hemoglobin level, history of stroke, and depression. However, there are limited HF specific factors linked to fatigue. Social factors related to fatigue included social roles, relationship strain, and loneliness/isolation. Few non-pharmacologic interventions have been tested by show some promise for alleviating fatigue in HF. Studies show conflicting evidence related to the prognostic implications of fatigue.

[*]**Corresponding Author:** Noelle V. Pavlovic RN, MSN, Johns Hopkins School of Nursing, 525 N Wolfe Street, Baltimore, MD, npavlov3@jhmi.edu, 703-229-9288.

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Conclusions: Important biological correlates of fatigue were identified; however, psychological and social variables were limited to qualitative description. There is need for expanded models to better understand the complex physiologic nature of fatigue in HF. Additionally, more research is needed to 1) define the relationships between fatigue and both psychological and social factors, 2) better describe the prognostic implications of fatigue, and 3) develop more therapeutic approaches to alleviate fatigue with the goal of improving overall quality of life.

Lay Summary:

People living with heart failure often experience fatigue. Fatigue is distressing and can make living life and taking care of yourself difficult. In this article, we reviewed the current research on fatigue in heart failure. We were looking to understand fatigue and what new research is needed to help people with fatigue feel better. We found that in people with heart failure 1) we don't fully understand the physical causes of fatigue, 2) people with depression are more likely to have fatigue, 3) social support helps manage fatigue, and 4) we need more research on interventions to help reduce fatigue.

Graphical Abstract/Central Illustration.

The Biopsychosocial model includes three domains: 1) Biological, 2) Psychological, and 3) Social. These domains interact in a dynamic way and construct the health/disease experience for individuals.[1] This literature review examined the literature related to fatigue in heart failure and synthesis was organized around the domains of the this model.

Keywords

fatigue; heart failure; cardiomyopathy; quality of life; patient-reported outcomes

Introduction

Symptoms in heart failure (HF) cause significant distress to patients, are the primary reason for healthcare seeking[1], and when left untreated can lead to significant increases in unplanned healthcare utilization.[2] Early recognition and increased attention to symptoms is associated with increased HF self-care behaviors[3], and more prompt healthcare seeking[4], which is shown to improve HF outcomes such as hospitalization reduction.[5,6]

Fatigue is one of the most frequently reported symptoms in HF.[7] Generally, fatigue can be described as a persistent, full-body experience with physical and psychological aspects that are not relieved by usual recuperative methods.[8,9] Fatigue has been studied in a number of conditions (eg., cancer[10], chronic obstructive pulmonary disease (COPD)[11], rheumatoid arthritis[12]), and has been found to be associated with reduced quality of life[13,14], poorer health and function[15], and increased symptoms of depression[16]. Fatigue in HF can be divided into two different, often co-occurring experiences: general fatigue and exertional fatigue with general fatigue being unrelated to exertion[8,9] and exertional fatigue occurring during and/or after exertion (i.e., exercise intolerance).[17] Previous literature reviews on fatigue in HF have provided a synthesis of either qualitative literature[18,19] or quantitative literature focusing specifically on biologic correlates of fatigue.[20,21] However, systematic

reviews on fatigue in HF that incorporate both quantitative and qualitative literature or guidance by a theoretical framework are lacking. Thus, the purpose of this systematic review was to synthesize both quantitative and qualitative contemporary literature on fatigue in HF, using the biopsychosocial model of health[22] as a guiding framework and identify knowledge gaps and opportunities for future research.

Methods

Theoretical Framework

Because fatigue is a subjective experience with varied contributing factors and sequelae, using a theoretical framework guides holistic investigation of the fatigue experience. The biopsychosocial model of health was developed as an expansion of the biomedical model to encompass the biology of disease, the larger context of a person's life, and how each influence an individuals' health and disease experience.[22] The model includes three domains: 1) Biological, 2) Psychological, and 3) Social. These domains interact dynamically to influence the health/disease experience (fatigue in the case of this review) and that health/disease experience also affects patient-reported and clinical outcomes (Figure 1). Organizing this literature review around the biopsychosocial model of health allows better understanding of which areas of the model have been addressed by the current literature and where evidence is lacking. Identification of these knowledge gaps can guide future research in fatigue in HF.

Literature Search

We performed a systematic search of the literature, using a search strategy developed with a library informationist, using the Pubmed, Embase, and CINHAL databases. We used the following search strategies, respectively: ("Heart Failure"[Mesh]) AND ("Fatigue"[Mesh] OR "Fatigue Syndrome, Chronic"[Mesh]); ('fatigue'/de OR fatigue*:ti,ab OR 'exercise intolerance'/de OR 'exercise intolerance*':ti,ab) AND ('acute heart failure'/de OR 'heart failure'/de OR 'heart failure*':ti,ab) AND adult*:ti,ab; (MH "Heart Failure") AND (MH "Fatigue"). The literature search was performed on March 18th, 2020.

Literature Selection

To document the systematic literature review process, we utilized the PRISMA guidelines (Figure 2).[23] Articles were screened by two reviewers (NP, DM) on the basis of title and abstract, then on the full-text level, to determine eligibility for full-text data extraction and evidence synthesis. Articles were included if they were full-text, primary research articles that were written in English and investigated the symptom of fatigue either quantitatively or qualitatively in adults (>18 years) with a diagnosis of HF. These articles must have examined 1) the relationship between predictor variables and fatigue and/or 2) fatigue's relationship to patient-reported and clinical outcomes and/or, 3) interventions targeting fatigue. Qualitative and quantitative literature were both included in this literature review because fatigue is an individually experienced symptom and the lived experience of those with HF and fatigue may provide insight for future research opportunities that have been un- or under-addressed in the current literature. Further, the biopsychosocial model of health asserts that quantitative and/or biological measures alone do not necessarily fully illuminate

the meaning of symptoms to patients, thus requiring the inclusion of qualitative research to enhance our understanding.[24] Articles were excluded if they were published before the year 2000. This timeframe was selected due to the introduction of guideline-directed medical therapy for HF in the early 2000's which included widespread changes to medical management for HF. Discrepancies for inclusion were resolved by consensus and a third expert reviewer input (MA).

Data Extraction and Appraisal

Two reviewers (NP, DM) independently performed data extraction using a standard data extraction form. During data extraction, each reviewer identified which domains of the biopsychosocial model of health the article addressed. Criteria were not determined *a priori* but were determined during data extraction, article review, and synthesis using the definitions of the biological, psychological, and social domains by Lehman et al. [25] Biological variables are defined as those that capture the physical elements of the body. Psychological variables are those related to cognitive, emotional, motivational, attitudinal, and behavioral systems. Social variables are perceived or actual contacts or connections with others and society that impact health.[25] Discrepancies in domain categorization were resolved by consensus and a third expert reviewer input (MA).

We also appraised each article for level of evidence and evidence quality using the Johns Hopkins Nursing Evidence-Based Practice Appraisal tools.[26] Each reviewer assigned articles an evidence level ranging between I and V. Level I evidence is the highest (e.g., experimental studies, randomized controlled trials, meta-analyses) while level V is the lowest (e.g., case report, opinion article). The reviewers then gave each article an evidence quality grade of A (high quality), B (good quality), or C (low quality) depending upon consistency of findings, adequacy of sample size, presence of a control group, generalizability of results, and whether conclusions could be drawn from the data presented. Additionally, all randomized control trials were assessed for risk of bias using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials.[27] This tool evaluates a randomized control trial on the following 5 potential biases: 1) randomization process, 2) effect of assignment to the intervention (participant and researcher blinding), 3) missing outcome data, 4) measurement of the outcome, and 5) reporting bias (selection of the reported result). Discrepancies regarding data extraction, evidence level/quality appraisal, and risk of bias were resolved by consensus with a third expert reviewer (MA).

Statistical methods

The summary of demographic variables describing the study samples were calculated by taking the mean (SD) or median (IQR) of the study reported statistics. Means of demographic variables (age, proportion female) were weighted by sample size. Meta-analysis was not performed due to heterogeneity of fatigue measurement and associated variable selection in the synthesized studies.

Qualitative Meta-synthesis methods

Synthesis of qualitative studies was performed using the cross-case analysis method of qualitative meta-synthesis.[28] Categories and themes were identified from individual studies,

then these themes were cross-referenced and iteratively refined with other studies to produce a final synthesis of qualitative results.

Results

The systematic literature search yielded 1138 articles for screening. After duplicates were removed, 986 unique articles were screened by title and abstract leaving 66 articles for full text screening. Ultimately, 33 articles were selected based on our inclusion criteria for data extraction and synthesis (Figure 2).

A summary of all articles selected for synthesis including study designs and key findings is shown in Tables 1 and 2. Articles were published between the years 2002 and 2019. Of the 33 articles selected, 27 where quantitative, 5 were qualitative, and 1 was a mixed-methods study. The 27 quantitative studies consisted of 15 descriptive cross-sectional correlational studies, 7 longitudinal cohort studies, and 5 randomized controlled trials. Mean sample size across quantitative studies was 765 patients (SD ± 2412; range 21–12,285). The standard deviation was large because there were two studies that had much larger sample sizes than the others (n=3,830 and n=12,285). Median sample size across quantitative studies was 112 (IQR = 201). The mean sample size of the qualitative studies was 19 (SD ± 6.5; range 10–26). The one mixed-methods study had a sample size of 158 participants.

The mean age (weighted by sample size) of participants was 64.8 years across quantitative studies, 70.4 years across qualitative studies, and 81 years in the single mixed methods study. The mean % (weighted by sample size) of participants that were female sex was 42.7% in quantitative studies, and 47.4% in qualitative studies. Of the 26 studies that reported New York Heart Association (NYHA) functional class, 14 had a sample with ≥ 50% of participants with advanced HF (NYHA class III or IV), 3 had a majority of participants with NYHA class III or lower, 9 had a majority of participants with NYHA class II or lower.

Evidence level and quality appraisal showed the majority of articles to be of high quality (grade A or B) with only one low quality (grade C) article. Twenty-eight articles were evidence level III (non-experimental, descriptive correlational, mixed-methods, and/or qualitative descriptive) and 5 were level I. Risk of bias analysis showed 3 of the 5 studies with some concerns for risk of bias, and 2 with high risk of bias. The domains which showed risk of bias included the randomization process (due to lack of methodological reporting), effect of assignment to intervention (due to lack of participant/interventionist/data analyst blinding), and measurement of the outcome (due to lack of blinding of data collectors). The results of evidence level, quality, and risk of bias appraisal are presented in Supplement 1.

Each study addressed at least one of the biopsychosocial model domains. Overall, 24 studies examined the biological domain; 25 the psychological domain; and 13 the social domain. The majority of studies (25 out of 33) included >1 domain of the biopsychosocial model, yet only 4 studies included all three domains. Four articles examined variables in the biological domain[29,30, 31,32], 2 examined the psychological domain[33,34], 2 examined the social domain[35,36], 5 examined both the psychological and social domains[37,38,39,40,41], 2

examined both the biological and social domains[42,43], 13 examined both the psychological and biological domains[44,45,46,47,48,49,50,51,52,53,54,55,56], and only 4 articles examined all 3 domains together.[57,58,59,60]

Biological Variables

Most articles examining biological variables were cross-sectional, descriptive correlational studies seeking to describe the associations between biological variables and the presence and severity of fatigue. The variables investigated were organized in the following categories: 1) patient and clinical characteristics, 2) laboratory values, 3) and medications.

Patient and clinical characteristics that were found to be associated with worse fatigue in HF in at least 2 articles were increased NYHA functional class[57,29,45,46,30,52,50,54], increased number of comorbidities (count)[49,52,55], stroke[45,59,30,55], diabetes mellitus (DM)[30,59,52], hypertension (HTN)[30,50,59], poor physical functioning[44,57,48,58], and reduced exercise capacity[50,52]. Some patient and clinical characteristics had conflicting associations with fatigue levels across studies. Increased age[30,59,52,55,61], female sex[49,58,30,52,54,55,61], decreased left ventricular ejection fraction (LVEF)[51,54,59], increased dyspnea[45,50,55], and sleep problems[47,59,50,55] were found to be associated with increased fatigue in approximately 50% of studies that reported them, and not associated with fatigue in the other half (Figure 3).

The only laboratory value that was associated with fatigue in at least two studies was hemoglobin level. Three of the 33 studies examined hemoglobin level and found decreased hemoglobin level was associated with worse fatigue, while 1 study used a diagnosis of anemia based on hemoglobin level, with worse fatigue being found in those with anemia versus those without[29].

The association between medications and fatigue was measured in 5 studies, all of which were observational with 4 being cross-sectional and 1 longitudinal. Kessing et al. examined the relationship between fatigue type (general fatigue or exertional fatigue) and medications including beta-blockers, nitrates, statins, diuretics, anticoagulants, calcium antagonists, and psychotropic medications.[59] They showed that the use of beta-blockers was associated with decreased exertional fatigue, but not associated with general fatigue. Diuretics, nitrates, and psychotropic medications were associated with increased general and exertional fatigue while all other medications were not associated with either general or exertional fatigue. Smith et al. found that increases in exertional fatigue over the course of 12 months were predicted by *not* using beta-blockers.[51] However, Tang et al. found that beta-blocker use was associated with increased fatigue but the investigators did not distinguish between general and exertional fatigue.[54] In another study, Smith et al. longitudinally examined the relationship between medications and general and exertional fatigue *trajectory* categories.[52] In multivariable regression, they showed that individuals were 5.43 times more likely to exhibit the severe exertion fatigue trajectory as compared to the reference group (low exertional fatigue trajectory) if they took psychotropic medications at baseline (OR = 5.43, p=0.003) but found no significant association between beta-blocker or diuretic use and fatigue trajectory category. The fifth study that examined the relationship between

medications and fatigue showed no significant association between any medication and fatigue score.[44]

Psychological variables

Psychological variables were measured in 24 of the 33 studies; the most commonly measured variable was depression. Thirteen studies consistently reported an association between depression and increased fatigue levels.[27,45,33,34,35,36,37,38,39,40,61,42,43] Interestingly, Fink et al. found that there was no difference in fatigue level in patients with versus without HF in multivariate analysis controlling for depression.[47] Additionally, increased fatigue was associated with increasedanxiety [45,57,59] and symptom distress related to HF symptoms.[45,57]

One study examined women's mental representations of fatigue in HF. These representations were constructed based on individual beliefs about the identity, cause, timeline, consequences, and cure/control of fatigue symptoms.[34] Women who reported fatigue representations that included increased emotional distress, increased attribution to HF, and more severe consequences from fatigue had higher levels of healthcare utilization. However, adjusted multivariate analyses showed that this relationship was not statistically significant.[34]

Qualitative and mixed-methods studies explored the psychological perception and impact of fatigue in greater depth. Four of 5 qualitative studies and the one mixed-methods study described patient perceptions of the physical experience of fatigue in HF. Participants described the experience as unpredictable with variations in their physical abilities throughout the day and over time.[37,39] They described their energy as being drained more than expected[38,39] with low energy levels leaving them feeling exhausted and sleepy, but with little if any relief from sleep and difficulty falling and staying asleep.[38,39,60]

Qualitative studies also described the emotions elicited by the fatigue experience. Participants explained that they felt a sense of loss related to their physical energy and their increased dependence upon other people; they felt as if their world had been made smaller by fatigue.[37–39] Negative feelings, such as helplessness and vulnerability, were common themes which led to anxiety and fear about mortality and what fatigue meant for the future.[38,39] Four studies elicited themes about coping with fatigue. Participants described feeling forced to adapt their lives to accommodate and anticipate their fatigue. Knowing the warning signs of fatigue and acknowledging their limits were essential to coping.[38,39] The study by Ekman et al. elicited more strategies related to distraction from fatigue rather than long-term coping mechanisms.[60] Similarly, Falk et al. found that participants described three types of activities that aided in distraction from fatigue including 1) involuntary attentive activities such as those without a specific purpose (e.g., observing nature, mental experiences), 2) socially interactive activities such as meeting new people, and 3) mental absorption activities such as reading or hands-on tasks.[41]

Social Variables

Examination of social variables was lacking in the literature. The only individual social characteristic that was examined in quantitative studies was marital status. The evidence

supporting an association of marital status with fatigue levels was sparse and conflicting amongst the 3 studies that investigated it.[53,59,48] Social determinants of health were not examined in any of the articles synthesized here.

The qualitative literature provided descriptions of the social impact of fatigue. Because of the increased reliance on others for physical functioning due to fatigue, participants commonly described changes in relationship roles which resulted in feelings of burden and guilt.[37,39,40,41] Whitehead et al. also described such role changes from the perspective of the family of the fatigued person. [40] This study elicited themes of familial relationship strain between family members who understood/perceived the person's fatigue as real and those who did not due to the "invisibility" of fatigue symptoms. Fatigue was also described as isolating due to the amount of energy required for social activities. Social circles were said to shrink as fatigue became a larger part of an individual's life.[38,60,41] Interestingly, Falk and colleagues found socialization as an extremely valuable method of distraction from fatigue.[41] Socializing made participants forget about their fatigue symptoms during the interactions, but would often lead to negative consequences from overexertion.[41]

Clinical and patient-reported outcomes

Seven studies examined patient reported outcomes such as quality of life and functioning. Increased fatigue was found to be correlated with poorer satisfaction with life[53], quality of life[42,53], decreased patient perceived physical and emotional health[44], poorer physical functioning, role functioning, and patient perception of general health.[58] Increased severity of fatigue was also associated with poorer occupational performance, increased ADL and IADL dependence,[43,57] and poorer self-care.[59] Nine studies investigated the relationship between fatigue and clinical outcomes such a hospitalization and mortality. Fatigue was shown to be associated with higher healthcare utilization[61], and increased hospital length of stay.[61,56] In several studies, greater severity of fatigue was also associated with a higher likelihood of mortality[47,52], adverse cardiovascular events.[62] and hospitalization.[30,51] However, the evidence examining the relationship of fatigue in HF with hospitalization and mortality is conflicting, with some studies showing no significant association. [55,31]

Interventions

Of the 33 articles, 5 examined the effect of different interventions to manage fatigue levels in HF. These interventions often fell under multiple domains of the biopsychosocial model of health. Two studies investigated physical activity interventions to reduce fatigue in persons with HF. Austin et al.[42] randomized participants with heart failure to standard care or standard care plus cardiac rehabilitation intervention. The standard care consisted of eight weekly monitoring sessions of clinical status (functional performance, fluid status, cardiac rhythm, laboratory values) and standard HF education by a clinical nurse specialist. The intervention consisted of standard care plus a cardiac rehabilitation program with a clinical nurse specialist. Rehabilitation exercise sessions were 2.5 hours each twice weekly for 8 weeks. After the 8-weeks, intervention participants then entered a 16-week community-based exercise program of weekly 1 hour exercise sessions led by a professional exercise rehabilitation instructor. Exercise consisted of aerobic endurance training and low-resistance, high repetition muscular strength exercise.[42] The investigators found statistically significant

reductions in fatigue severity in the intervention cardiac rehabilitation group at 2 months and 6 months post-intervention initiation. However, there were no significant reductions in fatigue beyond 6 months and the distribution of fatigue ratings had returned to nearly baseline levels. [42]

Pozehl et al. implemented an exercise intervention consisting of 3 days per week of aerobic and muscle strengthening exercise training for 24 weeks total.[32] The first 12 weeks was standard cardiac rehabilitation while the second 12 weeks was self-guided exercise performed at the cardiac rehabilitation facility. Additionally, this intervention implemented goal-setting and problem-solving guidance to attempt to improve adherence to the program. They found no significant improvement in overall fatigue or dyspnea severity compared to the control group at 24-week follow-up.[32] Exercise interventions primarily fall under the biological domain of the biopsychosocial model of health, but these interventions may also reflect the psychological and social domains because of the use of theory-driven goal-setting strategies[42] and the emphasis on inclusion of the patient's spouses, friends, other patients, and trainers in the exercise program. [42,32]

One study, by Seifi et al.[33], examined mindfulness strategies for the relief of fatigue in HF. Participants were randomized 1:1 to either intervention or control. The intervention consisted of either Benson muscle relaxation guided by a research interventionist (20-minute progressive muscle relaxation) or listening to nature sounds (30–45 minutes) performed 2 times per day for 3 days while resting in a comfortable position. They found significant reductions in fatigue levels after 3 sessions for both interventions compared to control.[33] This intervention falls under the psychological domain of the biopsychosocial model of health due to its focus on relaxation techniques and use of mindfulness and distraction as a mode of reliving fatigue.

Two studies investigated nurse case management social support interventions to relieve fatigue. Wang et al. conducted a randomized control trial implementing a supportive educational nursing program for patients with heart failure.[36] The intervention consisted of three components: 1) fatigue assessment and monitoring, 2) fatigue management and education, and 3) outcome evaluation. Participants received a total of 4, 30-minute counseling and education sessions by a nurse comprised of the three intervention components and emotional support over the course of 12 weeks. Participants were counseled on strategies to manage their fatigue based on their individual needs, social support networks, and lifestyle. The investigators found significant reductions in fatigue levels at 12 weeks in the intervention group compared to control. [36] Smith-Love et al.[35] implemented a nurse practitioner supportive care intervention that involved daily in-person interactions during acute heart failure hospitalization and then daily telephone interactions for 1 to 3 weeks after discharge. The intervention consisted of education, coaching, counseling on fatigue identification, energy conservation during activities of daily living, HF self-care behaviors, and appropriate response to worsening symptoms.[35] No further details about the intervention were provided by the authors. They found that fatigue levels were significantly decreased in the intervention group from baseline to follow-up compared to the control.

These interventions fall under both the social and psychological domains of the biopsychosocial model of health because of the use of provider social support (education, counseling, resource identification)[36,35], the engagement of the individual's social support network[36], and emotional support during counseling sessions.[36]

Fatigue Measurement

In the quantitative and mixed-methods studies (n=28), there were 17 different methods for measuring fatigue. Methods that were used in more than 1 study included the Minnesota Living with Heart Failure Questionnaire, the Piper Fatigue Scale, Profile of Mood States (fatigue subscale), Multi-dimensional Fatigue Inventory, Fatigue Symptom Inventory, Symptom Status Questionnaire – Heart Failure, ICD-9 diagnosis codes, Fatigue Assessment Scale, and a general visual analog scale. The most frequently used method of fatigue measurement was the Multi-dimensional Fatigue Inventory which was utilized in 5 studies. Ten scales were multi-dimensional measures of fatigue with at least 2 dimensions comprising the scale. Five were unidimensional, focusing on either the presence/absence of fatigue, fatigue severity on a visual analog or Likert scale, or the physical sensations of fatigue. Two scales used were components of larger scales intended to measure different constructs including mood and quality of life. Additionally, there were 3 articles that utilized multiple fatigue scales to distinguished between general versus exertional fatigue. In these studies, the Fatigue Assessment Scale[63] was used to measure general fatigue, and is conceptualized as multidimensional and not related to exertion. The Dutch Exertion Fatigue Scale[64] was used to measure exertional fatigue; the items of this scale address whether the individual experiences fatigue related to various activities. This type of fatigue is specifically related to exertion. All scales used in the reviewed studies are summarized in Table 3.

Discussion

Through systematic review, we have found that fatigue was measured differently amongst studies, there was a lack of clinically relevant and/or actionable biological correlates of fatigue, that fatigue is distressing and highly associated with depression, and it impacts the social lives and relationships of people with HF. Further, many important opportunities for future research emerged, including distinguishing between general and exertional fatigue in HF, the pursuit of novel non-pharmacological interventions for alleviating fatigue, and the inclusion of social determinants of health as potential predictors of fatigue. A summary of our main findings is shown in figure 4.

Biological variables

NYHA functional class is the most common method for classifying HF severity.[65] Since NYHA functional class is based on how severely HF symptoms interfere with an individual's physical functioning, it is logical that fatigue would increase with increasing NYHA functional class. However, the relationship between NYHA functional class and fatigue severity does not provide essential information about fatigue etiology, risk factors, and outcome implications, all of which are necessary for informing interventions to alleviate or prevent fatigue.

Hemoglobin level is used to diagnose anemia, which is common among patients with chronic HF.[66] The literature suggests that patients with HF and low hemoglobin levels tend to have higher severity of fatigue. This finding is consistent with literature in other disease states showing correlations between hemoglobin levels < 9 g/dl and increased severity of fatigue.[67] However, studies examining interventions for anemia-related fatigue have primarily been performed in cancer patients.

There have been some randomized controlled trials (FAIR-HF[68], CONFIRM-HF[69]) demonstrating the efficacy of IV iron replacement in improving clinical outcomes, physical function, and quality of life in HF patients. However, fatigue and other symptoms, specifically, were not evaluated as outcomes and should be included in future trials. Further, the threshold hemoglobin level of < 9 g/dl for iron therapy is low, and it is possible that hemoglobin levels higher than this but still below the normal range may also be associated with fatigue symptoms.

Polypharmacy may be a potentially modifiable source of fatigue. The evidence showed some association between medications used as mainstays of HF treatment (beta-blockers and diuretics) and fatigue in HF, although directionality of these associations cannot be certain due to the cross-sectional nature of these studies. Certain medications are essential to guideline-directed medical therapy for HF treatment and may not be able to be modified without compromising quality of HF care and increasing the risk of cardiovascular events, disease progression, or even mortality. Shared decision making is central to establishing and modifying treatment regimens with consideration of individual priorities and goals as well as the potential impact of various treatments on symptom burden and outcomes. This raises an important discussion about the balance between clinical and patient-reported outcomes in the HF literature.

Traditionally, clinical trials of medications in HF have focused primarily on hard clinical endpoints (i.e., mortality, hospitalization) with few patient-reported outcomes. However, more recent trials for HF pharmaceuticals have begun to include measures of quality of life.[70,71] A recent study by Luo et al. showed that individuals with declines in quality of life over a 3-month period were significantly more likely to die from all causes, including cardiovascular events, and were more likely to be hospitalized.[72] This data suggesting the association of patient-reported outcomes with clinical outcomes further emphasizes the importance of their inclusion in HF clinical trials. Further, outcomes such as quality of life are highly important to individuals and their families and addressing such outcomes is essential for providing patient/family-centered medical care.

Patient reported outcomes may also shed light on health disparities in HF. For example, a recent study of patients with HF with preserved ejection fraction (HFpEF) by Chandra et al. showed that after controlling for specific symptoms measured individually, health-related quality of life was significantly lower in women than in men, shedding light on a disparity that needs further exploration.[73] Therefore, including a more diverse array of patient-reported outcomes may be an important next step in HF clinical trials.

Psychological Variables

Few psychological variables were examined in the studies reviewed. However, depression stands out as the prominent variable associated with fatigue in those with HF. This is consistent with literature that describes fatigue and depression as having overlapping symptoms. Individuals with fatigue have been shown to be significantly more likely to report depression symptoms, even after controlling for the overlap in fatigue and depression symptom profiles.[16] This makes an interesting distinction between the two symptoms but highlights the importance of their co-occurrence. Treatment of one may impact the other but understanding the etiology of both is critical for optimal symptom control. Further, the replicable association between depression and fatigue suggests that intervention components should likely be targeted towards psychological variables such as depression to help alleviate fatigue symptoms. This is consistent with literature from other fatiguing conditions (such as chronic fatigue syndrome and cancer) that show cognitive behavioral therapy as an effective intervention for reducing fatigue severity and its impact on daily life.[74,75]

Additionally, the literature suggests that mental representation of fatigue, fatigue perceptions, and fatigue attribution to HF may be important to the fatigue experience and patient-reported and clinical outcomes. Symptom perception has been shown to influence many patient reported and clinical outcomes including general and physical health, decreased mortality, HF decompensation, hospital/emergency visits, shorter delays in seeking care, HF self-care behaviors and management, improved symptom recognition, decreased hospital length of stay and healthcare cost.[6] The evidence also describes fatigue in HF as distressing and having a wide range of negative emotional consequences which can significantly impact quality of life. These findings emphasize the importance of holistic understanding of such psychological variables and their inclusion in interventions to improve fatigue symptoms and patient-reported and clinical outcomes.

Social Variables

Social factors were largely unmeasured in the quantitative literature. The qualitative literature described the social impacts of fatigue on patients' lives including isolation, relationship role changes, and increased dependence on others. This limited evidence suggests that social factors are important to patients and to their families. However, we do not have enough evidence to guide the development of social interventions for alleviating social impacts of fatigue in HF. Understanding social support and social dynamics related to fatigue in HF will be an important area of study with the goal of improving quality of life and mitigating negative impacts of fatigue.

Social determinants of health in relation to HF fatigue were unexamined in the articles reviewed. Social determinants of health are important predictors of HF outcomes[76,77] and could play a role in the manifestation and experience of HF symptoms. The complexity of HF management is compounded among those individuals negatively impacted by the effects of social determinants of health. [77] Those with limited access to care are more likely to experience poor HF outcomes over time. The high cost of complex, chronic illness management often leads to difficult decisions about health and healthcare, particularly when the costs of medical appointments, medications and other treatment options are at

odds with basic food and housing needs. This body of literature also failed to examine community-level socioeconomic and environmental resources which influence factors that affect HF care such as individual lifestyle, cultural behaviors, and value systems. The high demands of HF care further exacerbate vulnerability among individuals and their families as a result of job loss, increased healthcare costs, and declining social connectedness. In the general population and among those with other chronic diseases, fatigue has been associated with higher levels of perceived stress and lower social class.[78,79,80] Therefore, we should examine social determinants of health and their relationships to fatigue in HF.

Interventions

There are few interventions focused on improving fatigue symptoms in HF populations. Exercise training and cardiac rehabilitation interventions to improve fatigue, as described here, have shown mixed results, but warrant further study. Austin et al.[42] saw significant reductions in fatigue short after the end of the intervention. However, longer-term follow-up showed a return to baseline fatigue levels. There may be many determinants of whether someone continues to exercise after an intervention is complete. Particularly, social determinants of health are shown to be associated with exercise and lifestyle changes. Variables such as community infrastructure[81], financial security[82], education level[82], and social support[83] are key determinants to understand when implementing such interventions and more support may be needed to help patients maintain these exercise regimens to alleviate their fatigue in the long term.

Behavioral interventions in fatigued HF patients are also not well defined. However, the evidence suggests that behavioral interventions – such as mindfulness practices - may be helpful in the treatment of fatigue. However, the interventions described in this review were performed on inpatient HF patients and were only performed over the course of 3 days. Their results are promising but such interventions require further study in both inpatients and outpatients over longer periods of time.

Despite numerous studies showing associations between fatigue and depression in HF, interventions addressing depression and mental health to relieve fatigue are largely absent. However, there are many examples of behavioral interventions targeting fatigue symptoms in other chronic conditions. A recent scoping review by Hulme et al.[84] described 52 systematic literature reviews that examined fatigue interventions across numerous chronic conditions. None of the reviews included fatigue interventions in HF populations. The types of interventions included pharmacological, exercise, psychological/behavioral, and complementary medicine practices. The body of evidence describing such interventions may serve as a guide for the future development and implementation of such interventions in HF populations.

It is also important to consider that existing interventions that may address fatigue in HF are likely not focusing solely on fatigue but are targeting symptom management or self-care more broadly. Self-care in heart failure includes multiple aspects related to symptom monitoring, recognition, and evaluation.[85] Effective HF self-care interventions have largely focused on behavioral modification strategies that promote self-efficacy and mastery of

such self-care behaviors.[86] Therefore, behavioral interventions that target fatigue, may help alleviate such symptoms.

Guideline-directed medical therapy (GDMT) is a powerful tool to improve symptoms and clinical outcomes in people with HF. However, we would expect that even individuals on GDMT will experience continued symptoms such as fatigue. Non-pharmacological and/or behavioral interventions may help optimize symptom control and quality of life. Many of the interventions described here fall under multiple domains of the biopsychosocial model health. This model asserts that interventions should target multiple domains and design interventions with multiple domains in mind to have the most impact on improving health and disease experiences.[25] Multi-modal interventions targeting the biological, psychological, and social domains of the biopsychosocial model of health developed by interdisciplinary care teams may provide further relief from distressing HF symptoms and provide an increasingly holistic approach to HF care.

Fatigue measurement

When evaluating the measurement of fatigue across studies, there is a clear distinction between those that conceptualize fatigue as a multi-dimensional construct and those that view it as unidimensional. The methods used to measure fatigue were heterogeneous. There were 17 different measurement methods used across all studies (table 3). Multi-dimensional scales such as the Piper Fatigue Scale or the Multidimensional Fatigue Inventory are more burdensome to measure and rely on patient self-report but may provide a more in depth understanding of the nature of fatigue. Unidimensional measures such as ICD-10 codes for fatigue diagnosis are accessible but may not be routinely billed in HF patients and likely have low sensitivity, in addition to limited ability to describe the nature of fatigue. Researchers seeking to understand fatigue should utilize psychometrically validated, reliable, and multi-dimensional scales to assess fatigue holistically and provide insight into the heterogenous effects fatigue has on individuals' lives.

Further, there is evidence to suggest that researchers should distinguish between two types of fatigue heart failure: general and exertional.[50,64,51,52] There were only a few studies that conceptualized fatigue in HF as "general" and "exertional" and pursued them as two phenomena. Fatigue in HF may be particularly unique from fatigue in other chronic conditions because of HF physiology. The involvement of dyspnea with activity as a component of exertional fatigue may indicate clinically a low output state or more advanced HF, requiring additional provider action that would be different than for general fatigue. Further research may benefit from distinguishing between these two types of fatigue to more fully understand the fatigue experience that is specific to HF.

Additionally, the majority of fatigue scales were originally developed to measure fatigue in chronic conditions other than HF. Validation of fatigue measurement tools in the HF population is important because fatigue in HF appears to be multi-dimensional and unique in its relationship to HF physiology. Fatigue, when measured as a component of larger health-related quality of life scales (e.g., Kansas City Cardiomyopathy Questionnaire) is likely not adequately assessing fatigue as an individual symptom. This impresses the importance of a cohesive understanding of the fatigue construct in HF, consistency in its measurement, and

robust validation of those measures in the HF population to allow for comparison of research results across multiple studies.

Recommendations to enhance future research on fatigue in HF

This literature review has discovered a number of opportunities to enhance future research on fatigue in HF. First, measurements of fatigue in HF need more consistency in both the scales used and their theoretical constructs. Consistent measurement and conceptualization of fatigue in HF will allow for more robust comparison of results between studies and meta-analysis of findings in future literature reviews. Further, scales should be appropriately validated in HF populations and be grounded in theory. Second, there is a need for more experimental studies examining fatigue in HF to diversify and improve the level and quality of evidence from which researchers and clinicians can draw conclusions from. Finally, there is a need for research examining novel, more holistic predictors of fatigue in HF that encompass a wider breadth of the patient experience, including physiology, social determinants of health, and psychosocial factors.

Strengths & Limitations

We acknowledge that there are limitations to this systematic literature review. Many of the studies had small sample sizes and were cross-sectional in nature which does not allow us to infer causation with many variables. Studies that were not published in English were also excluded. Other factors that may impact fatigue in HF are not included in this review because they were not examined in the literature synthesized. Particularly, the concept of frailty did not emerge in any of the literature synthesized in this review, therefore, no conclusions can be drawn about the linkage between fatigue in heart failure and the exhaustion component of frailty. Meta-analysis was not possible in this review because of the heterogeneity of fatigue and outcome measures. The majority of inferences in this review were made from articles of evidence level III A-B, which indicates a need for enhanced rigor of research related to HF fatigue. Additionally, the Johns Hopkins Nursing Evidence-Based Practice Appraisal tools[26] evaluate the quality of qualitative evidence similarly to quantitative evidence, despite the philosophical and epistemological differences in quantitative and qualitative methodologies. Despite these limitations, this study was strengthened by the use of the Biopsychosocial Model of Health as a guiding framework for critical synthesis of the HF fatigue literature and the engagement of multiple independent reviewers of articles for inclusion and data extraction. Additionally, the inclusion of both qualitative and quantitative literature provides a richness to the data synthesis.

Conclusions

We found, through a systematic review of the literature, that fatigue may not only carry prognostic implications in HF but is a significantly distressing symptom that interferes with multiple aspects of peoples' lives. We found that 1) the literature has focused primarily on biological correlates of fatigue, with disparate findings reported; 2) biological variables with the most evidence supporting their association with fatigue were NYHA functional class, hemoglobin level, and stroke; 3) psychological variables were limited in the quantitative literature in spite of the rich qualitative description of the distressing nature of fatigue

and its impact on emotional functioning; 4) Social variables were largely absent from the quantitative literature and described mostly in the qualitative literature; and 5) social determinants of heath were unaddressed even though they have been shown to be strong predictors of HF outcomes[76,77,87] and associated with fatigue in other chronic conditions.[78,79,80] These findings, based primarily on non-experimental research of good-to-high quality, highlight the need for further research and a more consistent framework for examining fatigue in HF. Further, measurement of fatigue in HF is inconsistent across studies with nearly 17 different scales in use, many of which are not validated appropriately in the HF population. Effectively treating fatigue symptoms and mitigating negative impacts of fatigue from a multi-dimensional and holistic perspective is crucial for improving the health outcomes and quality of life of patients living with HF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights:

- Fatigue in those with heart failure is distressing, interferes with multiple aspects of people's lives, and is associated with both clinical and patient reported outcomes.
- We have a limited physiologic understanding of fatigue in heart failure which impacts our ability prevent and treat it.
- Few interventions exist to alleviate fatigue in heart failure, but they are needed to improve patient outcomes and quality of life.

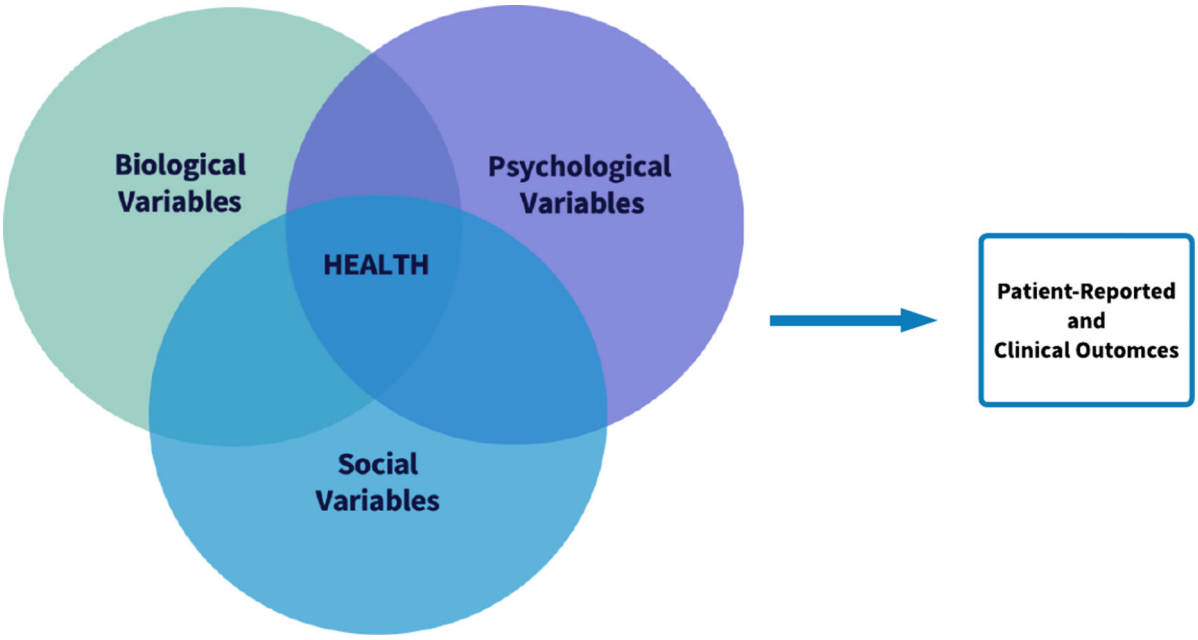

Figure 1. The Biopsychosocial Model of Health.

The biopsychosocial model of health was developed as an expansion of the biomedical model to encompass the biology of disease, the larger context of a person's life, and how they influence their health and disease experience (including but not limited to symptoms, and patient reported and clinical outcomes). The model includes three domains: 1) Biological, 2) Psychological, and 3) Social. These domains interact in a dynamic way that can change over time and depend upon context. The dynamics between these domains construct the health/disease experience for individuals and influence patient-reported and clinical outcomes.[22]

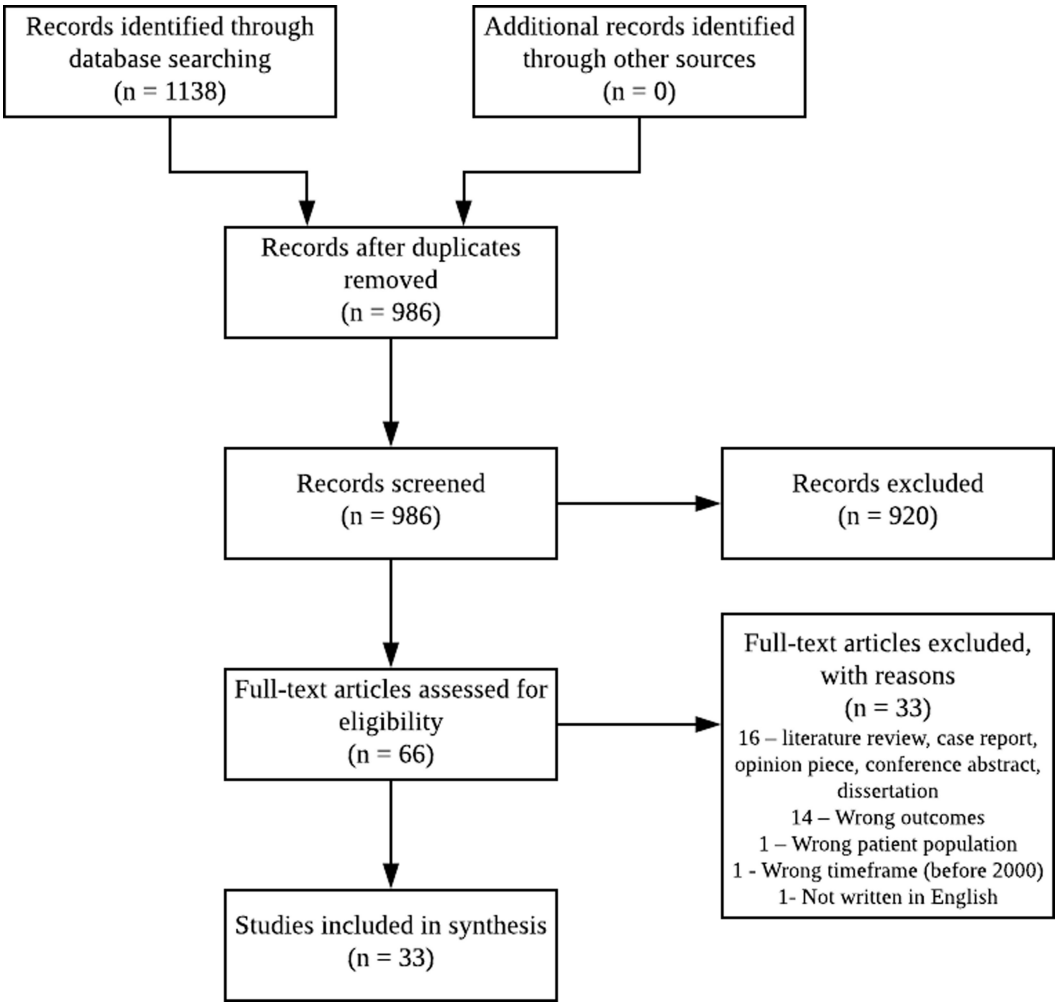

Figure 2.
PRISMA Flow Diagram of Systematic Literature Review Process[23]

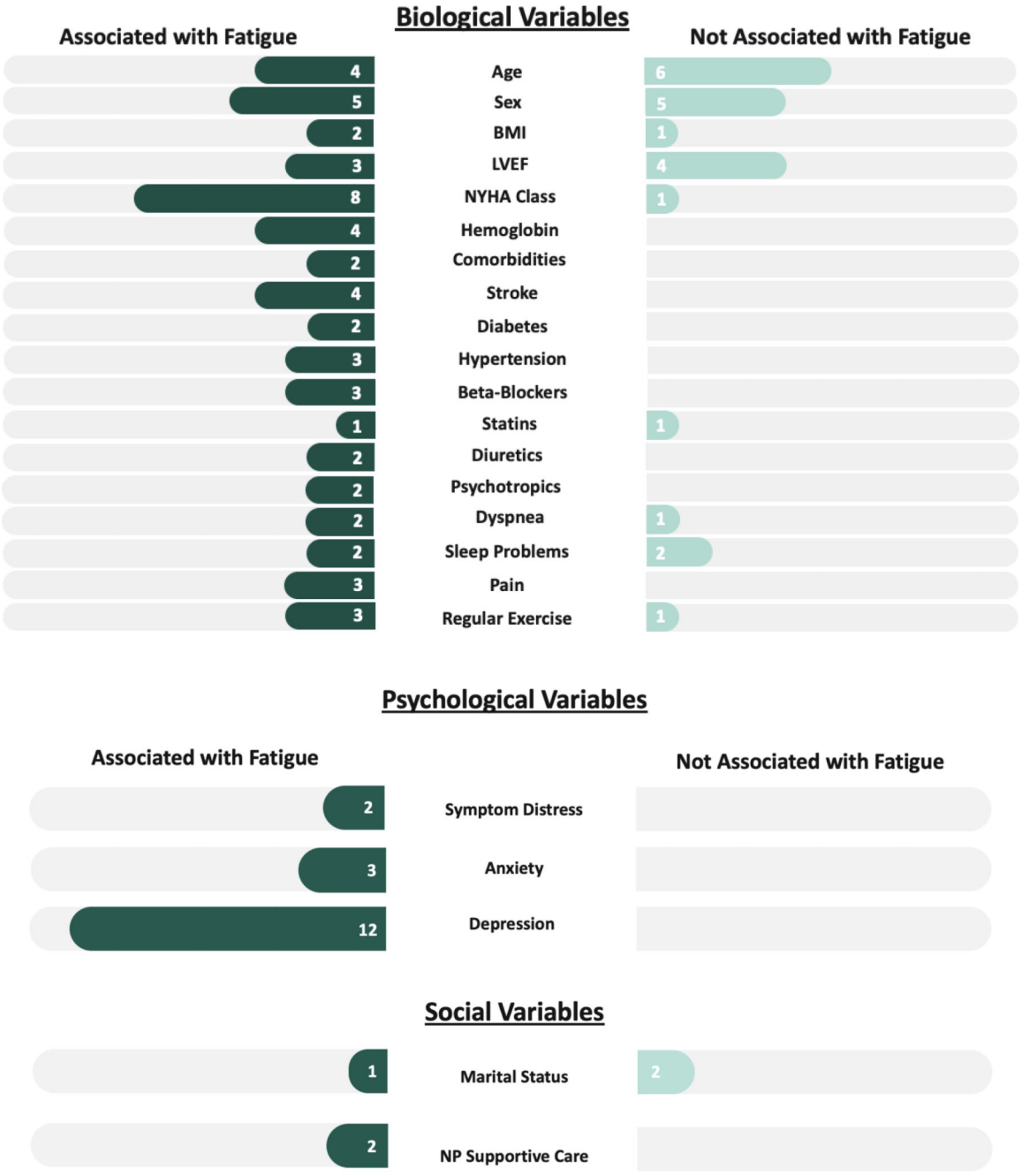

Figure 3. Summary of number of quantitative studies citing variables as either associated with fatigue or not assocaited with fatigue.

Variables were only included in this figure if there was more than one article that identified it as either associated with or not associated with fatigue in correlational or regression analysis. Direction of association (positive or negative) is not indicated in this figure, only presence or absence of association.

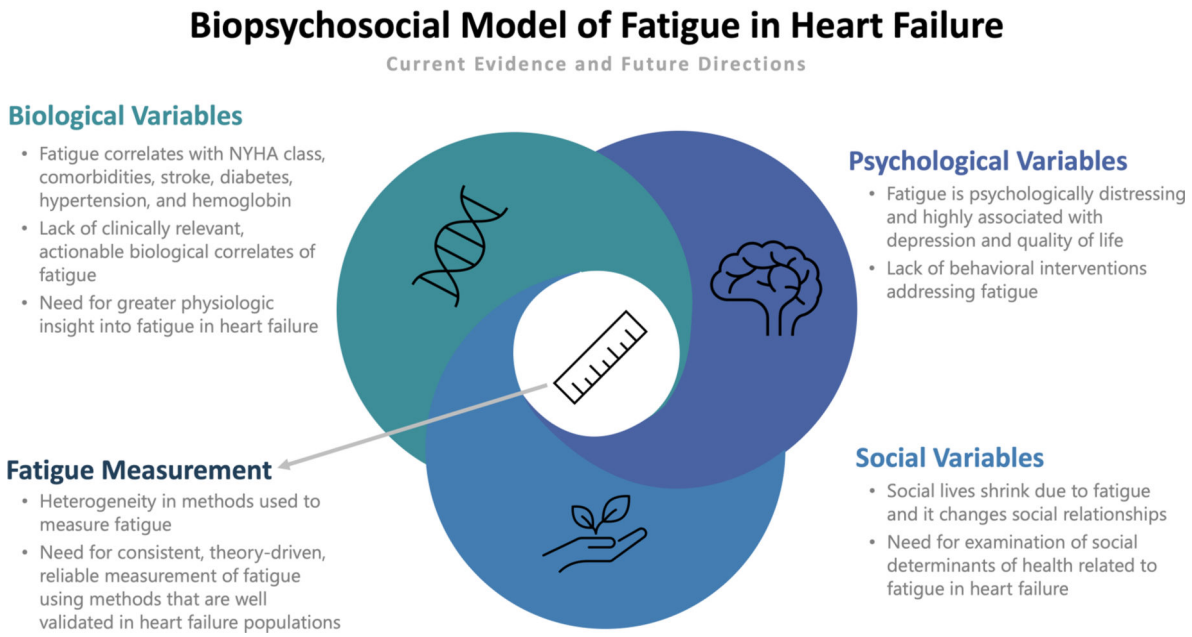

Figure 4.

Summary of findings from a systematic review and meta-synthesis of contemporary literature on fatigue in heart failure.

Table 1.

Summary of synthesized quantitative articles including study characteristics and key findings

Quantitative Studies									
Author/Date		Study Design	Sample	How was Fatigue Measured?	Biopsychosocial Model Domain(s)			Key Findings	Level and Quality
					Biological	Psychological	Social		
1	Austin et al. (2012)	Randomized Control Trial Follow-up period: 5 years	N=200 Mean age: 71.8 Female: 34% NYHA III/IV: not reported at baseline or follow up time points	Minnesota Living with Heart Failure questionnaire	√	√	√	• Participants were randomized to standard care or intervention • The standard care consisted of eight weekly monitoring sessions of clinical status (functional performance, fluid status, cardiac rhythm, blood labs) and standard HF education by a clinical nurse specialist • The intervention consisted of standard care plus an 8-week cardiac rehabilitation program with a clinical nurse specialist. Rehab sessions were twice weekly and 2.5 hours each. After the 8-weeks, intervention participants entered a 16-week community-based exercise program of weekly 1 hour exercise sessions by a professional exercise rehabilitation instructor. Exercise consisted of aerobic endurance training and low-resistance, high repetition muscular strength exercise. • Statistically significant reduction in fatigue in the intervention cardiac rehabilitation	I/B

Quantitative Studies									
Author/Date		Study Design	Sample	How was Fatigue Measured?	Biopsychosocial Model Domain(s)			Key Findings	Level and Quality
					Biological	Psychological	Social		
								group at 2 months and 6 months post-intervention initiation • No significant reductions in fatigue beyond 6 months and the distribution of fatigue ratings had returned to nearly baseline levels • Severity of fatigue score was correlated with quality of life (higher fatigue -> poorer quality of life)	
2	Chen et al. (2010)	Cross-Sectional Correlational	N=105 Mean age: 65.17 (15.1) Female: 35.2% NYHA III/IV: 54.3%	Piper Fatigue Scale	√	√	√	• 84.8% of participants experienced fatigue with the majority of patients having mild to moderate fatigue (75.3%) • 30% of those reporting fatigue symptoms also reported difficulty with physical, social, and sexual functioning • Majority of fatigue reported was intermittent (67.6%) • Fatigue is positively correlated with increased symptomatic distress, increased anxiety, and increased depression; it is negatively correlated with ADL capacity. • NYHA class, symptomatic distress, depression, anxiety, and healthcare provider support were all significant independent predictors of fatigue; symptomatic distress explained 39%	III/A

Quantitative Studies									
Author/Date		Study Design	Sample	How was Fatigue Measured?	Biopsychosocial Model Domain(s)			Key Findings	Level and Quality
					Biological	Psychological	Social		
								of the variance in the model	
3	Evangelista et al. (2008)	Cross-Sectional Correlational	N=150 Mean age: 55 (12.1) Female: 27.3% NYHA III/IV: 55.2%	Profile of Mood States Fatigue subscale	√	√		• Peak VO_2 and maximum workload on exercise testing were significantly lower in the high fatigue group vs. low fatigue group • No differences in any variables when comparing men and women • Fatigue was strongly correlated with quality of life, physical and emotional health, and depression • NYHA class, etiology of heart failure, and ejection fraction were not associated with fatigue • Statin use was associated with higher levels of fatigue • Multiple regression showed lower maximum workload, physical and emotional health, and depression were independent predictors of fatigue; together they accounted for 51% of the variance in fatigue	III/B
4	Falk et al. (2009)	Cross-Sectional Correlational	N=112 Mean age: 77 (10) Female: 40% NYHA III/IV: 79%	Multidimensional Fatigue Inventory MFI-20 (Swedish Version)	√	√		• No differences in fatigue based on sex • Women reported significantly more symptom distress than men • Fatigue was ranked as the most distressing symptom in the sample Breathing and mood were significantly	III/B

Quantitative Studies									
Author/Date		Study Design	Sample	How was Fatigue Measured?	Biopsychosocial Model Domain(s)			Key Findings	Level and Quality
					Biological	Psychological	Social		
								correlated with general fatigue • Appetite and pain were significantly correlated with physical fatigue • Multiple linear regression showed CVA, anxiety, depression, and symptom distress to be predictive of general fatigue • Multiple linear regression showed CVA, NYHA class, depression, and symptom distress to be predictive of physical fatigue	
5	Falk et al. (2007)	Cross-Sectional Correlational	N=93 Mean age: 74 (12) Female: 48% NYHA III/IV: 51%	Multidimensional Fatigue Inventory MFI-20 (Swedish Version)	√	√		• Prevalence of severe fatigue was highest in the physical fatigue dimension • NYHA class was significantly associated with general fatigue and physical fatigue • In multivariable regression analysis, sense of coherence and NYHA class significantly predicted general fatigue ($R^2 = 0.31$) • Uncertainty did not significantly predict fatigue	III/B
6	Falk et al. (2006)	Cross-Sectional Correlational	N=93 Mean age: 74(12) Female: 48% NYHA III/IV: 51%	Multidimensional Fatigue Inventory MFI-20 (Swedish Version)	√			• No differences in fatigue between men and women • Fatigue was significantly increased in patients with anemia compared to non-anemic patients • Multivariable regression analysis showed hemoglobin level and • NYHA class	III/B

Quantitative Studies									
Author/Date		Study Design	Sample	How was Fatigue Measured?	Biopsychosocial Model Domain(s)			Key Findings	Level and Quality
					Biological	Psychological	Social		
								were predictive of general fatigue (R^2 = 30%)	
7	Fink et al. (2012)	Cross-Sectional Case-Control	**HFrEF:** N=59 Mean age: 61 (1.9) Female: 42% NYHA III/IV: 39% **Controls:** N=25 Mean age: 57 (1.7) Female: 60% NYHA III/IV: n/a	Profile of Mood States Fatigue subscale	√	√		• Controlling for depressive symptoms, HFrEF patients did not have significantly different fatigue scores than controls • NHYA class was significantly associated with fatigue • Fatigue was significantly correlated with both depressive symptoms and poorer sleep quality • After controlling for depressive symptoms, only IL-10 levels were significantly different between HFrEF patients and controls • Plasma cytokine levels were not correlated with fatigue • Higher SHFM (mortality) scores were significantly correlated with increased levels of fatigue	III/A
8	Fink et al. (2009)	Cross-Sectional Correlational	N=87 Mean age: 57 (1.5) Female: 56% NYHA III/IV: 40%	Profile of Mood States Fatigue and Vigor subscales Fatigue Symptom Inventory	√	√		• Fatigue was significantly correlated with depressed mood, hemoglobin, NYHA class, and physical functioning • In multivariable linear regression, physical functioning and hemoglobin categories significantly predicted fatigue scores (R^2 = 0.30)	III/A

Quantitative Studies									
Author/Date		Study Design	Sample	How was Fatigue Measured?	Biopsychosocial Model Domain(s)			Key Findings	Level and Quality
					Biological	Psychological	Social		
9	Hagglund et al. (2008)	Cross-Sectional	N=49 Mean age: 77.7 Female: 57% All patients were NYHA class II or III	Multidimensional Fatigue Inventory MFI-20 (Swedish Version)	√	√	√	• All physical variables (physical functioning, role functioning, bodily pain, general health) were significantly associated with fatigue • Depression, female sex, living alone, emotional role functioning and social function were significantly associated with fatigue • Multivariable analysis also showed sex and physical functioning to be significantly predictive of fatigue (R^2 = 0.36)	III/B
10	Heo et al. (2019)	Cross-Sectional Secondary Analysis of Data	N=119 **Male: 58.8%** Mean age: 64.2 (10) NYHA I/II: 81.4% **Female: 41.2%** Mean age: 66.3 (9.7) NYHA I/II: 65.3%	Symptom Status Questionnaire – Heart Failure (Korean Version)	√	√		• Females had significantly greater fatigue and great frequency of fatigue than males • In males, multivariable regression showed that comorbidities, diuretics, depressive symptoms, and perceived control were all significantly associated with fatigue • In females, multivariable regression showed only depressive symptoms to be significantly associated with fatigue	III/B
11	Heo et al. (2019)	Cross-Sectional Secondary Analysis of Data	N=582 Female: 45.5% Mean age: 63.2 (14.4) NYHA III/IV: not reported	ICD-9 diagnosis codes of fatigue	√	√		• Patients with HFrEF had fewer number of hospitalizations and shorter hospital lengths of stay than those with HFpEF	III/B

Quantitative Studies									
Author/Date		Study Design	Sample	How was Fatigue Measured?	Biopsychosocial Model Domain(s)			Key Findings	Level and Quality
					Biological	Psychological	Social		
								• Patients with a diagnosis of fatigue were older, more often female, had lower BMI, diagnosis of depression, had higher use of medical services, hospitalizations, and longer lengths of stay • Fatigue was associated with higher utilization of medical services in HFrEF and HFpEF controlling for covariates	
12	Heo et al. (2016)	Cross-Sectional Secondary Analysis of Data	N=582 Female: 45.5% Mean age: 63.2 (14.4) NYHA II/ III: 82.7%	ICD-9 diagnosis codes of fatigue	√	√		• More men than women were in the no-symptom group • More women experienced depression-only and depression combined with fatigue than men • Individuals with both depression and fatigue had significantly lower heart rates, longer lengths of hospital stay, lower systolic and diastolic BP, increased age, increased LVEF, and more emergency department visits and hospitalizations compared to the no-symptom group. • Symptom grouping was associated with number of all-cause hospitalizations controlling for demographics, comorbidities, laboratory values, clinical characteristics, and medications ($p<0.001$).	III/B

Quantitative Studies									
Author/Date		Study Design	Sample	How was Fatigue Measured?	Biopsychosocial Model Domain(s)			Key Findings	Level and Quality
					Biological	Psychological	Social		
13	Kessing et al. (2016)	Secondary Analysis of Longitudinal Cohort Study Follow-up period: 18 months	N=545 Mean age: 66.2 (9.6) Female: 25% NYHA III/IV: 32%	Fatigue Assessment Scale Dutch Exertion Fatigue Scale	√	√	√	• Lower ejection fraction, stroke/TIA were significantly associated with general fatigue • Increased age, no partner, hypertension, diabetes mellitus, and higher BMI were significantly associated with exertional fatigue • Diuretics, nitrates, and psychotropic medication were associated with increased general fatigue • Beta-blocker use was associated with decreased exertional fatigue • Sleep problems, anxiety, and depression were associated with increased general and exertional fatigue • Fatigue (general and exertional) was a significant determinant of overall self-care • Adjusting for confounding variables, increased general and exertional fatigue was significantly associated with poorer self-care with no relationship to time	III/A
14	Norberg et al. (2010)	Cross-Sectional Correlational	N=40 Mean age: 80.6 (6.3) Female: 60% NYHA III/IV: not reported	Multidimensional Fatigue Inventory (Swedish Version)	√		√	• Persons who were categorized as dependent with ADLs reported the most severe levels of physical and general fatigue • Those dependent in	III/B

Quantitative Studies									
Author/Date		Study Design	Sample	How was Fatigue Measured?	Biopsychosocial Model Domain(s)			Key Findings	Level and Quality
					Biological	Psychological	Social		
								cooking, transportation, and cleaning reported significantly higher levels of fatigue that those who were not dependent in these activities, even when controlling for confounding variables. • Those that reported lower occupational performance reported significantly higher levels of fatigue • Those that used assistive devices in the home reported significantly higher levels of fatigue	
15	Perez-Moreno et al. (2014)	Secondary Analysis of Longitudinal Cohort Study Follow-up period: 6 months	N=3,830 Mean age: 73 (7.1) Female: 21.2% NYHA III/IV: 52.3%	Non-standardized or validated 5-point Likert scale (1 item)	√			• Patients with higher levels of fatigue were more likely to be older, female, higher NYHA class, and have lower systolic blood pressure and higher heart rates, pro-BNP levels, and CRP levels than patients with lower levels of fatigue • Those with higher levels of fatigue were more likely to have a history of MI, hypertension, diabetes, atrial fibrillation, or stroke • Higher severity of fatigue increased likelihood of mortality and hospitalization • Those who reported an increase in fatigue severity over six months were more likely to die from any cause as	III/A

Quantitative Studies									
Author/Date		Study Design	Sample	How was Fatigue Measured?	Biopsychosocial Model Domain(s)			Key Findings	Level and Quality
					Biological	Psychological	Social		
								compared to those that did not report a change in fatigue severity	
16	Plach et al. (2006)	Crosssectional Descriptive Correlational Secondary Analysis of Data	N=169 Mean age: 69 (12.1) Female: 100% NYHA III/IV: not reported	Fatigue Representations – Symptom Representation Questionnaire		√		• The majority of women moderately agreed that their fatigue as chronic, caused by heart failure, and that fatigue had serious consequences for themselves and others. • Younger women reported more severe consequences of fatigue and emotional distress related to fatigue than older women. • Those that perceived their health as worse reported more emotional distress from fatigue, identified their fatigue as more chronic, and experienced more severe consequences from fatigue. • Fatigue representations that included increased emotional distress from fatigue, more certainty that HF caused the fatigue, and more severe consequences from fatigue were associated with increased healthcare utilization (ED and physician visits). • In multivariable regression, fatigue representations did not significantly predict healthcare utilization and	III/B

Quantitative Studies									
Author/Date		Study Design	Sample	How was Fatigue Measured?	Biopsychosocial Model Domain(s)			Key Findings	Level and Quality
					Biological	Psychological	Social		
								psychological wellbeing.	
17	Pozehl et al. (2008)	Randomized Control Trial Follow-up period: 24 weeks	N=21 Mean age: 66.2 (10.2) Female: 9.5% NYHA III/IV: 61.9%	Piper Fatigue Scale	√			• Participants were randomized 2:1 to intervention or control • The exercise intervention consisting of 3 days per week of aerobic and muscle strengthening exercise training for 24 weeks total. The first 12 weeks were standard cardiac rehabilitation while the second 12 weeks were self-guided exercise performed at the cardiac rehabilitation facility. • The control group received no intervention. • They found no significant improvement in overall fatigue or dyspnea severity compared to the control group at 24-week follow-up.	I/B
18	Seifi et al. (2018)	Randomized Control Trial Follow-up period: 3 days (length of intervention)	N=105 **Benson Muscle Relaxation group:** Mean age: 48.5 (11.7) Female: 34.3% NYHA III/IV: not reported **Nature Sounds group:** Mean age: 51.1 (11.6) Female: 42.9% NYHA III/IV: not reported **Control group:** Mean age: 54.8 (10.7) Female: 33.3%	Fatigue Severity Scale		√		• Participants were randomized 1:1 to either intervention or control • The intervention consisted of either Benson muscle relaxation guided by a research interventionist (progressive muscle relaxation) or listening to nature sounds performed 2 times per day for 3 days while resting in a comfortable position. • Mean fatigue score after 3-day	I/B

Quantitative Studies									
Author/Date		Study Design	Sample	How was Fatigue Measured?	Biopsychosocial Model Domain(s)			Key Findings	Level and Quality
					Biological	Psychological	Social		
			NYHA III/IV: not reported					intervention was significantly higher in the control group as compared to the two intervention groups • There was a significant reduction in mean fatigue score comparing baseline and post-intervention for both intervention groups • There was no significant difference in fatigue score between the two intervention groups after the intervention period	
19	Smith-Love, J. (2019)	Randomized Controlled Trial Follow-up period: 30 days post hospital discharge	N=41 Mean age: 61.1 (16.3) Female: 56.7% NYHA III/IV: 96.6%	Piper Fatigue Scale			√	• Participants were randomized 1:1 to either intervention or control. • The intervention consisted of daily in-person interactions during acute heart failure hospitalization with a nurse practitioner and then daily telephone interactions for 1 to 3 weeks after discharge. • Intervention interactions consisted of education, coaching, counseling on fatigue identification, energy conservation during activities of daily living, HF self-care behaviors, and appropriate response to worsening symptoms. • No further details about the intervention were provided	I/B

Quantitative Studies									
Author/Date		Study Design	Sample	How was Fatigue Measured?	Biopsychosocial Model Domain(s)			Key Findings	Level and Quality
					Biological	Psychological	Social		
								by the authors. • There was a significant reduction in fatigue scores in the intervention group over time from hospital admission to discharge and to 30 days post discharge.	
20	Smith et al. (2007)	Cross-Sectional Correlational	N=136 Mean age: 65.6 (8.5) Female: 23.5% NYHA III/IV: 53.7%	Fatigue Assessment Scale (general fatigue) Dutch Exertion Fatigue Scale (exertional fatigue)	√	√		• Exertional fatigue and general fatigue were significantly different from each other using principal component analysis ($p<0.001$) • Univariate correlates of exertional fatigue were exercise capacity, NYHA class, dyspnea, cardiac pain, and depressive symptoms • Univariate correlates of generalized fatigue were sleep problems, dyspnea, cardiac pain, depressive symptoms, type-D personality • Predictors of exertional fatigue were exercise capacity, dyspnea, hypertension, and depressive symptoms. ($R^2 = 0.32$) • Predictors of generalized fatigue were dyspnea, depressive symptoms, type-D personality, and sleep problems ($R^2 = 0.37$)	III/B
21	Smith et al. (2009)	Longitudinal Correlational Follow-up period: 12 months (survey) and	N=387 Mean age: 66.4 (10.7) Female: 29.7% NYHA	Dutch Exertion Fatigue Scale Fatigue Assessment Scale	√	√		• Multiple regression analysis showed changes in exertion fatigue over 12 months	III/A

Quantitative Studies									
Author/Date		Study Design	Sample	How was Fatigue Measured?	Biopsychosocial Model Domain(s)			Key Findings	Level and Quality
					Biological	Psychological	Social		
		until adverse event for survival analysis	III/IV: 42.9%					were predicted by ejection fraction, having a biventricular pacemaker, use of beta blockers, and depressive symptoms. • Changes in general fatigue were only predicted by depressive symptoms • Univariate analysis showed increases in general and exertional fatigue were both associated with increased risk of cardiovascular re-admission or death • Multivariable analysis only showed increases in exertional fatigue to be predictive of cardiovascular readmission or death • Kaplan-Meier survival analysis showed that those with increases in exertional fatigue were nearly 2 times as likely to have an adverse event than those without increases in exertional fatigue	
22	Smith et al. (2010)	Longitudinal Correlational Follow-up period: 12 months for survey and until death for survival analysis	N=310 Mean age: not reported Age ≥ 60 = 72.6% Female: 30% NYHA III/IV: 39.4%	Dutch Exertion Fatigue Scale Fatigue Assessment Scale	√	√		• Levels of fatigue over time were generally stable • 6 exertional fatigue classes were identified (low exertion fatigue, mild exertion fatigue, moderate exertion fatigue, increased exertion with mild and moderate offsets, and severe exertion fatigue	III/A

Quantitative Studies									
Author/Date		Study Design	Sample	How was Fatigue Measured?	Biopsychosocial Model Domain(s)			Key Findings	Level and Quality
					Biological	Psychological	Social		
								• 4 general fatigue classes were identified (low general fatigue, moderate general fatigue, increased general fatigue with mild offset, severe general fatigue) • Multivariable regression analysis showed male sex, age, physical inactivity, diabetes, comorbidities, NYHA class, psychotropic medications, and poor performance on the 6-minute walk test were predictors of exertional fatigue class • Multivariable regression analysis showed smoking, physical inactivity, psychotropic medication, and poor performance on the 6-minute walk test to be predictive of general fatigue class • Exertional fatigue survival analysis showed a significant increase in hazard of death in the severe exertional fatigue class, and a significant decrease in hazard of death in the low exertional fatigue class as compared to the reference group (moderate fatigue class) • General fatigue survival analysis showed a significant increase in hazard of death	

Quantitative Studies									
Author/Date		Study Design	Sample	How was Fatigue Measured?	Biopsychosocial Model Domain(s)			Key Findings	Level and Quality
					Biological	Psychological	Social		
								in the severe general fatigue class compared to the references group (moderate fatigue class) • There was no significant reduction in hazard of death in the low general fatigue class	
23	Stephen (2008)	Cross-Sectional Correlational	N=53 Mean age: 77 (6.1) Female: 32% NYHA II/ III: 91%	Profile of Mood States Fatigue subscale Visual Analog Scale for Fatigue Fatigue Attribution Scale (author developed 5-point scale)	√	√		Symptom experience: • prevalence of fatigue was 96% with mild-moderate intensity on both scales used • Those with concurrent high severity symptoms rated their fatigue higher than those without high severity concurrent symptoms Symptom Outcome: • No significant relationship between fatigue intensity and selfreported functional status • Those that engaged in regular exercise reported lower rates of fatigue that those who did not exercise • Health related quality of life was positively correlated with fatigue (higher health related quality of life score = poorer quality of life) • Satisfaction with life was negatively correlated with fatigue Predictors of Fatigue: • Controlling for confounders, perceived health, life satisfaction, concurrent symptom severity, and	III/A

Quantitative Studies									
Author/Date		Study Design	Sample	How was Fatigue Measured?	Biopsychosocial Model Domain(s)			Key Findings	Level and Quality
					Biological	Psychological	Social		
								marital status explained 24.5% of the variance in fatigue • Marital status was the only independent predictor of fatigue	
24	Tang et al. (2010)	Cross-Sectional Correlational	N=107 Mean age: 69.31 (10.76) Female: 46.7% NYHA III/IV: 43.9%	Fatigue Visual Analog Scale Tang Fatigue Rating Scale	√	√		• Overall, females experienced higher levels of fatigue than males • Patients using beta-blockers experienced greater fatigue than those not using beta-blockers • NYHA class, depression, hemoglobin, and ejection fraction were significantly correlated with fatigue • Multivariate regression showed depression, NYHA class, and ejection fraction were significant predictors of fatigue and explained 73% of the variability in fatigue	III/A
25	Wang et al. (2016)	Randomized Controlled Trial Follow-up period: 12 weeks	N=92 Mean age: 65.7 (0.25) Female: 38% NYHA III/IV: 7.6%	Piper Fatigue Scale (Chinese Version)			√	• Participants were randomized 1:1 to either intervention or control. • The intervention consisted of three components: 1) fatigue assessment and monitoring, 2) fatigue management and education, and 3) outcome evaluation. • Participants received a total of 4, 30-minute counseling and education sessions by a	I/B

Quantitative Studies									
Author/Date		Study Design	Sample	How was Fatigue Measured?	Biopsychosocial Model Domain(s)			Key Findings	Level and Quality
					Biological	Psychological	Social		
								nurse comprised of the three intervention components and emotional support over the course of 12 weeks. • Participants were counseled on strategies to manage their fatigue based on their individual needs, social support networks, and lifestyle. • In the intervention group, fatigue significantly degreased over the 12-week follow up period as compared to the control group	
26	Williams, B. (2017)	Retrospective Cohort Study Follow-up period (survival analysis): until death or 10 years since HF diagnosis	N= 12,285 Mean age: 76 Female: 51% NYHA III/IV: not reported	ICD-9 billing codes (fatigue = yes/no)	√	√		• Patients who reported fatigue were more likely to be older, Female, have multiple comorbidities and concurrent symptoms, and to be prescribed multiple medications • Those with fatigue had significantly lower albumin and hemoglobin levels • 18 variables were found to be independent predictors of fatigue in multivariable analysis: depression, syncope, Female sex, hypovolemia, dyspnea, gastroesophageal reflux disease, chest pain, anemia, decreased BMI, abnormal weight loss, sleep apnea, palpitations, cerebrovascular disease, vitamin	III/C

Quantitative Studies									
Author/Date		Study Design	Sample	How was Fatigue Measured?	Biopsychosocial Model Domain(s)			Key Findings	Level and Quality
					Biological	Psychological	Social		
								D deficiency, edema, decreased hematocrit, hyponatremia, and increasing age. • No significant differences were found in mortality between those with fatigue and those without fatigue using Kaplan-Meier survival analysis	
27	Witte et al. (2008)	Longitudinal Cohort Study Follow-up period (survival analysis): 36 months	N= 271 Mean age: 67(10) Female: 19% NYHA III/IV: 22%	Patient report of yes/no to either “dyspnea” or “fatigue” as the reason for stopping the exercise test	√			• No differences in clinical characteristics of between those patients who stopped the exercise test due to “fatigue” versus “dyspnea” • There was no significant difference in hazard of death in those who stopped the exercise test due to “fatigue” versus “dyspnea” • Reason for stopping the exercise test was not associated with mortality at 36 months.	III/C

HFrEF: Heart failure with reduced ejection fraction

HFpEF: Heart failure with preserved ejection fraction

SHFM: Seattle Heart Failure Model mortality score

NYHA: New York Heart Association functional class (heart failure)

Pro-BNP: pro – brain natriuretic peptide

CRP: c-reactive protein

Table 2.

Summary of synthesized mixed-methods and qualitative articles including study characteristics and key findings

Qualitative/Mixed-Methods Studies									
Author/Date		Study Design	Sample	How was Fatigue Measured?	Biopsychosocial Model Domain(s)			Key Findings	Level and Quality
					Biological	Psychological	Social		
1	Ekman et al. (2002)	Descriptive Mixed-Methods	N= 158 Mean age: 81 Female: 41.8 % NYHA III/IV: 98%	Modified Fatigue Interview Schedule Qualitative Interview	√	√	√	• Categories participants identified as descriptive of their fatigue experience included: feebleness, listlessness, desire for rest, do not know, dyspnea, pain ○ Most commonly reported were feebleness, listlessness, and desire for rest • Participant identified potential causes of fatigue included: illness, age, do not know, listlessness, strained, drugs, loneliness, pain, bad condition ○ Most commonly reported were illness, age, do not know, and dyspnea • Men more often described their fatigue as “discomfort” than women • Categories participants identified that they would like to do if they had the strength included: everything, outdoor activities, do not know, hobbies, travelling, socialize, and nothing ○ Most commonly reported activities were everything, outdoor activities, and do not know ○ Significantly more men expressed uncertainty about what they would like to do if they had more strength than women • Participants described things that they do to try to relieve their fatigue which included: sleep and rest (most common), reading, watching TV, and other “distracting” activities • There was no significant difference in fatigue rating on the Fatigue Interview Schedule between men and women	III/B

Qualitative/Mixed-Methods Studies									
Author/Date		Study Design	Sample	How was Fatigue Measured?	Biopsychosocial Model Domain(s)			Key Findings	Level and Quality
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								• Women expressed feelings of happiness but loneliness • Men expressed feelings of happiness and restlessness • Very few participants endorsed their mood as "bad"	
2	Falk et al. (2007)	Qualitative Descriptive	N= 15 patients Female: 47% Mean age (patient): 76 NYHA II/III: not reported	Semi-structured Interview of participants and chat room conversations amongst anonymous patients (not the same sample as the interviews)		√	√	<u>Fatigue is described as a circular process:</u> • Fatigue experience → fatigue consequences → fatigue experience • This means that the fatigue experience leads to consequences of fatigue which then further influence the experience of fatigue <u>Fatigue Experience</u> • Lacking strength related to physical exertion and often related to other symptoms of heart failure such as shortness of breath, limb weakness, chest pain, and dizziness • Sudden, uncontrollable sleepiness • Overwhelming, whole body lack of energy • Leads to emotions such as sadness, anger, irritation, demoralization, intellectual deficiency, and embarrassment • Difficulty with short-term memory, learning new information, concentration, and lack of intellectual energy and creativity <u>Sacrificing</u> • Refraining from daily chores and exercise to prevent/mitigate fatigue • Denying oneself activities that they enjoy out of fear of failing to complete a valued task. Fear of disappointment. • Isolating themselves from others and feelings of a decreasing social life due to their fatigue. <u>Restoring</u> • Involuntary attentive activities: ○ Activities without	III/A

Qualitative/Mixed-Methods Studies									
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								a specific purpose or the require conscious effort (e.g. Observing nature, mental experiences of happiness, curiosity, and satisfaction, fishing, gardening, daydreaming) • Socially interactive activities: ○ Meeting with other people served as a distraction ○ Social events were described as so valuable that they would be willing to suffer the consequences to go • Mental absorption activities: ○ Helped participants forget about fatigue and improved feelings of loneliness and isolation. • Those that found new hobbies concordant with their abilities reported improved fatigue symptom experiences compared to those that did not and were primarily inactive	
3	Hagglund et al. (2008)	Qualitative Descriptive	N=10 Mean age: 83 Female: 100% NYHA III/IV: 100%	Open-ended interview		√	√	2 themes and 5 subthemes emerged: • Living with the loss of physical energy ○ Experiencing a substantial presence of feebleness and unfamiliar bodily sensations ○ Experiencing unpredictable variations in physical ability ○ Needing help from others in daily life • Striving for independence while being aware of deteriorating health ○ Acknowledging one's remaining abilities ○ Being forced to adjust and struggle for independence	III/A
4	Jones et al. (2012)	Qualitative Descriptive	N=26 Median age: 61 Female: 30.8% NYHA	Semi-Structured Interview		√	√	Two themes emerged: • Symptom experience ○ Knowing the symptom: recognizing the warning signs and anticipating the symptom, not	III/A

Qualitative/Mixed-Methods Studies									
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			III/IV: 57.6%					necessarily related to activities but a general “feeling”, understanding the consequences of not heeding warning signs ○ Physical experience of the symptom: physical burden of the symptom, the need to listen to their body, energy being “sapped”, mind and body disconnect, sleep making no difference, and ability to manage fatigue as part of the physical experience ○ Time management and planning necessary to adapt to the symptom: knowing how to optimize their reality, protecting their time as a way of protecting their energy, and planning as a coping strategy to prevent “overdoing” • Meaning ○ Existential meaning is the sense of vulnerability and mortality the patient feels as a result of experiencing fatigue ○ Contextual meaning involves the way the patient’s perceived the symptom as influencing their daily life, and understanding that their world is made smaller by the fatigue experience	
5	Walthall et al. (2019)	Qualitative Descriptive	N= 23 Mean age: 72.5 (9.5) Female: 43.5% NYHA III/IV: 100%	Semi-Structured Interview		√	√	Three themes emerged: • Fatigue as a physical barrier: ○ Physical debilitation: fatigue affected participants ability to perform activities of daily living or other physical activities; participants described reduction in physical strength that they did not attribute to age ○ Low energy levels: energy levels are much lower than they ever experienced; low energy is described as exhaustion rather than just not wanting to do something ○ Sleepiness: participants reported	III/A

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								having difficulty sleeping and finding no fatigue relief from sleep or rest; difficulty fighting falling asleep during the day • Psychological response to fatigue: ○ Variations in mood: negative feelings about the impact of fatigue on their lives such as frustration, depression, helplessness, and lack of motivation; some described positive thinking strategies to try to cope with their fatigue ○ Social Consequences: feelings of isolation as a consequence of fatigue; shrinking of social circles due to difficulty navigating life outside the home ○ Worries for the future: panic over fatigue and other symptoms and what they mean for the future • Fatigue as a part of daily life: ○ Learning how to live with fatigue: adaptation of daily life in response to fatigue ○ Striving for resilience every day: not letting fatigue beat you; acceptance of their condition; attempts to minimize negative feelings regardless of their fatigue	
6	Whitehead, L. (2017)	Qualitative Descriptive Secondary Analysis of Data	N= 22 patients 40 family members (62 total) Mean age (patient): 70 NYHA II/III (patient): 100%	Semi-structured Interview		√	√	Three themes emerged: • The unexpected severity of fatigue ○ Family did not anticipate fatigue to be so severe ○ Long periods of daytime sleeping ○ Concern that fatigue was a proxy for underlying issues/ worsening disease ○ Concern that patient has died, vigilance and checking on the patient while sleeping • The impact of fatigue on everyday life ○ Slowing down activity ○ Need to scale back	III/A

Qualitative/Mixed-Methods Studies									
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								expectations of the patient ○ Differences in sex: men reported impact of fatigue relating to being able to do less around the house, while women reported the impact as cognitive, emotional, and social ○ Recognition of why the impact of fatigue was so severe ○ Understanding the need to take over new roles in the house because of the patient's fatigue • The invisibility of fatigue ○ Described as one of the most difficult things to deal with relating to fatigue ○ Family members who did not live the house more often described not feeling as supportive or understanding of the patient's symptoms which lead to family tensions ○ Other family members who understood the symptom and its impact felt hurt by other family members who did not understand and were not a supportive	

Table 3.

Summary of fatigue measurement tools used in included articles

Fatigue Conceptualization	Fatigue Measure	# of articles	Developed for:	Validated in HF?
Multidimensional (at least 2 dimensions)	Multidimensional Fatigue Inventory[88]	5	Cancer	
	Piper Fatigue Scale[89]	4	Cancer	
	Fatigue Symptom Inventory[90]	1	Cancer	
	Fatigue Assessment Scale[63]	4	General Population	√
	Symptom Representations Scale[91]	1	Cancer	
	Fatigue Interview Schedule[92]	1	Heart Failure	√
	Symptom Status Questionnaire – Heart Failure[93]	1	Heart Failure	√
	Fatigue Severity Scale[94]	1	MS and SLE	
	Fatigue Attribution Scale[95]	1	CFS and Neuromuscular Disease	
	Tang Fatigue Rating Scale[54]	1	Heart Failure	√
Unidimensional	ICD-9 Fatigue Diagnosis Code	2	-	-
	Yes/No presence or absence of fatigue	1	-	-
	Visual Analog Scale	2	-	-
	Likert Scale	1	-	-
	Dutch Exertion Fatigue Scale[64]	4	Heart Failure	√
Fatigue included in a larger scale	Profile of Mood States Fatigue Subscale[96]	4	General Population	
	Minnesota Living with Heart Failure Questionnaire[97]	1	Heart Failure Quality of Life	√