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FRAILTY INTERVENTIONS IN ADULTS WITH HEART FAILURE: A SYSTEMATIC REVIEW AND META-ANALYSIS

by
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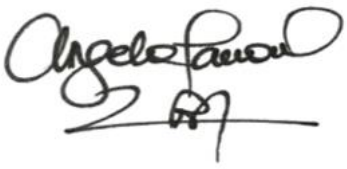

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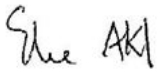

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ABSTRACT
OF THE THESIS OF

Sally Abdulhassan Atwi for Master of Science in Nursing
Major: Adult Care

Title: Frailty Interventions in Adults with Heart Failure: A Systematic Review and Meta-Analysis

Background**:** Frailty is common in patients with Heart Failure [HF] and is closely associated with poorer outcomes. The HF disease processes can accelerate the functional capacity decline experienced by pre-frail and frail patients. Furthermore, frailty contributes to worse repercussions in this chronically ill patient population and holds independent challenges beyond the HF disease process itself.
The relationship between frailty and HF is often closely interrelated and can increase patients' overall morbidity and mortality. Interventions that focus on behavioral, nutritional, and/or cognitive therapy can reduce the morbidity of HF patients and decrease the adverse effects related to inactivity such as dyspnea and functional dependence. Therefore, it is imperative to understand whether addressing frailty in patients living with HF would help mitigate unfavorable outcomes in those patients such as symptom burden, readmission rates, mortality.
Objectives: The aim of this systematic review and meta-analysis is to identify the different interventions that are currently in practice worldwide for the treatment of frailty in prefrail and frail adults with HF and assess their effects on mortality, symptom burden, and readmission rates of patients living with HF. The focus will be on interventions such as behavioral therapy, cognitive training, exercise, and nutritional based specific interventions
Methods: We included studies comparing the effects of interventions targeting frailty to no such interventions in prefrail and frail adults with HF and a New York Heart Association Functional Class II or III. Outcomes assessed included mortality, symptom burden, and readmission rates. CINAHL, Medline, and EmBase databases were searched for published and peer reviewed articles using the predefined selection criteria. All articles included in the meta-analyses were Randomized Control Trials (RCTs). Study risk of bias were assessed using the Risk of Bias 2 Tool after conducting search and article selection. Hazard Ratios and mean differences were pooled for the meta-analysis. Overlapping data were consolidated, and only unique data points were used.
Results: The search resulted in 3649 records that were identified through database search and grey literature. From these records, 2869 records remained after duplicate screening and were then screened for title and abstract by two independent reviewers. Following title and abstract screening, 37 full text articles were assessed for eligibility and 6 articles were included in the systematic review. Six articles were included for the systematic review, while 4 articles were included for the meta-analysis. To conduct the meta-analysis for Short Physical Performance Battery (SPPB) at 3 months, 2 articles were used with a total of 186 participants, 3 articles were used for 6 Minute Walking Distance (6MWD) at 3 months with a total of 150 participants, and 2 articles were used for 6MWD at 6 months with a total of 123 participants. Using a Minimally Clinically Important Difference (MCID) of >1, the meta-analysis for SPPB found that the mean difference in completing a frailty intervention vs. standard care is 1.31 with a 95% CI of 1.04-1.58, indicating a slight increase in SPPB in heart failure patients.

Using an MCID of a change of approximately 30-32 meters, the meta-analysis for 6MWD at 3 months found that the mean difference between completing a frailty intervention vs standard care is 18.04 with a 95% CI of 3.88 - 32.21; indicating that the intervention does not increase 6MWD in heart failure patients at 3 months. The meta-analysis for 6MWD at 6 months found that the mean difference between completing a frailty intervention vs standard care is 7.75 with a 95% CI of -21.52 to 37.01, indicating a little to no difference in 6MWD in heart failure patients at 6 months.
Summary of Findings: It is imperative to recognize the close relationship of frailty and HF for healthcare professions to provide better support for the management of HF and to facilitate the development of effective interventions that optimize patient care. Furthermore, by acknowledging effective interventions for this specific population, it will enhance HF treatment plans and maximize patient adherence.
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Registration: The protocol of this study was published on PROSPERO (Registration Number CRD42022260621)
Keywords: Heart Failure, Frailty Interventions, Exercise Therapy, Nutritional Therapy, Cognitive Therapy.

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ABBREVIATIONS

1. HF: Heart Failure
2. New York Heart Association: NYHA
3. Six Minute Walking Distance: 6MWD
4. Short Physical Performance Battery: SPPB
5. Risk of Bias 2: RoB2
6. Hazard Ratios: HR
7. Grading of Recommendations Assessments, Development and Evaluation: GRADE
8. Newcastle-Ottawa Quality Assessment Scale for Cohort Studies: NOS
9. Minimally Clinically Important Difference: MCID
10. Clinical Nurse Specialist: CNS

CHAPTER I

INTRODUCTION

Frailty is a complex systemic syndrome associated with poor outcomes, and in patients with Heart Failure [HF], it has been documented as an independent predictor of early disability, long-term mortality, and readmission (Vidan et al., 2016). According to a recent position paper on frailty in HF, frailty is defined as a multidimensional dynamic state, independent of age, that makes patients with HF more vulnerable to the effect of stressors (Vitale et al., 2019). Frailty is a multidimensional physiological syndrome that influences several aspects of a patient's daily life such as gait, mobility, balance, cognition, and physical activity and increases susceptibility to adverse events such as falls, infections, and disability (Weng et al., 2021). Several scales have been documented in the literature to define and measure frailty with the majority of scales assessing the following five domains: slowness, weakness, decreased physical activity, exhaustion, and decreased muscle mass (Goldwater & Altman, 2016).

Approximately 15% of adults in the United States have frailty and an estimated worldwide prevalence of 27.3% (Walston et al., 2018). Frailty leaves affected patients vulnerable, increasing overall hospitalization and mortality rates (Uchmanowicz et al., 2019). In patients with HF, frailty was shown to be highly prevalent with rates ranging from 15 to 74% (Uchmanowicz et al.). Alarmingly, HF patients with frailty have a two-fold increase in mortality risk, leaving them more susceptible to endure longer hospital stays, and report a lower quality of life (Goldwater & Altman, 2016).

A. Rationale

Frailty can be modifiable and reversible with appropriate management and interventions. Several complex frailty interventions for adults living with chronic illnesses have been documented in the literature, but no clear recommendations have been set in place for patients with HF. Interventions that are already in place for frail patients can have a potentially large positive impact on patients with HF and can be used to prevent or postpone further deterioration (Mcdonagh et al., 2018). Tailoring and individualizing HF management according to the coexisting diagnosis of frailty is an approach that is often recommended in recent literature and is particularly important (Uchmanowicz et al., 2019). Tailoring treatments according to each patient's specific needs with multidisciplinary teams, monitoring patients on a regular basis, and providing individualized support for patients' self-care are important steps that can potentially reduce the morbidity and mortality that is associated with these two intertwined disease processes (Uchmanowicz et al.).

Frailty interventions implemented by healthcare providers in patients with HF are crucial in helping alleviate the physical and social aspects of symptom burden. It is important to remember that although frailty is linked with aging, it is not synonymous with it and should not be overlooked. In fact, frailty in HF is not confined to older adults and can be often seen in younger HF patients (Denfeld et al. (2017). Even with optimal medical management and clinical stability, patients can still experience symptom burden due to the progression of the HF disease process, especially as the NYHA functional classification further develops (Walston, Buta, & Xue, 2018).

Exercise training has been noted to increase functionality in HF patients, without an associated improvement in cardiac output (De Labra et al., 2015). Exercise such as strength training can reduce the morbidity in patients with HF as well as their symptom burden particularly those related to inactivity such as dyspnea and functional dependence (De Labra

et al., 2015). Participating in regular physical activity that includes flexibility and balance, resistance, and endurance training helps protect against the adverse effects of frailty. This improves quality of life in adults, increases mobility and functionality, and prevents hospitalizations and mortality (De Labra et al., 2015). Furthermore, the American College of Sports Medicine guidelines recommend that frail adults undergo resistance and aerobic training (De Labra et al., 2015). Ng and colleagues compared and reported the effects of a twelve-month complex intervention involving physical exercise, nutritional supplementation, and cognitive training versus usual care in frail older adults significantly higher frailty reduction rates in the experimental group [ranging from 35.6 to 47.8%] (Ng et al., 2015). Similarly, nutritional and cognitive interventions were almost three times more likely to reduce frailty while physical interventions were linked to four times higher frailty reduction. Therefore, it will be important to understand whether addressing frailty in patients with HF helps improving their symptom burden, readmission rates, and mortality rates.

B. Objectives

The comorbidity of frailty and HF is associated with more frequent rehospitalizations, emergency department visits, and a decreased quality of life (Uchmanowicz et al., 2019). It is thus impetrative to identify the different interventions that are currently in practice globally for the prevention and treatment of frailty in prefrail and frail adults with HF and assess their effectiveness on selected outcomes.

This paper presents a systematic review and meta-analysis with the aim of assessing frailty interventions targeting prefrail or frail adults with HF in comparison to no frailty interventions and the effect on selected clinical outcomes. The focus will be on interventions such as behavioral therapy, cognitive training, exercise, and nutritional based specific interventions. The outcomes of interest are mortality, symptom burden, and readmission rates

of the HF population. In terms of symptom burden, functional capacity will be considered as assessed by the Six Minute Walking Distance [6MWD] and the Short Physical Performance Battery [SPPB].

In order to address the systemic impact associated with frailty in HF, health care providers must shift the current standard of disease-specific management to a more holistic and comprehensive view (Pandey, Kitzman & Reeves, 2019). A comprehensive approach can encompass exercise, physical rehabilitation, cognitive training, and nutritional support which leads to improved clinical, functional, and patient-reported outcomes (Pandey, Kitzman & Reeves, 2019). Furthermore, the routine identification and diagnosis of frailty in HF patients allows for better coordination, planning and adherence in the delivery of proper frailty interventions and care (Vitale et al., 2019).

It is imperative to conduct a systematic review and metanalysis focusing on the frailty interventions in HF patients in order to reduce cost of care, decrease mortality, and prevent hospital readmissions (Weng et al., 2021). Findings of this review will help fill the gap in knowledge in this area and provide a thorough analysis of the state-of-the science on interventions targeting frailty in patients living with HF. It is crucial to recognize the close relationship of frailty and HF for healthcare professions to provide better support for the management of HF and to facilitate the development of effective interventions that optimize patient care. Furthermore, by acknowledging effective interventions for this specific population, it will enhance HF treatment plans and maximize patient adherence (Pandey, Kitzman & Reeves, 2019).

CHAPTER II

REVIEW OF LITERATURE

A. Frailty in Patients Living with Heart Failure

The relationship between frailty and HF is often bidirectional whereby both conditions share similar underlying pathophysiologic processes [inflammatory, metabolic, and hormonal] that may increase patients' overall morbidity and mortality (Murad & Kitzman, 2012). The prevalence of HF has been shown to be greater in pre-frail and frail patients, as compared to non-frail patients (Denfeld et al., 2018). A meta-analysis demonstrated the high prevalence of frailty in HF in 6986 patients worldwide with an overall estimated prevalence of 44.5% [95% CI, 36.2% – 52.8%; $z = 10.54$; $p < 0.001$] (Denfeld et al., 2017). Coincidently, frail patients with HF have worse prognosis that non-frail patients, suggesting that multi organ disease such as HF further exacerbates frailty (Uchmanowicz et al., 2019).

The pathophysiology of HF and frailty have various similar paths including certain inflammatory markers (Uchmanowicz et al., 2019). Tumor Necrosis Factor Alpha, Interleukin-6, and C-Reactive protein are some inflammatory markers that are increased in both frailty and in HF, suggesting the deeply intertwined etiology in these two syndromes (Uchmanowicz et al.). Frailty and HF are both associated with circulating inflammatory cytokines and immune cells which cause damaging effects on the arterial wall, leading to continued acceleration of both diseases processes (Uchmanowicz et al.). Furthermore, these acute inflammatory cytokines elicit prolonged hospitalizations which continues the cycle of muscle loss, adipocyte proliferation and lipid accumulation, impacting functional status even more. (Pandey, Kitzman & Reeves, 2019). As frailty progresses, there is a continued over stimulation of compensatory mechanisms eventually leading to decreased tolerance to

stressors, infections, and increased morbidity and mortality, as well as cardiac effects such as myocardial ischemia, pressure and volume overload, and arrhythmias (Uchmanowicz et al.). All these acute influences contribute to prolonged physical decline of these patients with marked impairments in functionality and a higher symptom burden (Pandey, Kitzman & Reeves, 2019).

The coexistent presence of frailty and HF in patients involves disruptions in systems such as the neurohormonal, muscular, immune, metabolic, and endocrine systems which tends to worsen the prognosis of each disease process separately (Vitale et al., 2019). Frailty contributes to changes in the central nervous system related to vascular damage and blood-brain barrier dysfunction, which further contribute to cognitive impairment and depression, two conditions commonly found in HF patients (Uchmanowicz et al., 2019). Additionally, continued systemic inflammation leads to skeletal muscle apoptosis, sarcopenia, cachexia, and immobility associated with both HF and frailty (Uchmanowicz et al.). The combined detrimental effects of decreased functionality and impaired cognition leads to decreased quality of life, increased dependence in the performance of daily activities, and is associated with a higher occurrence of depression and isolation (Uchmanowicz et al.). Furthermore, frailty in HF is a significant predictor of all-cause mortality and hospitalization and as shown in a recent meta-analysis of 18,757 patients, frailty was associated with an average increase in all-cause mortality and hospitalization by 48% and 40% respectively (Uchmanowicz et al.).

The common pathophysiological processes often have joint consequences on patients such as decreased exercise tolerance leading to more rapid and advanced physical decline. Decreased exercise tolerance and functionality is a common symptom in patients with HF and can lead to further deterioration of strength and muscle mass (De Labra et al., 2015). Furthermore, nutritional intake in HF patients is massively affected due to early satiety,

impaired sense of smell and taste, chronic dyspnea, and nausea, as well as disease-specific dietary restrictions related to HF (Pandey, Kitzman & Reeves, 2019). As a result, patients with HF are at increased risk of malnutrition and nutritional deficiencies that can further exacerbate frailty as well (Pandey, Kitzman & Reeves).

There is growing evidence in the literature suggesting that HF can accelerate the functional capacity decline experienced by pre-frail and frail patients, leading to worse overall outcomes. Furthermore, frailty contributes to poorer outcomes in patients living with HF and presents independent challenges beyond the HF disease process itself. Frailty is a heavy burden, causing further difficulty in managing HF symptoms. Frail patients have been noted to have worse symptom management; specifically, significantly higher rates of dyspnea, sleep-wake disorders, and cognitive dysfunction, as compared to non-frail patients. Additionally, frail patients with HF tend to be of higher New York Heart Association [NYHA] functional classification, representing an overall higher symptom burden and lower functional capacity (Denfeld et al., 2018). Two common tools can be used to objectively assess and measure functional capacity, the SPPB and 6MWD. The SPPB has three tests, standing balance, walking speed, and chair stand tests. Each test is scored on a scale of 0 to 4, with an overall sum of 0 to 12, with 0 indicating the lowest performance and 12 being the highest (Bellettiere et al., 2020). The 6MWD is a walking test which consists of patients walking down a hallway between two points positioned 30 meters apart and the distance walked in 6 minutes was recorded (Kitai et al., 2021). The 6MWD has been used several times due to its feasibility as an alternative to cardiopulmonary exercise testing and is a significant factor of prognosis in HF patients (Kitai et al., 2021). In a recent study, patients with shorter 6MWD were associated with worse outcomes and showed predictive significance over conventional HF risk factors (Kitai et al., 2021). Another meta-analysis

with 22,598 patients with HF found that patients with lower 6MWD and SPPB tests had higher risk of hospitalization and mortality (Kitai et al., 2021).

Frailty and HF are both more commonly seen in older patients, but their occurrence is independent of age and should not be considered as part of the aging process or selective to only older patients (Vitale et al., 2019). Frailty leaves affected patients vulnerable, increasing overall hospitalization and mortality rates (Weng et al., 2021). With the global increase in HF incidence and its associated high morbidity, mortality, and rehospitalization rates (Mcdonagh et al., 2018), frailty research is on the rise.

B. Measuring Frailty

Although the conceptual definition of frailty is often agreed upon, the measurement tools used to objectively define it are more complicated. There are several measurement tools that can be used to measure and assess frailty; however, the two most common tools used are the Fried Phenotype Method and the Frailty Index (Pandey, Kitzman & Reeves, 2019).

The Fried Method is considered the standard tool to assess frailty using five domains: weight loss, weakness, poor endurance, slowness, and low physical activity level (Pandey et al.). In order to be diagnosed with frailty, three out of the five domains must be met while pre-frail is considered when one or two domains are present. However, the Fried Method has several challenges in its utilization within the HF population. The extensive overlap between the pathophysiological and clinical pathways of HF and frailty can present difficulties in differentiating where frailty symptoms are due to HF and where they are independent of HF (Pandey, Kitzman & Reeves, 2019). Moreover, the Fried Method primarily is focused on the physical aspect of frailty and does not acknowledge the cognitive impairments that are

commonly found in HF patients. This does not allow for a comprehensive and full assessment of HF patients with frailty (Pandey et al).

A second measurement tool is the Frailty Index, which uses a comprehensive assessment focusing on different variables such as signs, symptoms, comorbidity burden, lab results, and activities of daily living. The Frailty Index is a proportion of the total number of deficits existent to the number of deficits that have been assessed (Pandey et al., 2019). This results in patients scoring higher number of deficits as more frail compared to patients with less deficits. However, use of this tool can be limited as the number of deficits are often not standardized and may vary due to the population and the available data (Pandey et al.).

C. Frailty Interventions

There is significant research that examines the varying types of interventions and their effects on older adults with frailty. Interventions that are mentioned in articles can be a single component intervention, or multicomponent interventions that include exercise, nutritional supplementation, cognitive therapy, and mental health support (Oh et al., 2021). Perez-Zepeda and colleagues examined the impact of exercise intervention on frailty in hospitalized older adults and showed that over 80% of individuals included in the intervention group had improvement in their SPPB scores during hospitalization (Perez-Zepeda et al., 2022). Another study, The Aging Study of Pyeongchang Rural Area-Intervention Study [ASPRA-IS], delivered a 24-week multicomponent intervention consisting of group exercise, nutritional support, depression management, medication consultation, and home assessment in community dwelling older adults. Additionally, the ASPRA-IS followed these patients for 30 months and showed that due to the intervention that was provided, these patients had continued and long-term positive effects on their physical functionality that may delay mortality and hospitalizations in these patients. Furthermore, this study shows that a

multicomponent physical intervention is effective in reducing and even reversing frailty in older individuals (Oh et al.).

A recent systematic review and meta-analysis by Racey et al., discussed the effectiveness of nutritional interventions on frailty in prefrail and frail older adults (Racey et al., 2021). This study determined that there is a small but significant benefit of nutrition, including protein supplementation, on physical and mobility outcomes. Furthermore, nutritional interventions combined with physical activity interventions also showed a small but significant benefit on frailty outcomes (Racey et al., 2021). Looking at the available research on frailty interventions, it is mostly targeting older frail adults, therefore, more research is needed to determine what effect these interventions can have on frail adults with HF.

A conceptual framework of the above planned research steps was created to ensure proper flow and efficiency in completing the systematic review and the meta-analysis. The different steps and analyses that need to take place to complete this review are comprised into a conceptual framework that will allow for easy navigation and guidance. It is important to note 1. What the research question is, the inclusion/exclusion criteria, 2. Interventions and comparing to standard care, 3. Outcomes, 4. Search Strategy, 5. The screening process, 6. How the data is extracted, evaluated and analyzed, and 7. What the findings are of the review (Hallinger, 2013).

Figure 1.

Conceptual Framework

CHAPTER III
METHODS

A. Eligibility Criteria

To commence the study, a PICO table was created listing the following inclusion and exclusion criteria. Studies were required to meet all the inclusion criteria: 1) Patients: prefrail or frail adults with HF, and with a NYHA classification of II or III; 2) Intervention: selected interventions targeting frailty; 3) Comparison: no frailty interventions; and 4) Outcomes: mortality, symptom burden, and readmission rates. The focus will be on interventions such as behavioral therapy, cognitive training, exercise, and nutritional based specific interventions, and can be a single component intervention or a multicomponent intervention. Symptom burden will be assessed using 6MWD and SPPB to measure functional capacity. All articles included in the meta-analyses were Randomized Control Trials (RCTs).

Table 1.

PICO Table

Population	• Prefrail or frail adults with Heart Failure • New York Heart Association Functional class II or III
Intervention	Interventions targeting frailty
Comparison	No interventions targeting frailty (standard care)
Outcomes	• Mortality • Symptom Burden • Readmission Rates
Question	In prefrail or frail adults with Heart Failure, how do frailty interventions compared to standard care, affect mortality, symptom burden, and/or readmission rates?
Design	Systematic Review and Meta-Analysis

B. Information Sources

A systematic search of three electronic bibliographic databases, namely CINAHL, Medline, and EmBase was done under the guidance of the head of the medical library (OZ). Google Scholar was used as well to scan the grey literature. The interfaces used to search the databases were Ovid, EBSCOhost, and Elsevier and were accessed in November of 2021. Retrieved articles were combined and duplicates were removed using Endnote.

C. Search Strategy

Retrieved articles were combined and duplicates were removed using Endnote. The search strategy included controlled vocabulary terms and keywords for "Frailty" and "Heart Failure". The language used for the search strategies in the bibliographic databases was English. No limits were placed in the search strategy, including no limitation on the date or language of the study. This allows for the search strategy to be more comprehensive and encompasses a worldwide view. The protocol of this study was published on PROSPERO [registration number CRD42022260621]. Appendix A shows the detailed search strategy.

D. Selection Process

Title and abstract screening of the articles was done independently by two individuals [SA and MC] to decrease the risk of bias. Articles that do not meet the inclusion criteria were excluded and the remaining articles were fully reviewed. Articles that included pre-frail or frail HF patients undergoing frailty interventions and a NYHA classification of II to III were included. Additionally, included studies must have a comparison group that received standard care. Excluded articles consisted of case reports, abstract only papers, conferences, author

responses, or did not meet the requirements of the inclusion criteria. There were no language restrictions on the selection of the studies included in the systematic review. Disagreements, if any, were resolved by a third reviewer [AM]. One retrieved article needed translation into English and this process was done using Google translate in order to assess its eligibility.

E. Data Collection Process

A data collection tool was developed and used once selected articles were included for the full text screening. This form included: 1) Study name, 2) Author information, 3) Publication date, 4) Study setting, 5) Study design, 6) Sample size, 7) Participants, 8) Intervention, 9) Control, 10) Outcomes, 11) Country in which study was conducted, 12) Any conflicts of interest. A summary of the relevant studies was created for each outcome, since not all studies are guaranteed to contribute to all the outcomes. The rationale for excluding any article from the final review was in the data extraction form as well. The data extraction form was piloted initially with the first 10 papers selected to ensure the form is accurate in depicting all the necessary information. This information was used to analyze the commonalities between the selected studies and to ensure their eligibility. Disagreements in article selection and risk of bias assessment between the two individuals [SA and MC] was looked at by an independent third member [AM]. See Appendix B for the PRISMA 2020 Flow Diagram and the reasoning behind exclusion of the other articles and Appendix C for the full extraction form used.

F. Data Items

Outcomes focused on mortality, symptom burden, and readmission rates. Symptom burden was measured using 6MWD and SPPB to objectively assess for functional capacity.

The SPPB has three tests, standing balance, walking speed, and chair stand tests. Each test is scored on a scale of 0 to 4, with an overall sum of 0 to 12, with 0 indicating the lowest performance and 12 being the highest (Bellettiere et al., 2020). The 6MWD is a walking test which consists of patients walking down a hallway between two points positioned 30 meters apart and the distance walked in 6 minutes was recorded (Kitai et al., 2021). These outcomes were assessed at 3 months and 6 months, according to the selected articles.

G. Study Risk of Bias Assessment

A Risk of Bias Table was created for each included study to assess for possible biases using the Risk of Bias 2 [RoB2] Tool (Cochrane Methods, 2021). The RoB2 Tool included different domains that cover different biases and are the following: bias arising from randomization; deviations from the set interventions; missing outcome data; bias in measurement of outcome; and selective reporting of result. An overall risk of bias judgement was made for each study that summarizes and rationalizes the reasons for including or excluding the article, using the ROB2 tool and its specific domain requirements. Disagreements in the risk of bias assessment between the two primary reviewers [SA and MC] was looked at by an independent third member [AM].

H. Effect Measures

Articles that used validated methods to assess frailty interventions in HF patients and obtained Hazard Rations [HRs] or Mean Differences were pooled for the meta-analysis. Forest plots were used to express the effect size data of each study and the HRs for mortality and readmission rates. For continuous variables, SPPB and 6MWD, mean difference was obtained and pooled for the meta-analysis.

I. Synthesis Methods

1. Meta-Analysis

Articles that used validated methods to assess frailty interventions in HF patients and obtained Hazard Rations [HRs] were pooled for the meta-analysis. Separate meta-analyses were created for each outcome: mortality, readmission rates, and symptom burden. Forest plots were used to express the effect size data of each study and the HRs for mortality, readmission rates, and symptom burden. If HRs were not directly reported by any selected article, these were estimated using relevant data provided, whenever possible.

Publication bias was assessed to ensure there is no missing data using a funnel plot. Heterogeneity was assessed using I^2 statistic which indicates the percentage of variability that is not due to chance between the studies. An I^2 statistic of <40% is low for heterogeneity, 30-60% is moderate heterogeneity, 50-90% is substantial heterogeneity, and 75-100% to be considerable heterogeneity (Guyatt et al., 2011). If a low heterogeneity was observed, HRs were pooled using a fixed-effect model. However, if heterogeneity was assessed to be moderate, substantial, or considerable, HRs were pooled using a random effects model (Wang et al., 2018). Furthermore, if heterogeneity was found, the possible causes were assessed using a sensitivity analysis and were discussed. Subgroup analysis was done if there was high heterogeneity to assess for differences between pre-frail and frail participants, and the type of intervention. The meta-analysis was completed using Review Manager Software Version 5.4.1.

2. GRADE Assessment

A Grading of Recommendations Assessments, Development and Evaluation working group [GRADE] quality score was completed to rate the quality and confidence of the outcomes in the selected articles. GRADE is a framework used in making a summary of

evidence and presents it clearly using the following criteria: 1) Study limitations/risk of bias, 2) Inconsistency, 3) Indirect effects, 4) Inaccuracy, and 5) Publication bias (Guyatt et al., 2011). The certainty of the evidence in each selected article will be graded into either high, moderate, low, or very low (Guyatt et al., 2011). The GRADE software (GRADEPRO) was used to create a summary of findings table targeting the quality of evidence.

CHAPTER IV

RESULTS

A. Study Selection

The search strategy [Appendix A] resulted in 2869 articles which met the search criteria. Of these studies, 2832 articles were excluded by two reviewers, SA and MC, with 37 articles being selected for consideration based on title and abstract. 9 articles were not found as full text. Following the 28 articles undergoing full text screening, 6 articles were included for the final systematic review, 9 articles were excluded due to not being related to the research topic and selected outcomes; and 13 articles were excluded due to being literature reviews only with no intervention implementation. The reasoning behind exclusion of the other articles is presented in Appendix B in the PRISMA 2020 Flow Diagram.

The selected articles and their characteristics are presented in Appendix D. All 6 articles included are in the English language and were conducted between 2005-2021. Of the 6 articles included, two were conducted in the United States, one in United Kingdom, one in Bulgaria, one in Australia, and one in Japan. The sample sizes of the articles ranged from 27-3277 patients, with the total number in all the studies pooled together being 4,113 patients. Two articles included SPPB at 3 months and rehospitalization at 6 months as their outcomes (Kitzman et al., 2021 and Reeves et al., 2017); three articles included 6MWD at 3 months (Reeves et al., 2017; Witham et al., 2005; and Papathanasiou, 2020); two articles included 6MWD at 6 months (Witham et al., 2005 and Mudge et al., 2021); one article included all-cause mortality and HF related hospitalizations at 2.7 years (Kamiya et al., 2020). All articles assessed physical functionality and interventions encompassed physical activity and exercise interventions given over a specified number of sessions, as mentioned in Appendix D. One article is a pilot study (Reeves et al., 2017), an article is a secondary analysis of a randomized

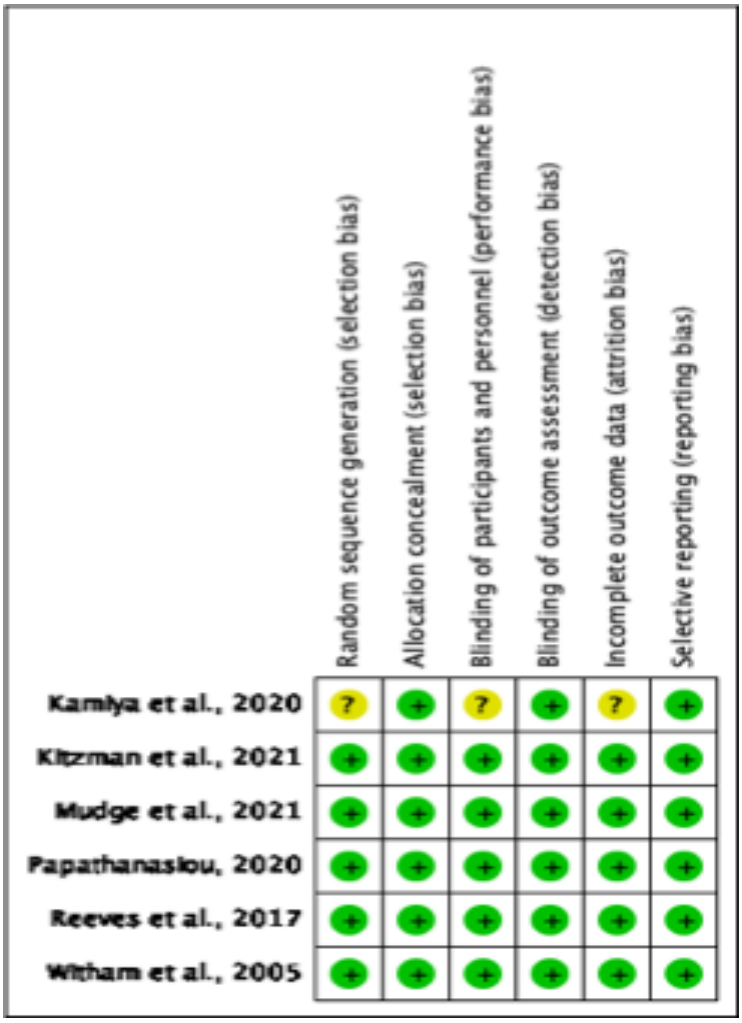
control trial (Mudge et al., 2021), and an article is retrospective study (Kamiya et al.); the remaining three articles are randomized control trials.

B. Risk of Bias in Studies

The ROB2 tool was used to assess risk of bias in the selected studies. Other tools were screened to assess their validity in using it for this systematic review. However, ROB2 tool was used as it is based on PRISMA checklist and is the recommended tool for use by Cochrane Reviews. Five out of the six selected studies were low risk of bias (Kitzman et al., 2021; Reeves et al., 2017; Witham et al., 2005; Papathanasiou, 2020; and Mudge et al., 2021). The sixth article by Kamiya et al., was not assessed by the ROB2 tool but instead the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies (NOS) since it is a cohort study. It is also included in Table 2 below to indicate the need for a separate tool to be used to assess it appropriately and fairly. According to NOS, this article is considered to be of good quality. Disagreements in the risk of bias assessment between the two primary reviewers [SA and MC] was looked at by an independent third member [AM]. Below is the ROB Summary Table that summarizes across all studies. Refer to Appendix G for the ROB2 that was used.

Table 2.

Risk of Bias



C. Results of Individual Studies

Results of individual studies can be found in Appendix D. Kitzman and colleagues assessed SPPB at three months in frail individuals (2021). The group who received the frailty interventions at baseline had 175 participants and a mean SPPB of 6.0 ± 2.8 while the group with the standard care had 174 participants with a mean SPPB of 6.1 ± 2.6. After three months, the intervention group had a mean SPPB of 8.3 ± 0.2 while the mean SPPB of the standard care group was 6.9 ± 0.2. This study revealed a mean between group difference of 1.5, with a 95% CI of 0.9 to 2.0, $p<0.001$. Additionally, the rate of hospitalizations in the

intervention group was 1.18 compared to 1.28 in the standard care group [Rate Ratio: 0.93 and a CI: 0.66-1.19].

Similarly, Reeves and colleagues measured SPPB and 6MWD at three months as well as rehospitalizations at six months in frail individuals (2017). The group that received the frailty interventions at baseline had 15 participants and a mean SPPB of 4.8 ± 2.8 while the group with the standard care had 12 participants with a mean SPPB of 6.0 ± 3.0. After three months, the intervention group had a mean SPPB of 6.9 ±- 3.0 while the standard care group had a mean SPPB of 6.8 ± 3.3. The intervention effect size is +1.1. In regard to the 6MWD, the frailty intervention group at baseline had a mean of 160 ± 85 meters while the group with the standard care had a mean of 201 ± 120 meters. After three months, the intervention group had a mean 6MWD of 247 ± 22 meters while the standard care group had a mean of 224 ± 22 meters. The intervention effect size is +23 meters. Lastly, this study measured rehospitalizations at 6 months and the rate of hospitalizations in the frailty intervention group was 1.16 ± 0.35 versus 1.64 ± 0.39 in the standard care group. The intervention effect size was -0.48.

In 2005, Witham and colleagues assessed 6MWD at 3 months and 6 months. Both groups had 41 participants each; the frailty intervention group at baseline had a mean of 261 ± 117 meters while the group with the standard care had a mean of 240 ± 93 meters. After three months, the outcomes of the study revealed that the intervention group had a mean 6MWD of 254 ± 107 meters while the standard care group had a mean of 228 ± 102 meters. Furthermore, at 6 months, the intervention group had a mean of 262 ± 110 meters while the standard care group had a mean of 246 ± 111 meters.

The study by Papathanasiou focused on 6MWD at 3 months (2020). Both groups had 60 participants each; the High Intensity Aerobic Interval Training (HIAIT) intervention group at baseline had a mean of 440.58 ± 39.79 meters while the Moderate Intensity Continuous

Training (MICT) intervention group had a mean of 442.90 ± 42.53 meters. After three months, the outcomes of the study revealed that the HIAIT intervention group had a mean 6MWD of 513.38 ± 37.73 meters while the MICT intervention group had a mean of 489.32 ± 43.45 meters.

Kamiya and colleagues assessed hospitalizations and all-cause mortality at 2.7 ± 1.6 years (2020). The frailty intervention group and the standard care group both had 796 participants after propensity score matching. Hazard Ratios [HR] were used which showed an HR of 0.82 95% CI 0.67-0.99 for hospitalizations. In all-cause mortality, HR was 0.67, 95% CI 0.51 - 0.87.

D. Results of Syntheses

1. Characteristics of Contributing Studies

Two articles were included in the meta-analysis for SPPB at 3 months, Kitzman et al., 2021 and Reeves et al., 2017. Both articles had low risk of bias as measured by the ROB2 tool by two individual readers [SA and MC] and any disagreements in the risk of bias assessment between the two primary reviewers was looked at by an independent third member [AM].

In Kitzman et al., 2021, the group who received the frailty interventions at baseline had a mean SPPB of 6.0 ± 2.8 while the group with the standard care had a mean SPPB of 6.1 ± 2.6. After three months, the intervention group had a mean SPPB of 8.3 ± 0.2 while the mean SPPB of the standard care group was 6.9 ± 0.2. The sample size for the intervention group was 175 while the standard group had 174. The mean age with SD for the individuals in the frailty intervention group was 73.1 ± 8.5 while the standard care group was 72.2 ± 7.7. In the intervention group, 33 individuals were classified as NYHA II while 100 individuals were classified as NYHA III. In the standard care group, 34 were NYHA II while 90 were

NYHA III. The mean difference between the intervention group and the standard care group was 1.40 with CI 95% [1.36,1.44]. Looking at these results, there was a statistically significant increase in SPPB in the intervention group as compared to the standard care group, which indicates that the frailty intervention was effective in HF patients.

In Reeves et al., 2017, the frailty intervention group at baseline had a mean SPPB of 4.8 ± 2.8 while the standard care group had a mean SPPB of 6.0 ± 3.0. After three months, the intervention group had a mean SPPB of 6.9 ±- 3.0 while the standard care group had a mean SPPB of 6.8 ± 3.3. The sample size for the intervention group was 15 while the standard group had 12. The mean age with SD for the individuals in the frailty intervention group was 72.7 ± 10.8 while the standard care group was 71.8 ± 9.1. NYHA classifications were not reported in this article. The mean difference between the intervention group and the standard care group was 1.10 with CI 95% [0.72, 1.48]. These results indicate that frailty interventions are related to a statistically significant increase in SPPB in the intervention group as compared to the standard care group in HF patients.

Three articles were included in meta-analysis for 6MWD at 3 months, Mudge et al., 2021, Reeves et al., 2017, and Witham et al., 2005. These articles had low risk of bias as well as measured by the ROB2 tool and as discussed earlier.

In Mudge at el., 2021, the frailty intervention group at baseline had a mean 6MWD of 360.62 ± 127.27 while the standard care group had a mean 6MWD of 362.50 ± 111.33. After three months, the intervention group's mean 6MWD was 383.42 ± 125.24 while the standard care was 389.196 ± 120.125. The mean difference in 6MWD between the intervention group and the standard care group was -5.77 with CI 95% [-38.94, 27.39]. These results indicate that frailty interventions had no effect on 6MWD at 3 months as the CI crosses 0, the no effect line.

In Reeves at el., 2017, the frailty intervention group at baseline had a mean 6MWD of 160 ± 85 meters while the group with the standard care had a mean 6MWD of 201 ± 120 meters. After three months, the intervention group's mean was 247 ± 22 meters while the standard care group had a mean of 224 ± 22 meters. The mean difference in 6MWD between the intervention group and the standard care group was 23 with CI 95% [6.30, 39.70]. These results indicate that frailty interventions are related to a statistically significant increase in 6MWD at 3 months in the intervention group as compared to the standard care group in HF patients.

In Witham et al., 2005, the frailty intervention group at baseline had a mean 6MWD of 261 ± 117 meters while the group with the standard care had a mean 6MWD of 240 ± 93 meters. After three months, intervention group had a mean 6MWD of 254 ± 107 meters while the standard care group had a mean of 228 ± 102 meters. The sample size for the intervention group was 41 while the standard group had 41. The mean age with SD for the frailty intervention group was 80 ± 6 while the standard care group was 81 ± 4. In the intervention group, 25 individuals were classified as NYHA II while 16 individuals were classified as NYHA III. In the standard care group, 21 were NYHA II while 20 were NYHA III. The mean difference in 6MWD between the intervention group and the standard care group was 26 with CI 95% [-19.25, 71.25]. These results indicate that frailty interventions had no effect on 6MWD at 3 months as the CI crosses 0, the no effect line.

In the meta-analysis for 6MWD at 6 months, two articles were used; Mudge et al., 2021 and Witham et al., 2005. In Mudge et al., after six months follow up, the intervention group's mean 6MWD was 396.77 ± 123.09. while the standard care group's mean 6MWD was 393.96 ± 125.94. The mean difference in 6MWD between the intervention group and the standard care group was 2.81with CI 95% [-34.19, 39.81]. These results indicate that frailty

interventions had no effect on 6MWD at 6 months as the CI crosses 0, the no effect line. Refer to Appendix E for the results of individual studies.

In Witham et al., after six months follow up, the intervention group had a mean 6MWD of 262 ± 110 meters while the standard care group had a mean 6MWD of 246 ± 111 meters. The mean difference in 6MWD between the intervention group and the standard care group was 16 with CI 95% [-31.83, 63.83]. These results indicate that frailty interventions had no effect on 6MWD at 6 months as the CI crosses 0, the no effect line.

2. Results of Meta-Analysis

In order to accurately interpret the results of the meta-analysis, it is important to know The Minimally Clinically Important Difference [MCID] for both SPPB and 6MWD. MCID is foundational to the analysis of clinical trials as it gives an understanding to the amount of change in an outcome measure that is clinically significant (Shoemaker et al., 2013). MCID indicates what the smallest change is needed that would be perceived as beneficial to patients (Shoemaker et al., 2013). The MCID for SPPB has been identified as an increase in score of more than 1 (Rinaldo et al., 2022). Furthermore, the MCID for 6MWD has been identified as a change of approximately 30-32 meters (Shoemaker et al., 2013).

Figure 1 below shows the results of the meta-analysis for SPPB at 3 months. As mentioned previously, SPPB contains three tests: 1) Standing balance, 2) Walking speed, and 3) Chair stand tests. Each test is scored on a scale of 0 to 4, with an overall sum of 0 to 12, with 0 indicating the lowest performance and 12 being the highest (Bellettiere et al., 2020). Two articles were used to undergo this meta-analysis (Kitzman et al., 2021 and Reeves et al., 2017). The total number of patients included in the intervention group was 190 and the control group had 186. Kitzman et al., held 70.6% for the weight of the meta-analysis while Reeves et al., held 29.4%.

The meta-analysis found that the mean difference in completing a frailty intervention vs. standard care in SPPB is 1.31 with a 95% confidence interval of 1.04-1.58. Since the MCID is >1, the meta-analysis indicates that an exercise intervention addressing frailty probably results in a slight increase in SPPB in heart failure patients.

A random effects model was used since the I^2 is 58% which indicates moderate heterogeneity.

Figure 2.

SPPB at 3 months - Random Effect Model

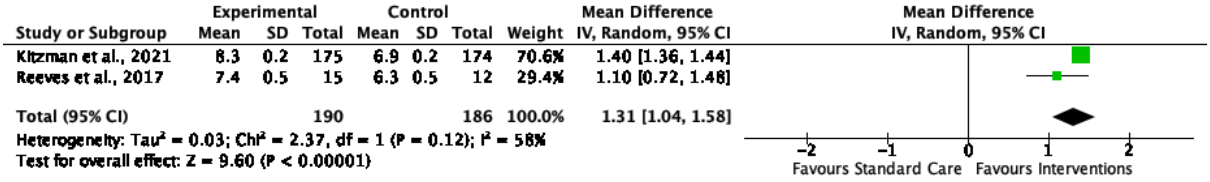


Figure 2 below shows the results of the meta-analysis for 6MWD at 3 months. The 6MWD is a walking test which consists of patients walking down a hallway between two points positioned 30 meters apart and the distance walked in 6 minutes is recorded, with patients measuring shorter 6MWD being associated with worse outcomes (Kitzman et al., 2021). Three articles were used; Mudge et al., 2021, Reeves et al., 2017, and Witham et al., 2005. The total number of patients included in the intervention group is 170 while the control group has 150. Mudge et al., carried 18.2% of the weight, Reeves et al., carried 72%, and Witham et al., carried 9.8%.

The meta-analysis found that the mean difference between completing a frailty intervention vs standard care in 6MWD is 18.04 with a 95% confidence interval of 3.88 - 32.21. As mentioned previously, the MCID for 6MWD is 30-32 meters, therefore, the meta-analysis indicates that an exercise intervention addressing frailty likely does not increase 6MWD in heart failure patients at 3 months.

A fixed effects model was used since the I2 is 18%, indicating low heterogeneity.

Figure 3.

6MWD at 3 months – Fixed Effects Model

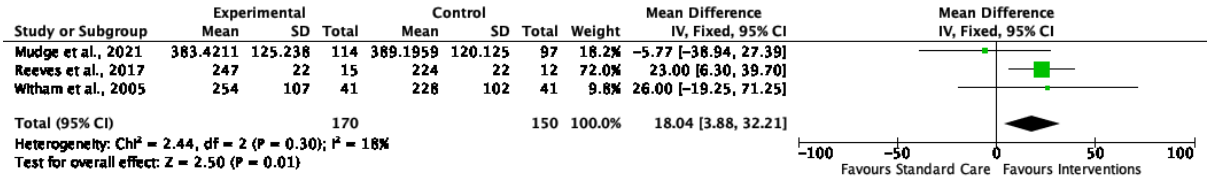


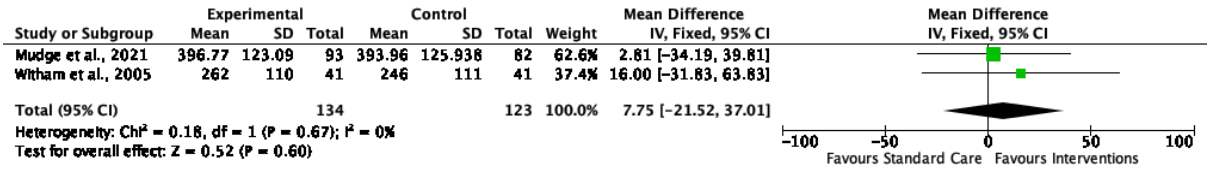
Figure 3 below shows the results of the meta-analysis for 6MWD at 6 months. Two articles were used; Mudge et al., 2021 and Witham et al., 2005. The total number of patients included in the intervention group is 134 while the control group has 123. Mudge et al., carried 62.6% of the weight while Witham et al., carried 37.4% of the weight of the meta-analysis.

The meta-analysis found that the mean difference between completing a frailty intervention vs standard care in 6MWD is 7.75 with a 95% confidence interval of -21.52 to 37.01. As stated before, the MCID for 6MWD is 30-32 meters, therefore, the evidence suggests that an exercise intervention addressing frailty results in little to no difference in 6MWD in heart failure patients at 6 months. Additionally, the confidence interval crosses the no effect line, therefore, the intervention is neither harmful or beneficial.

A fixed effects model was used since the I2 is 0%, indicating low heterogeneity.

Figure 4.

6MWD at 6 months – Fixed Effects Model



Three meta-analyses were completed with the data provided in the articles selected. A total of 4 out of the 7 articles were utilized for the meta-analyses. Kamiya et al., 2020 was not used in the meta-analyses as the follow up time was 2.4 years for all-cause mortality and HF rehospitalizations. Furthermore, Mudge et al., 2021, also assessed mortality but at 12 months.

Therefore, the data for mortality was not consistent between the two studies in order to create a meta-analysis.

The article by Papathanasiou et al., was not included in the meta-analysis since it compares two different types of exercise interventions, HIAIT (High Intensity Aerobic Interval Training) and MICT (Moderate Intensity Continuous Training). Other selected articles compared standard care vs. an exercise intervention instead. Therefore, the results could not be combined with other studies.

Rehospitalization rate at 6 months was measured by Kitzman et al., 2021, while rehospitalization days at 6 months were measured by Reeves at al., therefore the data from the two articles were not compatible to be combined in order to create a meta-analysis. The authors of both articles were contacted in an effort to retrieve more information in order to create a meta-analysis but there was no response.

E. Certainty of Evidence

A Grading of Recommendations Assessments, Development and Evaluation working group [GRADE] quality score was completed to rate the quality and confidence of the outcomes in the selected articles. The certainty of the evidence in each selected article was graded into either high, moderate, low, or very low (Guyatt et al., 2011). The GRADE software (GRADEPRO) was used to create a summary of findings table targeting the quality of evidence.

In total, six GRADE assessments were completed; 1) SPPB at 3 months, 2) All cause death at 12 months, 3) Readmissions at 6 months, 4) Readmission days, 5) 6MWD at 3 months, 6) 6MWD at 6 months. SPPB at 3 months showed moderate certainty of evidence, due to moderate heterogeneity being present of 58% and a small sample size as well. The

absolute effect mean difference with a 95% CI showed a mean of 1.4 points higher in the intervention group as compared to the standard group (1.35-1.44 higher).

All cause death at 12 months showed low certainty of evidence, due to information coming from one study with a relatively small sample size. Additionally, it was downgraded two levels in the imprecision section as the confidence interval includes values reflecting both benefit and harm. The risk ratio was 0.92. The absolute effect with a 95% CI showed from 150 fewer deaths to up to 65 more deaths in the intervention group as compared to the standard group.

Readmission at 6 months showed moderate certainty of evidence, as it was downgraded by one level for the CI included values reflecting both benefit and no effect. The risk ratio is 0.85. The absolute effect with a 95% CI showed from 183 fewer readmissions to up to 13 more readmissions in the intervention group as compared to the standard group.

Readmission days at 6 months showed low certainty of evidence, again, due to it being a single study with a very small sample size. The absolute effect with a 95% CI showed from 7.43 fewer readmission days to up to 3.37 fewer readmission days in the intervention group as compared to the standard group.

6MWD at 3 months had moderate certainty of evidence, as it is a small sample size. Additionally, MCID is 23 meters therefore rated down as serious as within the absolute CI. The absolute effect with a 95% CI showed from 7.69 to up to 39.03 higher 6MWD in the intervention group as compared to the standard group.

6MWD at 6 months had low certainty of evidence, as it is a small size. Additionally, MCID is 23 meters, therefore rated down as very serious as within the absolute CI and CI includes harm (a decrease in 6MWD). The absolute effect with a 95% CI showed from 31.83 lower 6MWD to up to 63.83 higher 6MWD in the intervention group as compared to the standard group. Appendix F lists the GRADE assessment.

CHAPTER V

DISCUSSION

A. Discussion

This systematic review and meta-analysis has focused on a question; In prefrail and frail adults with Heart Failure, how do frailty interventions compared to standard care, affect mortality, symptom burden and/or readmission rates? To answer this question, an extensive search strategy was conducted with a qualified librarian which focused on certain inclusion criteria; prefrail or frail adults with HF with a NYHA classification of II or III, interventions targeting frailty, a comparison control group that were not involved in any frailty interventions, and looking at select outcomes mortality, symptom burden, and readmission rates. This extensive search resulted in 2869 articles which were then narrowed down to 6 articles in the end to be included in the final systematic review. Furthermore, of these 6 articles, 4 were included in three different meta-analyses.

The search strategy resulted in articles focused on exercise interventions only. Unfortunately, no articles involving other interventions, such as nutritional, cognitive, behavioral, or psychosocial interventions, were found that were related to the PICO question.

Amongst the 6 articles retrieved, SPPB and 6MWD were primarily discussed as the main outcomes. Witham et al., main outcome was 6MWD at 3 and 6 months. Reeves et al., main outcomes were SPPB at 3 months, all-cause hospitalization days at 6 months, and 6MWD at 3 months. Kamiya et al., 2020, main outcomes were all cause mortality, and HF related hospitalizations at 2.7 years. Papathanasiou focused on 6MWD at 3 months. Mudge et al., 2021, main outcomes were 6MWD at 3 and 6 months, and all cause death at 12 months. Kitzman et al., 2021, main outcomes were SPPB at 3 months and all cause rehospitalizations rate at 6 months.

Three meta-analyses were completed: SPPB at 3 months, 6MWD at 3 months, and 6MWD at 6 months. The MCID used for SPPB was derived for elder patients in cardiac rehab after a cardiac event and was used for this meta-analysis. The results of the SPPB at 3 months showed that it was both statistically significant and clinically significant. The meta-analysis indicated that an exercise intervention addressing frailty probably results in a slight increase in SPPB in heart failure patients. This meta-analysis can help shape future guidelines in regard to integrating exercise interventions into the treatment plan of HF individuals with frailty, as it can increase their functional abilities and SPPB.

The MCID used for 6MWD was derived for HF patients with NYHA classifications of II and III and used for the next two meta-analyses. The results of the 6MWD at 3 months showed that although statistically significant, the results were not clinically significant. The meta-analysis indicates that an exercise intervention addressing frailty likely does not increase 6MWD in heart failure patients at 3 months. When looking at the MCID, this meta-analysis shows that no changes in treatment options should be done at this time as more research is needed to determine whether 6MWD is affected by frailty interventions targeting HF individuals.

The third and final meta-analysis that was conducted is 6MWD at 6 months. The results of this meta-analysis showed that it was both not statistically or clinically significant. The evidence suggests that an exercise intervention addressing frailty results in little to no difference in 6MWD in heart failure patients at 6 months. Furthermore, the confidence interval crosses the no effect line, therefore, the intervention is neither harmful nor beneficial.

Unfortunately, meta-analyses were not able to be conducted for readmission rates and mortality rates as not enough data was present in the articles. As discussed earlier, mortality rates were measured at completely different time intervals and therefore, could not be pooled together for a meta-analysis. Furthermore, rehospitalization days were measured at 6 months

by Reeves et al., and rehospitalization rate at 6 months was measured by Kitzman et al. and could not be pooled as they were different effect measures used. The authors were contacted to retrieve further data in an attempt to create similar effect measures, but no response was provided.

Looking at the results of the meta-analyses, 6MWD at 3 months and 6 months were both statistically significant but not clinically significant, however; their statistical significance is still noteworthy and must be assessed on an individual patient basis. Although it does not meet the MCID, exercise interventions is still a frailty intervention that can affect 6MWD. Frailty in HF patients will improve with interventions targeted towards improving functionality and improving quality of life.

B. Limitations

There were limitations that were noted while conducting this systematic review and meta-analysis. The articles that were included did not consistently use the same measurement tools to assess frailty. The different frailty measurement tools used can measure different aspects of frailty and can affect the definition of frailty; therefore, the overall results of the articles. As mentioned previously, the Fried Method is the standard tool used to assess frailty, but it does not allow for a comprehensive and full assessment for specifically HF patients as it does not consider cognitive impairments, and only focuses on physical impairments. The Frailty index is more comprehensive but often includes not standardized data that may vary depending on the population. This difference in measurement tools can affect the overall results of the meta-analyses.

The articles included in the meta-analyses are all of small size populations, ranging from 27 to 349 participants. The small sample size can alter the overall results of the study.

The small samples also meant that pre-frail and frail participants were grouped together, which did not allow for sub-analysis on frailty level to be conducted.

Different exercise intervention programs were utilized in each article. Some articles had a set amount of training sessions to complete while others had 3 months of supervised exercise classes twice weekly followed by 3 months of independent exercising. Additionally, there were some differences in the follow up schedule for each article.

Certain limitations were mentioned in the included articles that are noteworthy here. The results of certain articles did not show a beneficial effect on clinical events; therefore, this would also affect the meta-analysis results. However, according to Kitzman et al., HF patients' preferences indicated that improving physical function and maintaining independence are highly valued, independent of clinical events (Kitzman et al., 2021). Another limitation is that although staff members who assessed the outcomes were blinded, it was not possible for patients to be unaware of the group they were randomly placed in.

A specific limitation to the article by Reeves et al., is that it's a pilot study and is not considered to definitively assess the effect of exercise interventions on HF patients with frailty. However, the results derived from this article are preliminary and will be confirmed in a larger clinical trial.

The long-term durability of a set exercise program is important to consider as well. However, starting with a scheduled exercise program and slowly transitioning into a more independent and patient-based program would be more sustainable for individual patients and their specific needs.

C. Implications

1. Implication on Practice

Despite a deep understanding of the pathophysiology of heart failure and frailty separately, when the two conditions coexist, it is often difficult to treat these patients. There

is tremendous improvement in the pharmacological treatments and guidelines surrounding these populations, but it is important to investigate methods and interventions in reducing frailty in specifically heart failure patients. The involvement of a Clinical Nurse Specialist (CNS) in the interventions surrounding heart failure patients with frailty would include counselling, education, and a comprehensive assessment of any factors that can affect their self-care, and quality of life. A CNS would be able to play an integral part in acting as the case manager, leading the frailty interventions, and managing the treatment plan of individual patients due to the leadership and collaboration skills that are a necessity in coordinating care between all members of the multidisciplinary team. The CNS advances patient care and bridges the gap between evidence-based practice and research within healthcare and brings advanced knowledge and expertise in leading such initiatives. The CNS allows for a consistent and evidence-based approach that will elevate care for these patients. Furthermore, the CNS and the Registered Nurse are able to approach patients from a broad perspective of frailty; including the physical, psychosocial, and social domains that can impact, prevent or delay their frailty risk. Coincidingly, HF patients with frailty benefit more than non-frail HF patients from interdisciplinary approach that utilizes cardiologists, primary care physicians, and specialized nurses in all care settings to enhance management, ensure smooth transitions between in-hospital and out-patient care, and provide continued education (Goldwater & Altman, 2016). Additionally, it is imperative to educate patients and their families prior to discharge from hospital on proper frailty interventions as this allows for continuous improvement of frailty status even while they are out of hospital, and away from the health care team. The overall goal will be to improve the health of patients with heart failure and frailty and decrease their burden in living with these two diseases.

2. Implications on Research

Conducting meta-analyses is important in order to provide recommendations and evidence-based research for practice and future policy making. These results should be interpreted with caution that although there is no clinical significance, there is still statistical significance that needs to be considered. Furthermore, more research on this topic is needed. Future research should focus more on different intervention types such as nutritional, behavioral, cognitive, and psychosocial interventions to see if these would have a higher more clinically significant impact on frailty status in HF patients. Moreover, future research should account for the variability in exercise intervention programs and present a more uniform exercise program that can be followed.

It is important to keep in mind that interventions targeting frailty do improve the functionality and quality of life of individuals. This systematic review and meta-analysis were aimed at assessing the effect of frailty interventions directly on HF patients within the outcomes discussed. As mentioned previously, the statistical significance of the interventions would have to be assessed on a patient-to-patient basis and treatment plans need to be adjusted to best treat each individual patient. In combination with pharmacological and medical treatments, different types of frailty interventions will also improve the overall treatment goals and quality of life of patients.

APPENDIX
APPENDIX I. SEARCH STRATEGY

Search Strategy for Medline

1. Frailty/
2. Frail Elderly/
3. (((function* or activ* or ambulat* or motor*) adj2 (impair* or empair* or decreas* or weak* or d?sfunction* or d?s-function* or disabl* or disabilit* or dis-abilit* or insufficien* or in-sufficien* or depend* or loss* or limit* or debilit* or difficult* or d?sorder*)) or frail* or (pre adj frail*)).mp.
4. exp Heart failure/
5. exp Ventricular Dysfunction/
6. Dyspnea, Paroxysmal/
7. Cardiac Output/
8. Cardiomyopathies/
9. Cardiomyopathy, alcoholic/ or cardiomyopathy, dilated/ or cardiomyopathy, hypertrophic/ or cardiomyopathy, restrictive/
10. (((acute* or congest* or chronic*) adj1 (heart* or cardi*)) adj3 (s?ndrome* or decompensat* or de-compensate* or fail* or d?sfunction* or d?s-function* or insufficien* or in-sufficien* or edema* or oedema* or destabil* or (h?per adj troph*) or h?pertroph* or incompetenc* or in-competenc* or overload* or (over adj load*))).mp.
11. ((ventric* or s?stol* or s?s-tol* or dyastol* or diastol* or dia-stol* or m?ocardi* or m?o-cardi* or outflow* or (out adj flow*) or output* or (out adj put*) or cardi* or right* or left* or renocard* or renalcard* or cardiorenal*) adj3 (decompensat* or de-compensate* or fail* or d?sfunction* or d?s-function* or insufficien* or in-sufficien* or isc?emi* or iskemi* or edema* or oedema* or destabil* or de-stabil* or (h?per adj troph*) or h?pertroph* or incompetenc* or in-competenc* or overload* or (over adj load*))).mp.
12. ((takotsubo* or tako-tsubo* or brokenheart* or (broken adj heart*)) adj3 (s?ndrome* or decompensat* or de-compensate* or m?ocardiopath* or m?o-cardiopath* or cardiom?opath* or cardio-m?opath*)).mp.
13. (((renal* or reno* or kidn*) adj1 cardi*) adj3 (s?ndrome* or decompensat* or de-compensate* or fail* or d?sfunction* or d?s-function* or insufficien* or in-sufficien* or isc?emi* or iskemi* or edema* or oedema* or destabil* or de-stabil* or (h?per adj troph*) or h?pertroph* or incompetenc* or in-competenc* or overload* or (over adj load*))).mp.
14. ((parox* or nocturn* or night* or cardi* or heart*) adj3 (d?spnea* or d?spnae* or d?spnoea)).mp.
15. (HFpEF or HFrEF or ADHF or CHF). mp.

16. ((low* or decreas* or reduc* or diminish* or less*) adj3 ((eject* adj fraction*) or ((heart* or cardi* or ventricl* or m?o-cardi* or m?ocard*) adj (volum* or work* or (out adj put*) or output)))). mp.
17. ((conges* or heart* or heredi* or idiopath* or idio-path* or obstruct* or enlarg* or en-larg* or alcohol* or h?pertroph* or (h?per adj troph*) or dilat* or restric*) adj3 (m?ocardiopath* or m?o-cardiopath* or cardiom?opath* or cardio-m?opath*)). mp.
18. Early Medical Intervention/
19. nutrition therapy/ or diet therapy/ or physical therapy modalities/ or exercise movement techniques/ or exercise therapy/ or psychosocial intervention/
20. Cognitive Behavioral Therapy/

Behavior Therapy/ (((medic* or psycho* or cognit* or behavio?r* or be-havio?r* or physical* or nutri* or diet* or physio*) adj2 (therap* or modif* or interven* or treat* or condit* or train* or activ* or rehab* or remed* or re-med* or assess* or manag*)) or (cardi* adj rehab*) or CBT or CBSM or physiotherap* or kinesiotherap* or psychotherap*).mp.

Search Strategy for Embase

1. 'Frailty'/de
2. 'Frail Elderly'/de
3. ((function* OR activ* OR ambulat* OR motor*) NEAR/2 (impair* OR empair* OR decreas* OR weak* OR 'd$sfunction*' or 'd$s-function*' or disabl* or 'dis-abl*' or disabilit* or 'dis-abilit*' or insufficien or 'in-sufficien*' or depend* or loss* or limit* or debilit* or difficult* or 'd$sorder*') or frail* OR 'pre-frail*'):ti,ab,kw
4. 'heart failure'/de OR 'acute heart failure'/de OR 'cardiorenal syndrome'/de OR 'congestive heart failure'/de OR 'diastolic heart failure'/exp OR 'heart edema'/de OR 'systolic heart failure'/exp OR 'diastolic dysfunction'/exp OR 'forward heart failure'/de OR 'heart ventricle failure'/exp OR 'heart ventricle overload'/exp OR 'systolic dysfunction'/exp
5. 'paroxysmal dyspnea'/de
6. 'cardiomyopathy'/de OR 'alcoholic cardiomyopathy'/de OR 'congestive cardiomyopathy'/de OR 'hypertrophic cardiomyopathy'/de OR 'familial hypertrophic cardiomyopathy'/de OR 'restrictive cardiomyopathy'/de OR 'takotsubo cardiomyopathy'/de
7. 'heart work'/de
8. ((acute* or congest* or chronic*) NEXT/1 (heart* or cardi*) NEAR/3 ('s$ndrome*' or decompensat* or 'de-compensate*' or fail* or 'd$sfunction*' or 'd$s-function*' or insufficien* or 'in-sufficient*' or edema* or oedema* or destabil* or 'h$pertroph*' or 'h$per-troph*' or incompetenc* or 'in-competenc*' or overload* or 'over-load')):ti,ab,kw
9. ((ventric* or 's$stol*' or 's$s-tol*' or dyastol* or diastol* or 'dia-stol*' or 'm$ocardi*' or 'm$o-cardi*' or outflow* or 'out-flow' or output* or 'out-put*' or cardi* or right* or left* or renocard* or renalcard* or cardiorenal*) NEAR/3 (decompensat* or 'de-compensate*' or fail* or 'd$sfunction*' or 'd$s-function*' or insufficien* or 'in-sufficient*' or 'isc$emi*'

or iskemi* or edema* or oedema* or destabil* or 'de-stabil*' or 'h$pertroph*' or 'h$per-troph*' or incompetenc* or 'in-competenc*' or overload* or 'over-load*')):ti,ab,kw

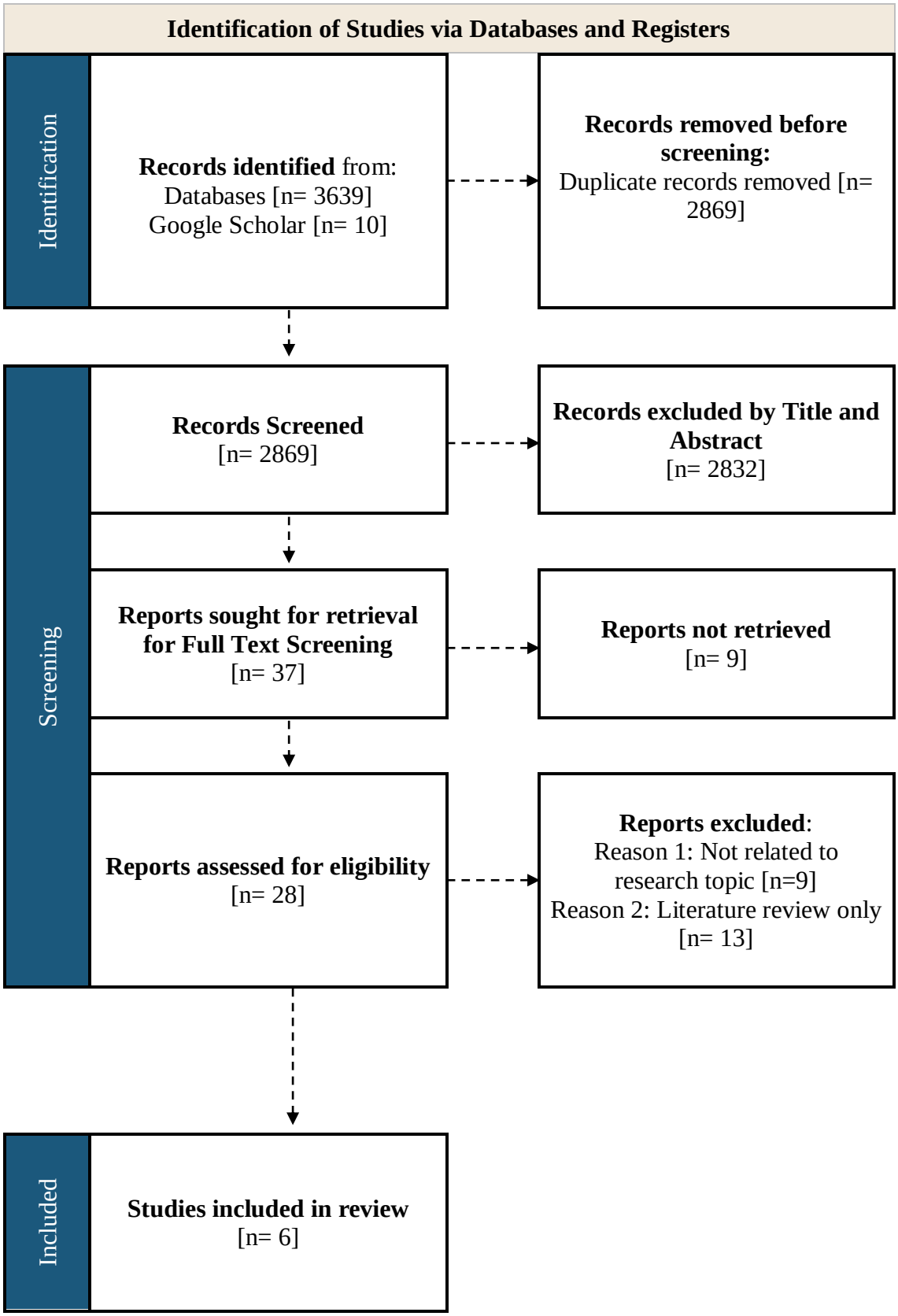
10. ((takotsubo* or 'tako-tsubo*' or brokenheart* or 'broken-heart*') NEAR/3 (s?ndrome* or decompensat* or 'de-compensate*' or 'm$ocardiopath*' or 'm$o-cardiopath*' or 'cardiom$opath*' or 'cardio-m?opath*')):ti,ab,kw
11. ((renal* or reno* or kidn*) NEXT/1 cardi* NEAR/3 ('s$ndrome*' or decompensat* or 'de-compensate*' or fail* or 'd$sfunction*' or 'd$s-function*' or insufficien* or 'in-sufficient*' or 'isc$emi*' or iskemi* or edema* or oedema* or destabil* or 'de-stabil*' or 'h$pertroph*' or 'h$per-troph*' or incompetenc* or 'in-competenc*' or overload* or 'over-load*')):ti,ab,kw
12. ((parox* or nocturn* or night* or cardi* or heart*) NEAR/3 ('d$spnea*' or 'd$spnae*' or 'd$spnoea')):ti,ab,kw
13. HFpEF:ti,ab,kw or HFrEF:ti,ab,kw or ADHF:ti,ab,kw or CHF:ti,ab,kw
14. ((low* or decreas* or reduc* or diminish* or less*) NEAR/3 'eject* fraction*'):ti,ab,kw
15. ((low* or decreas* or reduc* or diminish* or less*) NEAR/3 (heart* or cardi* or ventricl* or 'm$ocard*' or 'm$o-cardi*') NEXT/1 (volum* or work* or output* or 'out-put*')):ti,ab,kw
16. ((conges* or heart* or heredi* or idiopath* or 'idio-path*' or obstruct* or enlarg* or 'en-larg*' or alcohol* or 'h$pertroph*' or 'h$per-troph*' or dilat* or restric*) NEAR/3 ('m$ocardiopath*' or 'm$o-cardiopath*' or 'cardiom$opath*' or 'cardio-m$opath*')):ti,ab,kw
17. 'early intervention'/de OR 'movement therapy'/de OR 'physiotherapy'/de
18. 'diet therapy'/de
19. 'psychotherapy'/de OR 'behavior therapy'/de OR 'behavior modification'/de OR 'cognitive behavioral therapy'/de OR 'cognitive behavioral stress management'/de OR 'cognitive rehabilitation'/de OR 'cognitive therapy'/exp OR 'psychosocial intervention'/de
20. ((medic* or psycho* or cognit* or 'behavio$r*' or 'be-havio$r*' or physical* or nutri* or diet* or physio*) NEAR/2 (therap* or modif* or interven* or treat* or condit* or train* or activ* or rehab* or remed* or 're-med*' or assess* or manag*) OR 'cardi* rehab*'):ti,ab,kw
21. CBT:ti,ab,kw or CBSM:ti,ab,kw or physiotherap*:ti,ab,kw or kinesiotherap*:ti,ab,kw or psychotherap*:ti,ab,kw

Search Strategy for CINAHL

1. (MH "Frailty Syndrome")
2. (MH "Frail Elderly")
3. (((function* or activ* or ambulat* or motor*) N1 (impair* or empair* or decreas* or weak* or d#sfunction* or d#s-function* or disabl* or disabilit* or dis-abilit* or insufficien* or in-sufficien* or depend* or loss* or limit* or debilit* or difficult* or d#sorder*)) or frail* or (pre W0 frail*))
4. (MH "Heart Failure+")
5. (MH "Ventricular Dysfunction+") OR (MH "Heart Hypertrophy+")

6. (MH "Cardiac Output") OR (MH "Cardiac Output, Decreased")
7. (MH "Cardiomyopathy, Alcoholic") OR (MH "Cardiomyopathy, Dilated") OR (MH "Cardiomyopathy, Hypertrophic")
8. (((acute* or congest* or chronic*) W0 (heart* or cardi*)) N2 (s#ndrome* or decompensat* or de-compensate* or fail* or d#sfunction* or d#s-function* or insufficien* or in-sufficien* or edema* or oedema* or destabil* or (h#per W0 troph*) or h#pertroph* or incompetenc* or in-competenc* or overload* or (over W0 load*)))
9. ((ventric* or s#stol* or s#s-tol* or dyastol* or diastol* or dia-stol* or m#ocardi* or m#o-cardi* or outflow* or (out W0 flow*) or output* or (out W0 put*) or cardi* or right* or left* or renocard* or renalcard* or cardiorenal*) N2 (decompensat* or de-compensate* or fail* or d#sfunction* or d#s-function* or insufficien* or in-sufficien* or isc#emi* or iskemi* or edema* or oedema* or destabil* or de-stabil* or (h#per W0 troph*) or h#pertroph* or incompetenc* or in-competenc* or overload* or (over W0 load*)))
10. ((takotsubo* or tako-tsubo* or brokenheart* or (broken W0 heart*)) N2 (s#ndrome* or decompensat* or de-compensate* or m#ocardiopath* or m#o-cardiopath* or cardiom#opath* or cardio-m#opath*))
11. (((renal* or reno* or kidn*) W0 cardi*) N2 (s#ndrome* or decompensat* or de-compensate* or fail* or d#sfunction* or d#s-function* or insufficien* or in-sufficien* or isc#emi* or iskemi* or edema* or oedema* or destabil* or de-stabil* or (h#per W0 troph*) or h#pertroph* or incompetenc* or in-competenc* or overload* or (over W0 load*)))
12. ((parox* or nocturn* or night* or cardi* or heart*) N2 (d#spnea* or d#spnae* or d#spnoea))
13. (HFpEF or HFrEF or ADHF or CHF)
14. ((low* or decreas* or reduc* or diminish* or less*) N2 ((eject* W0 fraction*) or ((heart* or cardi* or ventricl* or m#o-cardi* or m#ocard*) W0 (volum* or work* or (out W0 put*) or output))))
15. ((conges* or heart* or heredi* or idiopath* or idio-path* or obstruct* or enlarg* or en-larg* or alcohol* or h#pertroph* or (h#per W0 troph*) or dilat* or restric*) N2 (m#ocardiopath* or m#o-cardiopath* or cardiom#opath* or cardio-m#opath*))
16. (MH "Psychotherapy") OR (MH "Behavior Therapy+") OR (MH "Support, Psychosocial")
17. (MH "Diet Therapy") OR (MH "Early Intervention") OR (MH "Nutritional Support")
18. (((medic* or psycho* or cognit* or behavio#r* or be-havio#r* or physical* or nutri* or diet* or physio*) N1 (therap* or modif* or modalit* or interven* or treat* or condit* or train* or activ* or rehab* or remed* or re-med* or assess* or manag*)) or (cardi* W0 rehab*) or CBT or CBSM or physiotherap* or kinesiotherap* or psychotherap*)

APPENDIX II. PRISMA 2020 FLOW DIAGRAM



APPENDIX III. EXTRACTION TOOL

Extraction Tool Title/Abstract

Characteristics of Included Studies	
Study Title	
Description of Participants	Prefrail or frail adults with HF
	Age 40-80 years
	NYHA Classification II-III
	Hospital or community setting
Exposure	Behavioral Therapy targeting frailty
	Cognitive Training targeting frailty
	Exercise interventions targeting frailty
	Nutritional based interventions targeting frailty
Comparison	Pre-frail or frail HF adults who are **not** involved in frailty interventions

Extraction Tool Full Text

Characteristics of Included Studies	**Screening Criteria**	**Criteria Met? Yes or No**
Study Title		
Author		
Publication Year		
Country of Publication		
Duration of Study		
Sample Size		
Study Design	Experimental Study (RCTs)	
	Quasi-experimental Study (Before-after studies)	
Description of Participants	Prefrail or frail adults with Heart Failure	
	Age 40-80 years	
	NYHA Classification II-III	
	Hospital or community setting	
Exposure	Behavioral therapy, cognitive training, exercise, or nutritional based interventions targeting frailty	
	How was the intervention delivered	
	How frequently was the intervention delivered	
	How long was the intervention delivered for	
Comparison	Pre-frail or frail Heart Failure adults who are **not** involved in frailty interventions	
Primary Outcomes	Mortality Rates	
	Symptom Burden: A validated comprehensive symptom assessment	

	tool; specify the name/type of the measurement tool	
	Readmission Rates	
Secondary outcomes (if applicable)		
Result	Effectiveness of the implemented intervention according to the outcome of each study.	

Complete if Article is Included:

	Citation from Article	**Page Number from Article**
Aim of study		
Design of study		
Duration of study		
Population description:		
Number of individuals included:		
Setting		
Recruiting process		
Type of intervention		
Inclusion criteria of article		
Exclusion criteria of article		
Primary outcomes measured		
Secondary outcomes measured		
Results		
Any limitations mentioned		
Conclusion		
Additional comments		

Additional Information:

Informed Consent		
IRB Approval		
Funding		
Study Authors Contact Details		

APPENDIX IV. CHARACTERISTICS OF INCLUDED STUDIES

Study Info	Design/ Funding/COI	Sample Size	Participants	Intervention	Control	Outcomes
Witham et al., 2005 United Kingdom	RCT Funding: Not specified COI: None Reported	84	• Age more than 70 • clinical diagnosis of HF, • NYHA class II-III • Echo evidence of LVSD	An exercise intervention was delivered, divided into two phases. Supervised phase was exercise classes twice a week for 30 minutes for the first 3 months, then for the remaining 3 months, the same exercises were completed at home.	Standardized written information was given regarding standard care.	• 6MWD at 3 and 6 months
Reeves et al., 2017 USA	RCT Pilot Study Funding: Multiple funding sources COI: None Reported	27	• Age more than 60 • ADHF • independent with basic ADLs • able to ambulate 4 meters • planned to be discharged home	Improve performance in 4 domains: strength, balance, mobility, and endurance through 60 minute long sessions, 3 days/week for 12 weeks then an independent maintenance phase with continued monitoring.	Received at least monthly contact from study personnel and scheduled phone calls at months 2, 4, 5, and 6 and follow up assessments at months 1 and 3.	• SPPB at 3 months • All- cause rehospitalization days at 6 months • 6MWD at 3 months

Kamiya et al., 2020 Japan	Retrospective Cohort Study. Funding: Grants from the Japan Agency for Medical Research and Development COI: None Reported	3277	• Consecutive patients admitted with HF from 15 Japanese hospitals between 2007-2016 were included.	CR was defined as participation in at least one CR sessions within 3 months of discharge, but no specific number of training hours were stipulated in the exercise programs. HF management was also provided.	Not specified, only mentioned as nonparticipants.	• All-cause mortality • HF related hospitalizations at 2.7 years

Study Info	Design/ Funding/COI	Sample Size	Participants	Intervention	Control	Outcomes
Papathanasiou, 2020 Bulgaria	RCT Funding: Not specified COI: None Reported	120	• Frail subjects with stable HF • NYHA classes II to IIIB	60 subjects were allocated to perform group based HIAIT over 12 weeks for a total of 24 training sessions.	60 subjects were allocated to perform MICT in electrically braked ergometers over 12 weeks for a total of 24 training sessions.	• 6MWT at 3 months

Mudge et al., 2021 Australia	Secondary Analysis of an RCT Funding: Multiple funding sources COI: None Reported	256	• Non-frail, frail, and very frail patients with HF hospitalized with evidence of acute HF	The intervention included what the control group received as well as a supervised center-based ET program twice weekly for 3 months and weekly for the subsequent 3 months for a total of 36 sessions.	Weekly group education sessions for 3 months, telephone and clinic follow-up, medication titration, and a home exercise program prescribed by a physiotherapist.	• 6MWT at 3 months • 6MWT at 6 months • All cause death or re-admission at 12 months
Kitzman et al., 2021 USA	RCT Funding: Multiple funding sources COI: None Reported	349	• Age more than 60 • had been admitted for ADHF • can walk 4 meters • functionally independent • expected to be discharged home	Improve physical function in 4 domains: strength, balance, mobility, and endurance through 60-minute-long sessions, 3 days per week for 12 weeks (36 sessions in total) then an independent maintenance phase for 3 months in 175 patients.	Received a telephone call every 2 weeks and an in-person clinic visit at 1 and 3 months after discharge in 174 patients.	• SPPB at 3 months • All- cause rehospitalization rate at 6 months

Legend: **ET** [Exercise Therapy] **COI** [Conflict of Interest]; **RCT** [Randomized Control Trials]; **HF** [Heart Failure]; **NYHA** [New York Heart Association]; **LVSD** [Left Ventricular Systolic Dysfunction]; **6MWD** [6 Minute Walking Distance]; **ADHF** [Acute Decompensated Heart Failure]; **ADLs** [Activities of Daily Living]; **SPPB** [Short Physical Performance Battery]; **CR** [Cardiac Rehabilitation]; **HIAIT** [High Intensity Aerobic Interval Training]; **MICT** [Moderate Intensity Continuous

APPENDIX V. RESULTS OF INDIVIDUAL STUDIES

	Frailty Interventions				Standard Care			
Article	**Mean Age ± SD**	**NYHA II no.**	**NYHA III no.**	**Sample**	**Mean Age ± SD**	**NYHA II no.**	**NYHA III no.**	**Sample**
Kitzman	73.1 ± 8.5	33	100	175	72.2 ± 7.7	34	90	174
Reeves	72.7 ± 10.8	Not Reported	Not Reported	15	71.8 ± 9.1	Not Reported	Not Reported	12
Witham	80 ± 6	25	16	41	81 ± 4	21	20	41
Papathanasiou	HIAIT: 63.65 ± 6.71	Not Reported	Not Reported	60	MICT: 63.82 ± 6.71	Not Reported	Not Reported	60
Kamiya	67.1 ± 16.3	112	306	796	67.8 ± 13.8	119	286	796

	Frailty Interventions			Standard Care			
Article	SPPB at baseline	SPPB at 3 months	Sample	SPPB at baseline	SPPB at 3 months	Sample	
Kitzman	6.0 ± 2.8	8.3 ± 0.2	175	6.1 ± 2.6	6.9 ± 0.2	174	Mean between group difference: 1.5, 95% CI 0.9 to 2.0; p<0.001
Reeves	4.8 ± 2.8	6.9 ±- 3.0	15	6.0 ± 3.0	6.8 ± 3.3	12	Intervention effect size: +1.1

	Frailty Interventions			Standard Care		
Article	**6MWD at baseline**	**6MWD at 3 months**	**Sample**	**6MWD at baseline**	**6MWD at 3 months**	**Sample**
Reeves	160 ± 85 meters	247 ± 22 meters	15	201 ± 120 meters	224 ± 22 meters	12
Witham	261 ± 117 meters	254 ± 107 meters	41	240 ± 93 meters	228 ± 102 meters	41
Mudge	360.62 ± 127.27 meters	383.42 ± 125.24 meters	114	362.50 ± 111.33 meters	389.196 ± 120.125 meters	97
Papathanasiou	HIAIT: 440.58 ± 39.79 meters	HIAIT: 513.38 ± 37.73 meters	60	MICT: 442.90 ± 42.53 meters	MICT: 489.32 ± 43.45 meters	60

	Frailty Interventions			Standard Care		
Article	**6MWD at baseline**	**6MWD at 6 months**	**Sample**	**6MWD at baseline**	**6MWD at 6 months**	**Sample**
Witham	261 ± 117 meters	262 ± 110 meters	41	240 ± 93 meters	246 ± 111 meters	41
Mudge	360.62 ± 127.27 meters	396.77 ± 123.09 meters	93	362.50 ± 111.33 meters	393.96 ± 125.94 meters	82

	Frailty Interventions		Standard Care		
Article	**Rate of Hospitalization**	**Sample**	**Rate of Hospitalization**	**Sample**	
Kitzman	1.18	175	1.28	174	Rate Ratio: 0.93 95% CI 0.66 to 1.19
Reeves	1.16 ± .35	15	1.64 ± .39	12	Intervention effect size: -0.48

Article	Frailty Interventions		
	Hospitalization	All Cause Mortality	Timeline
Kamiya	HR 0.82, 95% CI 0.67-0.99	HR 0.67, 95% CI 0.51 - 0.87	2.7 ± 1.6 years

APPENDIX VI GRADE ASSESSMENT

Symptom Burden assessed with the Short Physical Performance Battery (follow-up: 3 months; assessed with: 0-12 score, 0 indicating the lowest performance and 12 being the highest. MCID 1)

Certainty Assessment							No. of Patients		Effect		Other Parameters	
Number of Studies	Study Design	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Frailty Interventions	Standard Care	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
2[1,2]	RCT	Not Serious	Not Serious[a]	Not Serious	Serious[a]	None	190	186	-	Mean **1.4 higher** (1.35 higher to 1.44 higher)	⊕⊕⊕◯ Moderate	

All Cause Death (Follow-up: 12 Months)

Certainty Assessment							No. of Patients		Effect		Other Parameters	
Number of Studies	Study Design	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Frailty Interventions	Standard Care	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1[3]	RCT	Not Serious	Not Serious	Not Serious	Very Serious[b]	None	84/140 (60%)	90/138 (65.2 %)	**RR 0.92** (0.77 to 1.10)	**52 fewer per 1,000** (from 150 fewer to 65 more)	⊕⊕◯◯ Low	

Readmission (Follow-Up: 6 Months)

Certainty Assessment							No. of Patients		Effect		Other Parameters	
Number of Studies	Study Design	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Frailty Interventions	Standard Care	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance

1[2]	RCT	Not Serious	Not Serious	Not Serious	Serious[c]	None	94/175 (53.7%)	110/174 (63.2%)	**RR 0.85** (0.71 to 1.02)	**95 fewer per 1,000** (from 183 fewer to 13 more)	⊕⊕⊕◯ Moderate	

Readmission Days (Follow-Up: 6 Months)

Certainty Assessment							No. of Patients		Effect		Other Parameters	
Number of Studies	**Study Design**	**Risk Of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**Frailty Interventions**	**Standard Care**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**	**Importance**
1[1]	RCT	Not Serious	Not Serious	Not Serious	Very Serious[d]	None	15	12	-	MD **5.4 days fewer** (7.43 fewer to 3.37 fewer)	⊕⊕◯◯ Low	

Symptom Burden assessed with the 6 Minute Walking Distance (follow-up: 3 months; assessed with: MCID 23 meters)

Certainty Assessment							No. of Patients		Effect		Other Parameters	
Number of Studies	**Study Design**	**Risk Of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**Frailty Interventions**	**Standard Care**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**	**Importance**
3[1,3,4]	RCT	Not Serious	Not Serious[e]	Not Serious	Serious[f]	None	170	150	-	Mean **23.6 meters higher** (7.69 higher to 39.03 higher)	⊕⊕⊕◯ Moderate	

Symptom Burden assessed with the 6 Minute Walking Distance (follow-up: 6 months; assessed with: MCID 23 meters.)

Certainty Assessment							No. of Patients		Effect		Other Parameters	

Number of Studies	Study Design	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Frailty Interventions	Standard Care	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
2[3,4]	RCT	Not Serious	Not Serious[g]	Not Serious	Very Serious[h]	None	134	123	-	Mean **16 Meters higher** (31.83 lower to 63.83 higher)	⨁⨁◯◯ Low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

3. Overall certainty downgraded by one level due to moderate heterogeneity (I2 is 58%) and a small sample size.
4. Downgraded by two levels because the confidence interval includes values reflecting both benefit and harm. Also, information comes from one trial with a relatively small sample size.
5. Downgraded by one level because the confidence interval includes values reflecting both benefit and no effect.
6. Single study with small sample size
7. I squared is 18%
8. Small sample size. MCID is 23 meters, therefore rated down as serious as within the absolute CI.
9. I squared is 0%
10. Small sample size. MCID is 23 meters, therefore rated down as very serious as within the absolute CI. Additionally, CI includes harm (a decrease in 6MWD).

References

1. Reeves, G. R.,Whellan,D. J.,O'Connor,C. M.,Duncan,P.,Eggebeen,J. D.,Morgan,T. M.,. . . Kitzman,D. W. A Novel Rehabilitation Intervention for Older Patients With Acute Decompensated Heart Failure: The REHAB-HF Pilot Study.. JACC: Heart Failure, 5(5), 359-366.; 2017.
2. Kitzman, D. W.,Whellan,D. J.,Duncan,P.,Pastva,A. M.,Mentz,R. J.,Reeves,G. R.,. . . O'Connor,C. M.. Physical Rehabilitation for Older Patients Hospitalized for Heart Failure. The New England journal of medicine. ; (2021).

3. Mudge, A. M.,Pelecanos,A.,& Adsett,J. Frailty implications for exercise participation and outcomes in patients with heart failure.. A Journal of the American Geriatrics Society.; 2021.
4. Witham, M. D.,Gray,J. M.,Argo,I. S.,Johnston,D. W.,Struthers,A. D.,& McMurdo,M. E.. Effect of a seated exercise program to improve physical function and health status in frail patients > or = 70 years of age with heart failure. American Journal of Cardiology, 95(9), 1120-1124; 2005

APPENDIX VII. RISK OF BIAS 2 TOOL

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)
TEMPLATE FOR COMPLETION
Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne
on behalf of the RoB2 Development Group
Version of 22 August 2019

The development of the RoB 2 tool was supported by the MRC Network of Hubs for Trials Methodology Research (MR/L004933/2- N61), with the support of the host MRC ConDuCT-II Hub (Collaboration and innovation for Difficult and Complex randomised controlled Trials In Invasive procedures - MR/K025643/1), by MRC research grant MR/M025209/1, and by a grant from The Cochrane Collaboration.

Study Details

Reference	

Study Design

X Individually randomized parallel-group trial
☐ Cluster-randomized parallel-group trial
☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: | Comparator:

Specify which outcome is being assessed for risk of bias	
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR	

= 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Is the review team's aim for this result…?

☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions

☐ failures in implementing the intervention that could have affected the outcome

☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

☐ Journal article(s) with results of the trial

☐ Trial protocol

☐ Statistical analysis plan (SAP)

☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)

☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)

☐ "Grey literature" (e.g. unpublished thesis)

☐ Conference abstract(s) about the trial

☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)

☐ Research ethics application

☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)

☐ Personal communication with trialist

☐ Personal communication with the sponsor

Risk of Bias Assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of Bias Arising from the Randomization Process

Signaling Questions	Comments	Response options
1.1		
1.2		
1.3		

Domain 2: Risk of Bias due to Deviations from the Intended Interventions (Effect of Assignment to Intervention)

Signaling Questions	Comments	Response options

Domain 2: Risk of Bias due to Deviations from the Intended Interventions (Effect of Adhering to Intervention)

Signaling Questions	Comments	Response options

Domain 3: Missing Outcome Data

Signaling Questions	Comments	Response options

Domain 4: Risk of Bias in Measurement of the Outcome

Signaling Questions	Comments	Response options

Domain 5: Risk of Bias in Selection of the Reported Result

Signaling Questions	Comments	Response options

Overall Risk of Bias

Risk-of-Bias Judgement	Comments	Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favors experimental / Favors comparator / Towards null /Away from null / Unpredictable

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