THE ASSOCIATION OF FRAILTY AND LONG-TERM ADVERSE OUTCOMES IN PEOPLE WHO ATTEND CARDIAC REHABILITATION

by

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Dalhousie University is located in Mi'kma'ki, the
ancestral and unceded territory of the Mi'kmaq.
We are all Treaty people.

DEDICATION

To Mom, Dad, Ben, Terry, Henry, and William, thank you for your love and endless support. You are all the family anyone would ever need.

And to my biggest fan, confidante, and best friend. Your unconditional love, encouragement, and unwavering support made this possible. I love you, Jodi.

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ABSTRACT

Background: Cardiac rehabilitation programs are the gold standard for supporting patients to recover from cardiac events such as a heart attack. Patients who enrol in cardiac rehabilitation are often older and are burdened by health problems other than their cardiovascular disease. People who have many health problems can be described as frail. Although frailty is highly prevalent in people who attend cardiac rehabilitation, its implications for long-term outcomes of patients is yet to be elucidated.

Purpose: To examine the association between 1) admission frailty and 2) frailty changes during cardiac rehabilitation with long-term outcomes (due to all-causes or cardiovascular diseases) including time to mortality, first hospitalization, first emergency department (ED) visit, and number of hospitalizations, hospital days, and ED visits over a 5-year follow-up.

Methods: We analyzed data from patients admitted to cardiac rehabilitation in Halifax, Nova Scotia from May 2005 to April 2015 (N=3,371). The cardiac rehabilitation programme included group-based exercise and education performed twice weekly for 12 weeks. A 25-item frailty index (FI) estimated frailty levels at cardiac rehabilitation admission and discharge. FI improvements were determined by calculating the difference between admission and discharge FI. Cardiac rehabilitation data were linked to administrative health data to examine 5-year outcomes (all-cause and cardiovascular disease mortality, hospitalization, and ED visits). Cox regression, Fine-Gray models, and negative binomial hurdle models were used to determine the association between FI and outcomes. Hazard ratios, incident rate ratios, and confidence intervals correspond to a 1% change in the FI.

Results: The mean (standard deviation) age of the patients were 62 (11) years old; 74% were male. Mean admission FI scores were 0.34 (0.13). On average, FI improved by 0.07 (0.09) from cardiac rehabilitation admission to discharge. Admission FI was associated with time to mortality (HRs: all-cause=1.02[95% CI 1.01,1.04]; CVD=1.03[1.02,1.05]), hospitalization (all-cause=1.02[1.01,1.02]; CVD=1.02[1.01,1.02]), and ED visit (all-cause=1.01[1.00,1.01]), and the number of hospitalizations, hospital days, and ED visits. FI improvements during CR had a protective effect regarding time to all-cause hospitalization (0.99[0.98,0.99]), but was not associated with other outcomes.

Conclusion: Frailty status at cardiac rehabilitation admission was related to long-term adverse outcomes. Frailty improvements during cardiac rehabilitation were associated with delayed time to all-cause hospitalization.

LIST OF ABBREVIATIONS USED

AC	All-cause
AHA	American Heart Association
BACPR	British Association of Cardiovascular Prevention and Rehabilitation
CACPR	Canadian Association of Cardiovascular Prevention and Rehabilitation
CI	Confidence interval
CIHI	Canadian Institutes for Health Information
CR	Cardiac rehabilitation
CSHS	Cost-of-standard-hospital-stay
CVD	Cardiovascular disease
DAD	Discharge Abstract Database
eFI	Electronic Frailty Index
EFS	Edmonton Frailty Scale
EJECTION-HF	Exercise Joins Education: Combined Therapy to Improve Outcomes in Newly Discharged Heart Failure
FI	Frailty Index
FP	Frailty Phenotype
HF-ACTION	Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training
HR	Hazard ratio
ICD-10	International Classification of Diseases 10th Revision
IPR	Insured Patient Registry
IRR	Incident rate ratio
KCL	Kihon Check List
NACRS	National Ambulatory Care Reporting System
NS	Nova Scotia
OR	Odds ratio
RR	Relative risk
SD	Standard deviation
UK	United Kingdom

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Chapter 1 Introduction

Cardiovascular diseases (CVDs) are a considerable health and economic burden. They accounted for 32% of global deaths in 2019[1] and cost hundreds of billions of dollars to the United States of America and Canada.[2,3] The prevalence of CVDs also increases with older age. Thus, in conjunction with the rising global life expectancy,[4,5] the burden of CVDs will continue to escalate. Furthermore, because CVDs rarely exist on their own, their management requires careful consideration of various other age-related health problems.[6] Variability in health outcomes means that some individuals have more favourable prognoses from CVD than others of the same age. This variable vulnerability to adverse outcomes can be referred to as *frailty*.[7]

Frailty has been described as a means to quantify health amongst people of the same age.[7] It recognizes that some people age slowly while others will rapidly decline as they get older. In other words, frailty indicates the inter-individual variability in rates of ageing. High levels of frailty increases the risk of mortality,[8–10] morbidity,[11] and disability.[12] Frailty is thus an age-related and multiply determined loss of the ability to respond to stressors.[7]

Frailty is more common in those with CVDs than in those without (50-54% vs 14-24%).[13,14] Importantly, people who are frail have an increased risk of CVD morbidity and mortality compared to those who are not.[15] Thus, to effectively manage and treat patients living with CVD and a high degree of frailty, an individualized model addressing both frailty and CVD is required. Cardiac rehabilitation (CR) is a comprehensive CVD care model for patients who have recently experienced an adverse cardiovascular event.[16–20]

CR focuses on nutritional counseling, risk factor modification, psychosocial management, patient education, and exercise training to improve outcomes for patients.

Previous research has shown that multicomponent interventions are effective in improving frailty.[21–25] Hence, CR may be well-equipped to contend with the many complexities of frailty due to its multidimensional nature. In fact, completion of CR can improve frailty.[26–30] However, there is sparse evidence showing how frailty at CR admission will impact long-term outcomes such as premature mortality and rehospitalizations. Importantly, there are no previous investigations about whether frailty improvements during CR can improve such long-term outcomes.

Thus, the purpose of this thesis was to explore the association between frailty at CR admission, frailty changes during CR, and 5-year outcomes of people who attend CR. Specifically, the objectives were to 1) examine the association between admission frailty and 5-year mortality, hospitalizations, and emergency department visits due to all-causes and CVDs in people who attend CR and to 2) investigate the association between frailty changes during CR and 5-year mortality, hospitalizations, and emergency department visits due to all-causes and CVDs in people who attend CR.

Chapter 2 Literature Review

2.1 Cardiovascular Disease

2.1.1 Burden of Cardiovascular Disease

CVDs are a group of disorders of the heart and blood vessels. They commonly include coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic and congenital heart diseases, and venous thromboembolism.[1] CVDs are the leading cause of mortality globally, accounting for 32% of deaths in 2019.[1] They affect 1 in 2 Americans[2] and 1 in 3 Canadians over the age of 60[31,32] and are the leading cause of disability-adjusted life years lost due to ill-health, disability, or early mortality worldwide.[33] Furthermore, CVDs are economically burdensome, costing Canada $21.2 billion per year[3] and the United States approximately $363.4 billion per year.[2] A variety of risk factors, both modifiable and non-modifiable, contribute to the development of CVD globally, including age, sex, gender, high blood pressure, dyslipidemia, diabetes, and obesity.

2.1.2 Burden of Cardiovascular Disease in Nova Scotia

Nova Scotia has a high prevalence of CVD risk factors compared to all of Canada, including smoking (24% vs 22%), heavy drinking (29% vs 22%), body mass index >30 (20% vs 16%), high blood pressure (19% vs 16%), and diabetes (7% vs 6%).[34] Importantly, Nova Scotia has the second-oldest population of all Canadian provinces (by mean and median age), only behind Newfoundland and Labrador (Figure 2.1).[35] Together, these highly prevalent risk factors are detrimental to the health of Nova Scotians. In fact, Nova Scotians have the second-highest CVD-related mortality risk of all Canadian provinces at 261.0 deaths per 100,000, behind Newfoundland and Labrador

at 274.3 deaths per 100,000.[36] For context, these rates are significantly higher than the 2018 Canadian average of 192.6 deaths per 100,000.[36]

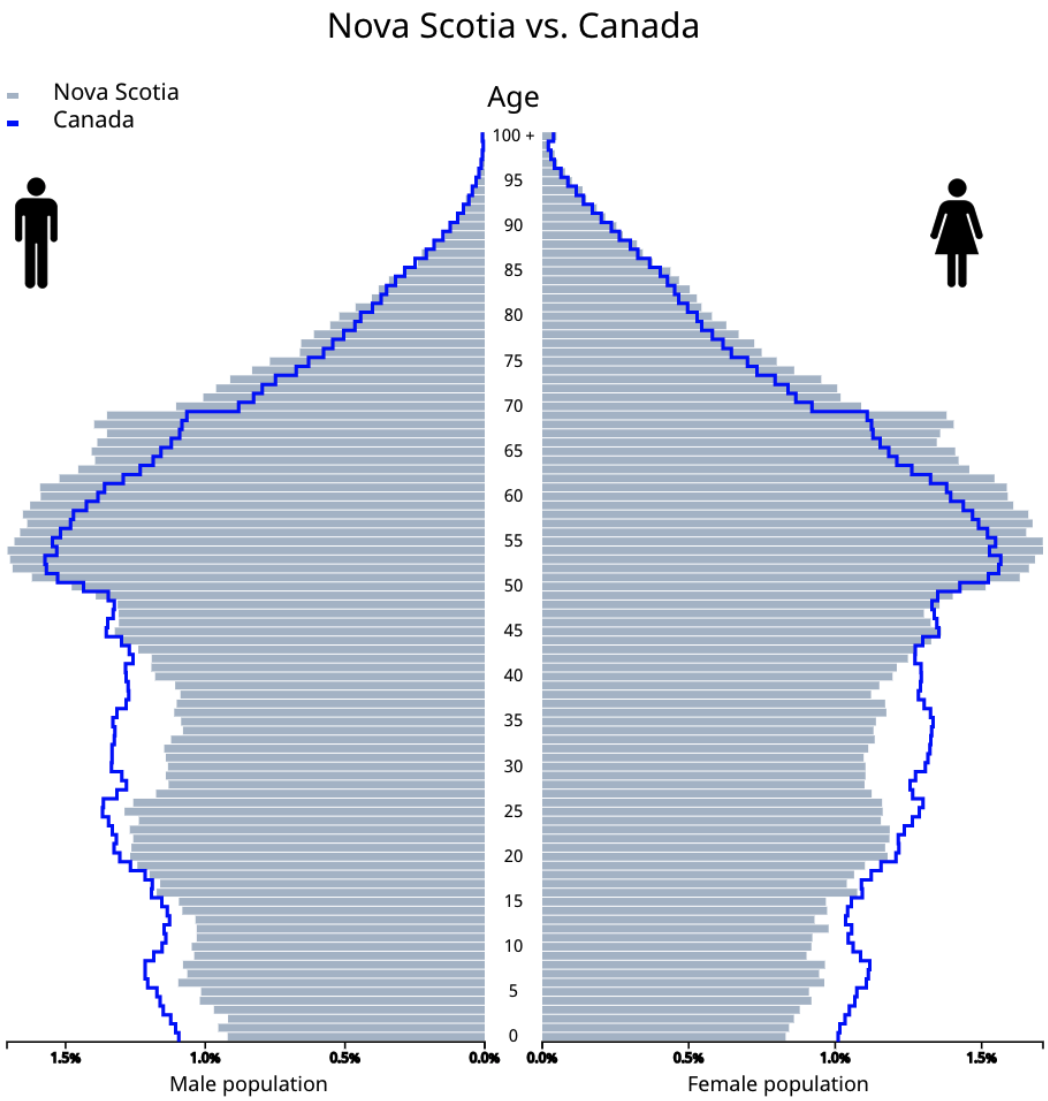

Figure 2.1. Population pyramid by age and sex of Nova Scotia and Canada in 2016. Generated from Statistics Canada's interactive comparison age pyramid.[37]

2.1.3 Ageing and Cardiovascular Diseases

Older age remains the most important predictor of CVD.[38,39] The prevalence of CVD increases with age, from 17.5-33.4% in males and females aged 20-38 to 89.4-90.8% in those 80 years and older.[2,40] Thus, in conjunction with the rising global life

expectancy,[4,5] the burdens associated with CVD will continue to escalate. As CVDs rarely exist on their own, effective management of CVDs require careful consideration of other age-related health problems (e.g. cognitive decline, functional limitations, multi-morbidities, lifestyle, environmental factors).[6] Variability in health outcomes means that some individuals will have more favourable prognoses from CVD than others of the same age. This variable vulnerability to adverse outcomes can be referred to as *frailty*.[41]

2.2 Defining and Measuring Frailty

2.2.1 Definition of Frailty

Frailty has been described as a means to quantify health amongst people of the same age.[7] It recognizes that some people age slowly while others will rapidly decline as they get older. In other words, frailty indicates the inter-individual variability in rates of ageing. Frailty increases the risk of mortality,[8–10] morbidity,[11] and disability[12] among people of the same age. Importantly, while conceptually distinct, frailty and ageing are strongly associated.[41,42]

While frailty has emerged as an important area of research in the past three decades,[43] there is still no consensus for its definition. Researchers have proposed several operational approaches and developed many instruments to measure frailty. Of these, the two most common approaches – the frailty phenotype[44] and the frailty index (FI)[45] – agree that the definition of frailty should include robustness (ability to withstand stress) and resilience (ability to remove or repair damage).[10] Frailty is thus an age-related and multiply determined loss of the ability to respond to stressors.[7]

2.2.2 Frailty Phenotype

The frailty phenotype proposed by Fried et al.[44] views frailty as a syndrome that emphasizes physical decline. It includes five physical criteria (involuntary weight loss, exhaustion, slow gait speed, poor handgrip strength, and physical inactivity) that interact in a continuous cycle, with frailty able to arise from any of the five domains. These five criteria are further categorized into a 3-level variable describing the grade of frailty. The levels are: robust (0 criteria met), pre-frail (1 to 2 criteria met), or frail (3 or more criteria met).[44] Fried et al.[44] validated their frailty phenotype by evaluating its prevalence, incidence, correlation, and validity in terms of predicting outcomes associated with frail older adults including poor mobility, disability, falls, hospitalizations, and mortality.

2.2.3 Frailty Index

The accumulation of deficits approach by Rockwood and Mitnitski,[45] operationalizes frailty with a FI, which includes how *many* things are wrong with a person as opposed to the exact nature of problem.[10,46] This approach proposes that frailty stems from the accumulation of unrepaired damage across multiple systems, leading to the inability to repair damage caused by internal or external stressors.[45,47] Thus, the FI dynamically measures the accumulation of deficits. Here, the nature of the deficit is less important than the number of deficits, suggesting that many randomly determined pathways are responsible for the state of vulnerability to adverse outcomes.

The FI is measured by counting deficits in health; it is a ratio of deficits relative to the total number of deficits considered.[45,48] In 2008, Searle et al.[48] published a standard procedure for creating an FI. For a deficit to be included in the FI, they should 1) be associated with health status (graying hair should not be included as it is an attribute), 2)

generally increase with age, 3) not saturate too early, 4) cover a wide range of health systems (e.g., cognition, chronic conditions, mobility), and 5) if to be compared serially in the same individual, items should be the same as that of the previous iteration. The FI can accommodate items that are binary (0 = no deficit, 1 = deficit), ordinal, or continuous. Furthermore, a minimum consideration of 30 to 40 deficits is recommended, as estimates tend to become unstable when few deficits are used.[48] Once all deficits have been selected and recoded according to standard procedures, the FI can be calculated by dividing the number of deficits present to the total number of deficits considered. For example, if 40 deficits were considered and 10 were present in an individual, the FI would be 10/40 = 0.25.[48]

2.2.4 Other Frailty Instruments

Although the frailty phenotype and the FI are the primary instruments used to measure frailty, various other tools which grade the degree of frailty exist, including the Clinical Frailty Scale[49] the Edmonton Frailty Scale,[50] the Vulnerable Elders Survey,[51] the Tilburg Frailty Indicator,[52] the Groningen Frailty Indicator,[53] the Kaigo-Yobo and Kihon Checklist,[54] and the Survey of Health, Ageing and Retirement in Europe Frailty Instrument.[55]

2.2.5 Frailty Phenotype versus Frailty Index

Despite differences in their operational definition, both the frailty phenotype and the FI approaches share important characteristics: right-skewed density distributions in community-dwelling samples, frailty scores that increase nonlinearly with age, higher mortality risk with higher frailty scores, and higher frailty scores in women than in men.[9,10] However, one of the FI's greatest strengths over the frailty phenotype stem from

its flexibility and reproducibility across multiple databases. A FI can be created from most clinical or administrative databases, and despite differences in the nature and number of deficits included, its predictive ability for outcomes (e.g., mortality, institutionalizations) remains similar.[46,56] As a result, many FIs created using standard procedures are well-validated in predicting various adverse outcomes including mortality,[41] dementia,[57] CVDs,[58] other chronic diseases,[59] healthcare use, and cost.[60]

There are uncertainties regarding the ability of frailty instruments to detect intervention-induced changes over time.[61,62] To assess the effect of interventions, frailty tools need to be multidimensional and sensitive to change. Instruments such as the frailty phenotype,[44] may be unsuitable due to their lack of granularity.[61,63] The European Association of Preventive Cardiology posits that the FI may be the most appropriate instrument to capture intervention-induced change due its ability to detect finer changes over time.[62]

2.3 Frailty and Cardiovascular Disease

The emergence of research containing both the terms "geriatrics" and "cardiology" may be attributable to higher life expectancies across the globe;[4,5,64] frailty and CVD are common as people age. Importantly, frailty is more prevalent in older patients with CVDs than those without (50-54% vs 14-24%).[13,14] For patients living with CVD, the presence of frailty (measured by the frailty phenotype and the CFS) increases the risk of adverse outcomes after acute CVD events and CVD interventions including mortality,[65–68] length and frequency of hospitalization,[68,69] coronary artery disease, cardiac surgery, peripheral arterial disease, heart failure, and atrial fibrillation.[58,70,71] Additionally, a meta-analysis of 18,970 people from six longitudinal cohorts showed that

frailty increased the risk of CVD morbidity (HR [95% CI] = 1.70 [1.18-2.45]) and CVD mortality (HR [95% CI] = 3.89 [2.39-6.34]) when compared to their non-frail peers.[15] Interestingly, frailty predicts CVD events (myocardial infarction, stroke, CVD-related hospitalization) and CVD mortality *independently* of traditional CVD risk factors;[58,70] frailty also adds prognostic value above CVD risk factors when predicting outcomes.[58]

Several complex pathways increase the risk of both frailty and CVD.[72] However, one prevalent theory posits that ageing-associated inflammation, called inflammageing, underly both frailty and CVD.[72–76] Normally, inflammation is a key immune mechanism to defend against infections, toxic compounds, or irradiation. However, persistent and unregulated inflammation can accelerate the progression of both frailty and CVD;[74] this co-existence may worsen the negative health outcomes for patients living with frailty and CVD. To effectively manage and treat the unique challenges of this population, an individualized model addressing both frailty and CVD is required.

2.4 Reversing Frailty and Treating Cardiovascular Disease

2.4.1 Frailty Treatments

There is increasing evidence suggesting that frailty is reversible and thus can be targeted by treatments.[27,77–84] A scoping review in community-dwelling older adults from 2017[78] found that 9 of 14 interventions reduced frailty levels. The interventions included physical activity, nutritional, medication management, multicomponent, and patient-centered geriatric interventions. The most effective exercise interventions for older adults living with frailty were long lasting (more than 5 months), involved multiple components (flexibility, balance, resistance, and endurance), and were performed three times per week for 30-45 minutes per session.[79] Nutritional interventions modified nutritional

quality by giving supplements or improving diet. However, the effect of nutritional intervention alone on reducing frailty level was mixed, suggesting that more than one type of intervention may be required to improve frailty.[85,86] In 2019, a systematic review showed that 65% of frailty interventions (30 of 46 interventions) incorporated at least two components.[87] Importantly, multicomponent interventions that combined physical activity, nutrition, and/or cognitive training[21–25] improved frailty levels to the greatest extent.

2.4.2 CVD Treatments

Treatment of CVDs vary based on disease severity. However, most treatments involve medication management, medical procedures (e.g., coronary angioplasty), surgeries (e.g., coronary artery bypass graft surgery), and lifestyle changes. Categories of medications include lipid-lowering drugs (e.g., statins, fibrates), antihypertensive agents (e.g., β-blockers, diuretics, angiotensin converting enzyme inhibitors), anti-platelets or anti-coagulants (e.g., cyclooxygenase-1 inhibitor, P2Y12 receptor antagonists).[38] While pharmacologic therapies are limited in that they do not completely cure CVDs, they improve CVD risk factors and are generally effective at decreasing CVD mortality and morbidity.[38] Lifestyle interventions can include a physical activity prescription or intervention from the patient's primary care team. A meta-epidemiological study from 2013[88] comparing physical activity to pharmacologic interventions of patients living with CVD suggested that both interventions had similar benefits to mortality. The authors further emphasized the viability of physical activity as an alternative or addition to pharmacologic therapies for the management of CVDs. However, previous reviews have reported uncertainty about the effectiveness regarding the referral and promotion of

physical activity interventions.[89,90] Whether physical activity alone is more effective than other approaches such as counselling or nutritional interventions is unknown.[89] A more comprehensive and systematic care regime for patients with CVD, called cardiac rehabilitation (CR), will be discussed in the following section.

2.5 Cardiac Rehabilitation

2.5.1 Definition and Scope

CR is a comprehensive CVD care model for patients who have recently experienced an adverse cardiovascular event.[16–20] The Canadian Association of Cardiovascular Prevention and Rehabilitation (CACPR) defines CR as:

> *"The enhancement and maintenance of cardiovascular health through individualized programs designed to optimize physical, psychological, social, vocational, and emotional status. This process includes the facilitation and delivery of secondary prevention through risk factor identification and modification in an effort to prevent disease progression and the recurrence of cardiac events".*[91]

The secondary prevention aspect of CR, which focuses on reducing the impact of CVD before critical damage, is integral for the management and treatment of patients living with CVD who are at high risk of recurrent adverse events.[16,92]

Major CR organizations around the world have established their own guidelines for the delivery of CR including American,[93] Australian,[94] British,[17] Canadian,[16] and European[95] associations. While the content of guidelines may vary, the International Council of Cardiovascular Prevention and Rehabilitation (ICCPR) has agreed upon the following as core components of CR: 1) nutritional counseling, 2) risk factor

modification, 3) psychosocial management, 4) patient education, and 5) exercise training.[96] Systematic patient referral, assessment, audit, and evaluation are also considered important by the CACPR and the British Association of Cardiovascular Prevention and Rehabilitation (BACPR) (Table 2.1).[16,17]

To effectively deliver these core components, CR requires a multidisciplinary care team, which can consist of a medical director, physicians, nurses, physiotherapists, occupational therapists, mental health specialists, and dieticians.[16,17,96,97] This patient-centric process begins with identifying the cardiac patient, assessing and tailoring an individualized care plan, then delivering the CR programme, and 'ending' with a final assessment and long-term management of the patient.[17] CR emphasizes the translation of contemporary clinical experience and scientific research into clinical practice with the goal to heal, maintain, and even enhance the health of patients living with CVD. Furthermore, CR considers the myriad of detrimental effects of CVD on health, including physical health, psychological and social well-being, nutrition, and vocational status.[16]

Table 2.1. Core components of cardiac rehabilitation in Canada and the UK.

BACPR Components	CACPR Components	Component Elements
Systematic patient referral and assessment	Patient referral	1. Automated referral 2. Opt-out (must decline rather than request cardiac rehabilitation) 3. A mechanism of re-offer and re-entry should be put in place for patients who initially decline
	Patient assessments	1. History and physical examination 2. Risk stratification 3. Exercise stress testing 4. Risk factor assessment 5. Psychosocial assessment 6. Nutritional assessment

BACPR Components	CACPR Components	Component Elements
Management of risk factors and health behaviours	Health behaviour interventions and risk factor modification	1. Nutritional counselling 2. Lipid management 3. Hypertension management 4. Smoking cessation 5. Weight management 6. Diabetes management 7. Adherence to appropriate pharmacotherapy 8. Psychosocial management 9. Physical activity counselling
Patient education	Development of self-management techniques based around individualized assessment, problem-solving, goal setting and follow up	1. Problem-solving (how to define their disease-related problems and find solutions to daily problems due to chronic illness) 2. Decision-making (assist patients in acquiring the necessary health-related information sufficient to enable effective decision-making about health-related problems and changes in their disease condition) 3. Resource utilization (be assisted in finding and utilizing common community-based resources) 4. Partnership formation (learn how to form productive partnerships with healthcare providers) 5. Action planning (learn to be more self-efficacious) 6. Self-tailoring (encouraged to self-tailor health-enhancing programmes or activities such as exercise or dietary change based on the above skills)
Physical activity intervention	Exercise training	1. Aerobic training 2. Strength (resistance) training 3. Flexibility training
Long-term management and assessment of outcomes	Outcome assessment programs and performance measures	1. Clinical outcomes 2. Health outcomes 3. Educational outcomes 4. Behavioural outcomes 5. Service outcomes
Audit and evaluation	N/A	1. Registration and submission of data to the National Audit for Cardiac Rehabilitation (NACR) 2. Participation in the National Certification Programme

BACPR = British Association of Cardiovascular Prevention and Rehabilitation, CACPR = Canadian Association of Cardiovascular Prevention and Rehabilitation. Adapted from Stone et al.[16] and Cowie et al.[17]

CR is primarily delivered at health centers or hospitals.[16,18,98] Alternative but similarly effective methods of delivery are home-[16,18,98,99] or virtual-based CR.[100–103] Due to the complex nature of CR, there are significant variations between types of CR programs within and across nations.[104] American, Canadian, Australian, and European organizations have established their own quality indicators and performance measures for CR.[104] While the approach to CR may vary, all CR programs aim to improve cardiovascular risk factors, psychological and social health, as well as physical and cognitive function.[16,20,105,106] The ambition is to promote long-lasting lifestyle changes and give patients the necessary tools to self-manage their chronic conditions.

2.5.2 Exercise in CR Compared to Current Exercise Prescription

Aerobic endurance training is the foundation of the CR exercise component and is incorporated universally across international CR guidelines. However, the intensity of aerobic training varies significantly across programmes. There is consensus that moderate to vigorous CR-based exercise interventions result in significant improvements in exercise capacity (measured by maximal exercise testing, 6–minute walk test, or incremental shuttle walk test) compared to non-exercising controls across many countries including Belgium, Italy, Germany, Canada, and the US.[107] Conversely, light to moderate intensity exercise training interventions has limited efficacy for exercise capacity and morbidity compared to non-exercising controls in people who attend CR.[107] In addition, American, European, and Canadian CR associations recommend a minimum of 3 sessions per week while Australia, Austria, Japan, and the UK recommend 3 or fewer sessions per week. A minimum of 3 sessions per week may be required to meet the 150

minutes per week of moderate-intensity exercise recommended by the World Health Organization.[108]

2.5.3 Benefit of CR

There is vast evidence reviewing the benefits of CR from meta-analyses, Cochrane reviews, and clinical reviews.[98,109–114] CR reduces all-cause mortality (RR [95% CI] = 0.87 [0.75,0.99]),[115] CVD mortality (RR [95% CI] = 0.74 [0.63,0.87]),[115] CVD morbidity, all-cause hospitalizations (RR [95% CI] = 0.75 [0.62,0.92])[98] and hospitalization due to heart failure (RR [95% CI] = 0.61 [0.46,0.80]).[114] CR also improves mental health (anxiety, depression, and hostility, psychological distress),[116–118] quality of life,[115] physical activity status, and cardiovascular risk factors.[114,119–121] The positive impact of CR has led to its unanimous recommendation for the management of CVD in Canada and by international health organizations including the ICCPR, the National Institute for Health and Care Excellence, the Department of Health, the BACPR, the CACPR, the American Heart Association (AHA), and various other European CR organizations.[16,17,122–124]

2.6 Cardiac Rehabilitation and Frailty

As discussed in section 2.3, the management of patients living with both CVD and a high degree of frailty is uniquely challenging. Previous research showed that patients of varying ages enter CR with significant degrees of frailty (Table 2.2).[26–29,125–132] Thus, CR must address the complications of frailty throughout the care process.[133]

In fact, previous work has already shown that frailty may interfere with CR intake. Frailer people such as patients who are older, have worse health, have poor perception of their health, or are women[134–136] are less likely to be referred to and

participate in CR.[61,137–139] For older people, this may be due to the perception of being too "unfit" or "frail" to benefit from CR.[140–142] However, more recent evidence has challenged these views,[26–28,30,140] suggesting that improving the referral and retention of patients with frailty in CR could be key for better outcomes post-CR.[27,29]

Table 2.2. Prevalence of Frailty in Cardiac Rehabilitation Programs.

Year	Authors	N	Pre-frailty	Frailty	Frailty Measure
2019	Arai et al.[126]	78	-	26%	FP
2019	Kunimoto et al.[130]	845	32%	34%	KCL
2019	Mathew et al.[29]	1,049	13%	0%	EFS
2020	Aida et al.[128]	895	45%	43%	FP
2020	Honzawa et al.[129]	255	32%	39%	KCL
2020	Kehler et al.[27]	2,322	28%	54%	25-Item FI
2020	Lutz et al.[28]	243	30%	30%	Modified FP
2020	Nozaki et al.[131]	387	-	54%	Modified FP
2021	Mudge et al.[26]	256	-	57%	41-Item FI
2021	Nishitani-Yokoyama et al.[125]	102	34%	34%	KCL
2021	Ushijima et al.[127]	89	62%	25%	FP
2022	Pandey et al.[132]	2,130	-	59%	36-Item FI

N = sample size, FP = Frailty Phenotype, KCL = Kihon Checklist, FI = Frailty Index, EFS = Edmonton Frailty Scale

Beyond challenges to CR referral and enrolment, frailty may affect the delivery and effectiveness of the CR core components.[62] For example, the initial assessment (physical examination and stress test) should consider patient's vulnerability and level of risk. Exercise programs tailored for frail older adults improve physical function, quality of life, and reduce disability.[143] Thus, subsequent CR exercise interventions should be individualized according to assessed physical function and disability.[62,144] Furthermore, any pharmacological treatments delivered in CR should consider frailty's impact on drug pharmacokinetics, pharmacodynamics, toxicity, and therapeutic efficacy;[145] the risk for iatrogenesis is greater in frail older adults.[146] Specifically, the degree of frailty can affect how individuals respond to cardiovascular medications. For instance, a secondary

analysis of clinical trial data showed that an anti-coagulant (edoxaban) was ineffective for severely frail participants.[147]

2.6.1 Frailty Improvements from Cardiac Rehabilitation

CR is well-equipped to contend with the many complexities of frailty. As previously mentioned, multicomponent interventions can reverse frailty or prevent its progression.[21–25] CR is also a multicomponent intervention, one that is personalized, comprehensive, and continuously evolving based on growing evidence. Completion of CR can improve frailty (Table 2.3).[26–30] Kehler et al.[27] showed that participation in a 3-month CR programme reduced frailty (measured by FI) in at least 65% of patients. Mudge et al.[26] showed that mean FI improved by 0.03 (95% CI 0.02–0.04, $p < 0.001$) at 6-months after CR admission. Lutz et al.[28] showed that more than 20% of patients improved their frailty phenotype status. Mathew et al.[29] and Fonteles Ritt et al.[30] showed that people who attend CR experienced improvements in their Edmonton Frailty Scale scores after completing the programme. Importantly, Kehler et al.[27] and Mudge et al.[26] found that the frailest CR patients at admission derive higher frailty improvements upon completing their programme compared to their less frail peers.[26,27]

Table 2.3. Frailty improvements from cardiac rehabilitation participation.

Year	Author	N	Frailty Improvement	Frailty Measure
2019	Mathew et al.[29]	1,049	35.9% of patients improved	EFS
2020	Kehler et al.[27]	2,322	>65% of patients improved	25-Item FI
2020	Lutz et al.[28]	243	>20% of patients improved	Modified FP
2021	Mudge et al.[26]	256	Mean FI improved by 0.03 (95% CI 0.02–0.04, p<0.001)	41-Item FI
2021	Fonteles Ritt et al.[30]	51	Mean EFS improve from 5.4 ± 2.0 to 4.8 ± 1.9 (p=0.034)	EFS

N = sample size, EFS = Edmonton Frailty Scale, FI = Frailty Index, FP = Frailty Phenotype, CR = Cardiac Rehabilitation, CI = confidence interval.

2.6.2 Admission Frailty and Long-Term Outcomes in Cardiac Rehabilitation

Frailty status at CR admission may be important for knowing the prognosis of people who attend CR. In 2020, Kamiya et al.[148] used survival analysis to show that admission frailty (19-item FI) was associated with the composite outcome of mortality and heart failure-related hospitalization in 3,277 patients with heart failure (26% participated in CR) (Figure 2.2). In addition, Aida and colleagues[128] showed using a simplified frailty phenotype that being frail was associated with a greater risk of the composite outcome of all-cause mortality and CVD-hospitalization (HR [CI]: 3.27 [1.49-7.21], p = 0.003) when compared to being robust. Conversely, in 2021, Mudge et al.[26] analyzed data from a hospitalized population who attended CR to find that compared to a non-frail group ($0.0 \leq FI < 0.2$) the frail/very frail group ($0.2 \leq FI$) did not have increased risk for mortality or hospital readmission at 12-months. However, their analyses were limited by the low sample size (n=256) and having only used two frailty groups (frail and non-frail). These limitations motivate further investigation with larger sample sizes and more robust frailty measures (i.e., using continuous FI and/or using at least 4 FI groups). Other than the two studies described above[26,148], there is sparse evidence directly exploring how admission frailty may impact long-term adverse outcomes of people who attend CR.

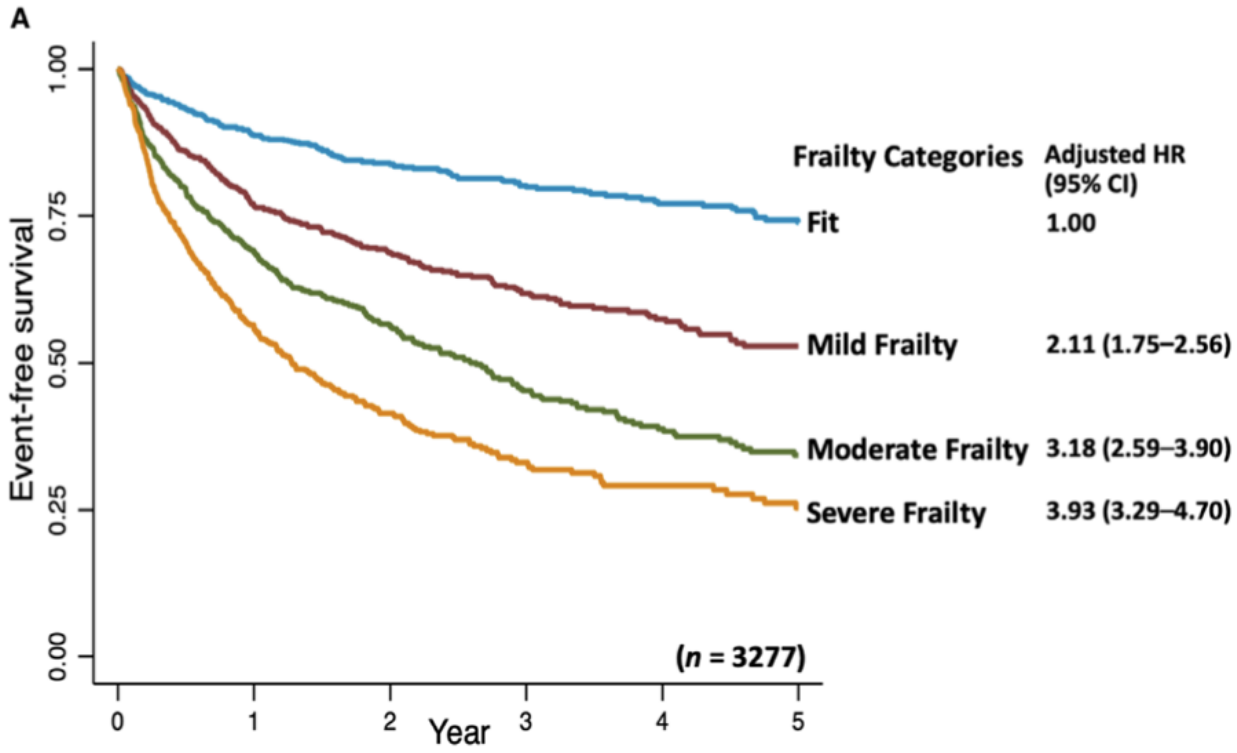

Figure 2.2. Association of admission frailty level with the composite outcome of all-cause mortality and heart failure-related hospitalization. Adapted from Kamiya et al. (2020).[148]

Of greater interest is whether frailty improvements through CR will improve long-term health outcomes such as mortality, time to hospitalizations, and frequency of hospitalizations from all-causes or causes related to CVD. Previous research has shown that the progression of frailty is associated with increased mortality risk and healthcare costs.[149–151] While the idea that frailty is reversible is emerging (for example, see section 2.4.1), there is little evidence to show that improvements in frailty can reduce adverse outcomes. Crucially, no current research has directly examined whether reversing frailty will lower the risk for long-term adverse outcomes including mortality and rehospitalizations after CR.

2.6.3 Importance of Research

Showing whether changes to frailty from CR participation benefit patient prognosis will strengthen the body of evidence advocating for the integration of frailty assessment and management in CR. Indeed, assessing and tracking the frailty status of people who attend CR may provide more personalization to CR treatments. For example, frailty status-based adjustments to physical activity, nutritional, and pharmacologic treatments can ensure that patients receive the most suitable care for their needs.

Chapter 3 Objectives and Hypotheses

3.1 Objectives

The negative impact of frailty and CVD on health outcomes is projected to increase alongside extended longevities across the globe. Furthermore, their interaction will exacerbate poor outcomes and appreciably burden healthcare systems. The main purpose of this thesis was to explore the association between frailty, frailty changes, and long-term outcomes of people who attend CR. Specifically, the objectives were to:

1. To examine the association between admission frailty and mortality, hospitalizations, and emergency department visits due to all-causes and CVDs over a 5-year follow-up period in people who attend CR.
2. To investigate the association between frailty changes during CR and mortality, hospitalizations, and emergency department visits due to all-causes and CVDs over a 5-year follow-up period in people who attend CR.

3.2 Hypotheses

I hypothesized that frailty status at admission of CR and frailty changes during CR will be associated with all-cause long-term outcomes including time to mortality, first hospitalization, first ED visit and total number of hospital visits, days in hospital, and ED visits. In addition, I expected that frailty status at admission and frailty changes during CR would be associated with mortality and hospitalizations that was due to CVD.

Chapter 4 Manuscript

Title

Association of Admission Frailty and Frailty Changes During CR with 5-Year Outcomes

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Abstract

Aims: Examine the association between 1) admission frailty and 2) frailty changes during cardiac rehabilitation (CR) with long-term outcomes including time to mortality, first hospitalization, first emergency department (ED) visit, and number of hospitalizations, hospital days, and ED visits over a 5-year follow-up.

Methods: We analyzed data from patients admitted to CR in Halifax, Nova Scotia from May 2005 to April 2015 (N=3,371). The CR programme included group-based exercise and education performed twice weekly for 12 weeks. A 25-item frailty index (FI) estimated frailty levels at CR admission and completion. FI improvements were determined by calculating the difference between admission and discharge FI. CR data were linked to administrative health data to examine 5-year outcomes (due to all-causes and CVD). Cox regression, Fine-Gray models, and negative binomial hurdle models were used to determine the association between FI and outcomes. Outcomes correspond to a 1% change in the FI.

Results: People who attend CR were 62 (SD:11) years old on average; 74% were male. Mean admission FI scores were 0.34 (0.13) which improved by 0.07 (0.09) by CR completion. Admission FI was associated with time to mortality (HRs: all-cause=1.02[95% CI 1.01,1.04]; CVD=1.03[1.02,1.05]), hospitalization (all-cause=1.02[1.01,1.02]; CVD=1.02[1.01,1.02]), and ED visit (all-cause=1.01[1.00,1.01]), and the number of hospitalizations, hospital days, and ED visits. FI improvements during CR had a protective effect regarding time to all-cause hospitalization (0.99[0.98,0.99]), but was not associated with other outcomes.

Conclusion: Frailty status at CR admission was related to long-term adverse outcomes. Frailty improvements during CR was associated with delayed all-cause hospitalization.

4.1 Introduction

Cardiovascular diseases (CVDs) accounted for a third of global deaths in 2019[1] and cost hundreds of billions of dollars to European and North American countries.[2,3,152] The prevalence of CVDs also increase with older age. Thus, in conjunction with the rising global life expectancy,[4,5] the burden of CVDs will continue to escalate. Furthermore, because CVDs rarely exist on their own, their management requires careful consideration of various other age-related health problems.[6] Variability in health outcomes at a given age means that some individuals will have more favourable prognoses from CVD than others.

Frailty quantifies the variability in health amongst people of the same age.[7] It recognizes that some people accumulate health problems more slowly while others rapidly develop health problems as they get older. Frailty is more common in those with CVDs than in those without (50-54% vs 14-24%).[13,14] Importantly, people who are frail have an increased risk of CVD morbidity and mortality compared to those who are not.[15] Thus, to effectively manage and treat patients with frailty and CVD, an individualized approach addressing both frailty and CVD is required.

Cardiac rehabilitation (CR) is a comprehensive, multidisciplinary CVD care model for patients who have recently experienced an adverse cardiovascular event.[16–20] CR is multidimensional and implements nutritional counseling, risk factor modification, psychosocial management, patient education, and exercise training to improve patient outcomes and quality of life. The benefit of multicomponent interventions for improving frailty[21–25] means that CR may be well-equipped to address both CVD and frailty. In fact, there is a call to action by the European Association of Preventive Cardiology to address

frailty in CR.[62,153,154] Indeed, the global ageing climate require clinicians, researchers, and policy makers to better understand the implications of frailty in the care of older patients living with CVD. For instance, the use of frailty tools can promote more appropriate allocation of limited healthcare resources such as CR.

While most patients of varying ages enter CR with high degrees of frailty,[26–29,125–131] completion of CR is associated with frailty improvements.[26–30] However, there is sparse evidence showing how frailty at CR admission will impact long-term outcomes such as mortality and hospitalizations. Importantly, there are no previous investigations about whether frailty improvements during CR are associated with such long-term outcomes.

Thus, the purpose of this paper was to explore the association between frailty at CR admission, frailty changes during CR, and long-term outcomes of people who attend CR. Long-term outcomes include time to mortality, first hospitalization, first emergency department (ED) visit, and number of hospitalizations, hospital days, and ED visits over a 5-year follow-up due to both all-causes and CVDs. Specifically, the objectives were to 1) examine the association between admission frailty and long-term outcomes and to 2) investigate the association between frailty changes during CR and long-term outcomes.

4.2 Methods

4.2.1 Design

This study was a secondary analysis of data from patients who enrolled in a CR programme called Hearts and Health in Motion offered within Nova Scotia Health at a single center in Halifax, NS, Canada. This data contains information from participants who previously enrolled in the CR programme from 1995 to 2015. Data from 2005 to 2015 was used for the current project due to the lack of information required to construct the FI in the data from 1995 to 2004. All participants experienced an adverse cardiovascular event (e.g., a heart attack, cardiac surgery, or heart failure) prior to their CR referral. Data collected as part of the CR programme were included in a Cardiac Rehabilitation Database and were linked to administrative health databases to examine outcomes. This study was approved by the Nova Scotia Health research ethics board (REB identifier number: #1023328).

4.2.2 Cardiac Rehabilitation

The CR programme was a group-based 12-week exercise and education programme delivered at a single center in Halifax, Canada. CR staff included a medical director, a programme lead, nurses, dieticians, and physiotherapists with a 7:1 patient-to-staff ratio. The goal of this CR programme was to improve CVD risk factors by modifying health behaviours including physical activity, diet, and smoking. Patients received two weekly center-based exercise sessions (60 min duration) and one weekly education session. The exercise sessions were led by a licensed physiotherapist and individualized according to exercise stress testing and prescription; each session included warm-ups and cool-downs, 40 minutes of continuous or interval aerobic training

(treadmill, cycling, or arm ergometer), and 10 minutes of resistance training. Aerobic training progressed by increasing treadmill speed or incline, or ergometer resistance while maintaining revolution speed. Resistance training focused on major muscle groups (legs, back, chest, shoulders, core) with the use of body weight exercises (wall push-ups, sit-to-stand chair exercises, and leg lifts), resistance bands, and dumbbells. Patients were also prescribed an individualized home-based CR programme consisting of moderate aerobic and resistance training; frequency and duration were adjusted according to individual needs. CR staff provided group-based education sessions focusing on how to manage CVD risk factors through health behaviour changes to diet, exercise safety, and medication management. Completion of CR was defined as completion of the outtake CR assessment appointment at 12 weeks after admission.[155]

4.2.3 Frailty Index and Frailty Index Change

We used a previously validated FI from Kehler et al.[27] in the same database. This FI was developed following standard protocols[48] from routinely collected CR data at both admission and completion (12 weeks after admission). The FI included 25 variables in multiple domains: cardiovascular biomarkers, symptoms, quality of life, cardiovascular fitness, body composition, and diet. The full list of variables, coding, and prevalence is available in Table S4.1. Further information on FI score calculations are available in Section 4.6.1.3. Patients who had less than 30% (8/25) of variables missing were considered to have sufficient data for calculating a FI score.[156] For illustrative purposes, the FI was divided into five groups: <0.2 = non-frail/very mildly frail, $0.2 \leq FI < 0.3$ = mildly frail, $0.3 \leq FI < 0.4$ = moderately frail, $0.4 \leq FI < 0.5$ = severely frail, and $0.5 \leq FI$ = very severely frail.

A continuous value for frailty change was calculated by subtracting the CR admission FI by the CR completion FI; a positive FI change value represents an improvement in FI from CR admission to CR completion (e.g., $0.20_{admission} - 0.10_{completion} = 0.10$; FI improved by 0.10). Conversely, a negative FI change represents a worsening in FI from CR admission to CR completion. Only patients who completed CR had available FI change data. Clinically meaningful changes in FI, defined as a change of at least 0.03 in the FI,[157,158] were used for descriptive purposes. The categories used were improvement - FI decreased by at least 0.03; stable - FI changed by less than 0.03, worsened - FI increased by at least 0.03.

4.2.4 Linking to Administrative Databases

To investigate associations of admission frailty and frailty changes from CR with long-term adverse outcomes, we linked the Cardiac Rehabilitation Database (May 1st, 2005 to April 30th, 2015) with several health administrative databases managed by Health Data Nova Scotia (Figure S4.1), including the Canadian Institutes for Health Information's (CIHI) Discharge Abstract Database (DAD – hospital use; linked from Jan 1st, 2009 to December 1st, 2020), CIHI's National Ambulatory Care Reporting System (NACRS – emergency services use; linked from April 1st, 2011 to December 1st, 2020) Metadata, and Vital Statistics Canada (mortality; linked from May 1st, 2005 to December 31st, 2019). Due to unavailable DAD data before Jan 1st, 2009, and NACRS data before April 1st, 2011, we excluded from analyses with DAD and NACRS data patients who were admitted to CR before Jan 1st, 2009, and April 1st, 2011, respectively. Our application to link the above databases was approved by Health Data Nova Scotia on

June 4th, 2021. Table S4.2 provides a list of all outcomes used and their associated database.

4.2.5 Outcomes

All outcomes were censored at a maximum follow-up of 5 years (Table S4.2). A small subsample of participants (n = 102/3,371) who began CR after Dec 31st, 2014, had a maximum follow-up period of less than 5 years (range: 4.7 to 5.0 years).

4.2.5.1 Mortality

Time to mortality from CR admission was determined using the Vital Statistics database and the Cardiac Rehabilitation Database. CVD as the underlying cause of mortality was discerned from all-cause mortality by using the International Classification of Diseases 10th Revision (ICD-10) codes I00 to I99. Mortality status was censored at a maximum of 5 years after CR admission.

4.2.5.2 Hospitalization Data

The outcomes of time to first hospitalization from CR admission, total number of hospital days, and total number of hospitalizations were determined using the CIHI Discharge Abstract Database. The time to first hospitalization outcome was censored at 5 years after CR admission. The total number of hospital days and hospitalizations were summed from the beginning of CR admission to a maximum of 5 years post-CR admission. Patients who did not have a hospital stay in this period had their total number of hospital days and hospitalizations set to zero. The CIHI Discharge Abstract Database identifies the ICD-10 code that represent the *Most Responsible Diagnosis* (MRDx) for each hospitalization. This MRDx was determined to have been responsible for the

greatest portion of the patient's length of stay. All ICD-10 codes from I00 to I99 were used to discern CVDs hospitalizations from all-cause hospitalizations.

4.2.5.3 Emergency Department Data

The outcomes of time to first ED visit from CR admission and total number of ED visits were determined using the CIHI National Ambulatory Care Reporting System. The time to first ED visit outcome was censored at 5 years after CR admission. The total number of ED visits were summed from the beginning of CR admission to 5 years post-CR admission. Patients who did not have a hospital stay had their total number of ED visits set to zero. ED visits due to CVDs were not explored due to high levels of missingness (44%) in the cause of ED visit variable available in this database.

4.2.6 Data Analysis

Summary statistics were presented as mean (standard deviation) or frequency (%). Admission characteristics were compared across admission FI levels using t-tests (continuous descriptors) and chi-square tests (categorical descriptors). Various regression models were used to examine the association between admission FI and FI change with mortality, hospitalizations, and emergency department visits in people who attend CR. We used Cox regression models for time to all-cause mortality. To account for mortality from other causes as a competing risk for CVD-related mortality and all-cause mortality as a competing risk for hospitalizations and ED visits, Fine-Gray[159] competing risk models were used for time to CVD-related mortality, time to all-cause and CVD-related first hospitalization, and time to all-cause ED visit analyses. Schoenfeld residuals with graphical diagnostics were performed to assess the proportional hazards assumption. Negative binomial hurdle regression models were used for all-cause and CVD-related

total hospital length of stay, all-cause and CVD-related total number of hospital visits, and all-cause total number of ED visits to account for the zero-inflated nature of hospital-based outcomes (Figure S4.2). To account for death as a competing risk for hospitalizations and ED visits, we excluded patients who died within the 5-year follow-up from CR admission in negative binomial hurdle regression models (n_{died} = 157/2,422 [6.5%] for DAD data, n_{died} = 100/1,602 [6.2%] for NACRS data for objective 1; n_{died} = 72/1,469 [4.9%] for DAD data, n_{died} = 42/996 [4.2%] for NACRS data for objective 2). Previous literature suggest interactions between admission FI, age, and sex, for mortality outcomes, therefore we checked for these interactions using a 3-way interaction term, and we also checked for 2-way admission FI by sex, admission FI by age, admission FI by referring diagnosis interactions if the 3-way interaction was not significant (objective 1). The same approach was used for checking interactions in the frailty change models (objective 2), with an additional interaction term for FI change by percent exercise sessions. We also explored non-linear relationships (quadratic and cubic) between admission FI and FI change with all outcomes in additional models. All analyses were adjusted for sex, age, referring diagnosis, exercise sessions attended, education, employment, smoking status, marital status, year of CR, and CR completion. Models with admission FI did not adjust for exercise sessions attended. Models with FI change did not adjust for CR completion as all patients with a valid FI change measure completed CR. An alpha value of less than 0.05 was considered as statistically significant. Cell sizes ≤ 5 were suppressed in compliance with Health Data Nova Scotia policy. The statistical software *'R'* version 4.0.5 was used to perform all analyses.

4.3 Results

4.3.1 Participant Characteristics

Of 3,982 patients who enrolled in CR, 3,371 (84.7%) patients had sufficient data for calculating a FI at CR admission. Sample sizes for mortality, hospital, and ED outcomes varied due to different time periods for which each dataset was available for linkage (Figure 4.1). Patients with available CR admission FI were 61.9 (SD: 10.7) years old on average and 74.2% (n=2,503) were male (Table 4.1). The greatest proportion of patients attended CR from 2009 to 2012 (45.5%). On average, patients attended nearly 80% of all exercise sessions prescribed in CR. The mean admission FI was 0.34 (0.13). The most common education level attained was technical college (31.8%) and the most common employment status was retired (45.6%). The most common referring diagnoses to CR were coronary artery disease (26.7%) and myocardial infarction (28.3). For patients admitted to CR, a lower education level, unemployment, long-term disability, current or former smoking, lower exercise sessions attended, and a referring diagnosis of coronary artery disease were associated with higher frailty levels (Table 4.1). From 3,371 patients who had a FI at CR admission, 2,127 (63.1%) patients completed CR and had sufficient data for calculating a FI at CR completion (Figure 4.1). For these patients, the FI improved by 0.07 (0.09) on average from CR admission to completion (Table S4.3). 66.7% (n=1,418) of patients had a clinically meaningful improvement in FI during CR (Table S4.4).

4.3.2 Frailty at CR Admission and Adverse Outcomes

There were no significant 3-way, or 2-way interactions found between admission FI, age, and sex ($p>0.05$) for all outcomes considered. Generally, patients who were

frailer at CR admission had higher mortality rates (Figure 4.2), number of hospitalizations, number of days in hospital, and number of ED visits regardless of the cause (Figure 4.3).

4.3.2.1 Mortality

The 5-year all-cause and CVD-related mortality rates were 6.9% (232/3,371) and 2.8% (94/3,371), respectively (Table S4.5 and Figure 4.2). CVD mortality rates increased according to admission frailty status, from 1.3% in patients who were very non-frail/mildly frail (FI<0.2) to 6.5% in those who were very severely frail (FI>0.5) (Figure 5.1). A 0.01 higher admission FI was associated with a 2% (95% CI: 1-4%) greater risk of all-cause mortality and 3% (2-5%) greater risk of CVD mortality (Table 4.2 and Figure 4.4A).

4.3.2.2 Hospitalization

43.3% (1,049/2,422) and 19.4% (471/2,422) of patients were hospitalized at least once within 5 years of CR admission due to all-causes and CVDs, respectively (Table S4.5). The total number of all-cause and CVD hospitalizations were generally greater in patients who were frailer at CR admission. For instance, only 28.6% of non-frail/very mildly frail (FI<0.20) patients were hospitalized at least once compared to almost double the proportion (54.0%) in patients who were very severely frail (FI>0.5). A 0.01 higher admission FI was associated with a 2% (1-2%) greater risk of all-cause and CVD hospitalization (Table 4.2 and Figure 4.4C). Similarly, a 0.01 higher admission FI was associated with a 2% (1-3%) greater number of all-cause and 2% (0-4%) greater number of CVD hospitalizations over 5 years of follow-up (Table 4.2).

4.3.2.3 Days in Hospital

The mean (SD) number of days spent in the hospital was 7.3 (22.3) and 2.3 (9.2) days due to all-causes and CVDs, respectively. Approximately 20.8% (504/2,422) and 9.2% (222/2,422) of all CR patients spent 7 or more days (in 1 or multiple visits) in the hospital in the 5 years after their CR admission due to all-causes and CVDs, respectively (Table S4.5). Patients who were frailer at CR admission typically spent a greater number of days in hospitals regardless of the cause (Figure 4.3C). A 0.01 higher admission FI was associated with a 1% (1-3%) greater number of days spent in hospitals due to all-causes over the follow-up period (Table 4.2). FI at CR admission was not significantly associated with the number of days in the hospital due to CVD.

4.3.2.4 ED Visits

Four in five CR patients had at least one visit to the ED in the 5-year follow-up (Table S4.5). About one-third of patients living with severe or very severe frailty (FI>0.4) visited EDs at least 7 times during the follow-up period, compared to less than 10% for patients in the non-frail/very mildly groups (FI<0.2). A 0.01 higher admission FI was associated with 1% (0-1%) greater risk of visiting the ED (Table 4.2 and Figure 4.4E).

4.3.3 Frailty Change During CR and Adverse Outcomes

FI change analyses were done on participants who completed CR (63.1%; 2,127/3,371). There were no significant 3-way, or 2-way interactions found between FI change, age, sex, and exercise sessions ($p>0.05$) for all outcomes considered.

4.3.3.1 Mortality

Patients who had FI improvements during CR (FI reduced by at least 0.03) had the lowest mortality rates (all-cause=4.7%; CVD=1.8%) compared to patients whose FI

remained stable (FI changed by less than 0.03) (all-cause=6.3%; CVD=2.2%) or worsened (FI increased by more than 0.03) (all-cause=6.7%; CVD=2.7%) (Figure 4.2B). Even so, improvements in FI from CR admission to completion were not significantly associated with lower risks of all-cause and CVD mortality (Table 4.2 and Figure 4.4B).

4.3.3.2 Hospitalizations

Patients whose FI improved during CR had fewer all-cause hospitalizations in the follow-up period than those whose FI remained stable or worsened (Figure 4.3B). A 0.01 higher improvement in FI from CR admission to completion was associated with a 1% (1-2%) lower risk of all-cause hospitalization but not CVD hospitalization (Table 4.2 and Figure 4.4D). In addition, improvements in FI during CR were not significantly associated with the number of hospitalizations due to all-causes or CVDs (Table 4.2).

4.3.3.3 Days in Hospital

Patients whose FI improved during CR had fewer hospital days due to all-causes than those whose FI remained stable or worsened (Figure 4.3D). For example, 16.2% of patients whose FI improved spent at least 7 days in the hospital versus 23.7% in patients whose FI worsened (Figure 4.3D). There were little differences across FI change categories for hospitals days due to CVDs (Figure 4.3D). With the hurdle regression models, improvements in FI were not associated with the total number hospital days due to all-causes or CVDs over the 5-year follow-up period (Table 4.2).

4.3.3.4 ED Visits

17.8% of patients whose FI improved during CR had at least 7 visits to the ED compared to 24.1% in patients whose FI worsened (Figure 4.3F). Changes in FI during CR were not significantly associated with the risk of visiting the ED (Table 4.2 and

Figure 4.3F). In addition, changes in FI during CR were not significantly associated with the total number of ED visits over the 5-year follow-up period (Table 4.2).

4.3.4 Non-Linear Relationships Between FI and Outcomes

Quadratic and cubic terms were included in additional models for both objectives 1 (admission FI) and 2 (FI improvements). Although several models demonstrated significant quadratic or cubic relationships ($p<0.05$) between FI and outcomes (Table S4.6 and Table S4.7), the effect sizes were consistently small (HRs, IRRs, ORs < 1.0001) – at least 100-fold smaller than the lowest relative risk ratio for linear terms. The impact of these non-linear terms was negligible and were thus not presented in the primary results.

4.3.5 Sensitivity Analysis

We found that the 2-way admission FI and FI change interaction with referring diagnosis was significant for several models (Table S4.8). The referring diagnosis that interacted with frailty the most frequently was percutaneous coronary interventions (PCIs). Since patients who recently underwent a PCI (treatment) may follow a distinct recovery frailty trajectory from other referring diagnoses,[160] we re-analysed all models and excluded patients who were referred to CR due to a PCI ($n_{excluded}$ = 516/3,371 [15.3%] from admission FI models and 319/2,127 [15.0%] from FI change models). Results regarding admission FI mirrored the main analysis. Models with FI change showed that while the association between FI change and the risk of all-cause hospitalization was no longer significant ($p=0.072$ without PCI, $p=0.014$ with PCI), the p-value was still relatively small.

4.4 Discussion

4.4.1 Summary of Results

For objective 1, we demonstrated that higher FI at CR admission was associated with a greater 5-year risk of mortality and hospitalization due to all-causes and CVDs, and ED visits due to all-causes. In addition, higher FI at CR admission was also associated with a greater number of hospitalizations due to all-causes and CVDs, and greater numbers of days in hospital and ED visits due to all-causes over a 5-year follow-up (Table 4.2 and Figure 4.4). For objective 2, we demonstrated that FI improvements during CR was associated with a lower 5-year risk of all-cause hospitalization, but not with other outcomes (Table 4.2 and Figure 4.4).

4.4.2 Admission FI and 5-Year Outcomes

The mortality and hospitalization results are consistent with a recent secondary analysis of the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training; 3-month long, 3 times per week aerobic exercise training programme) trial[132] which found that a higher baseline FI score was associated with greater risk of mortality and hospitalization due to all-causes and CVDs (median follow-up 2.9 years). However, another secondary analysis[26] of the EJECTION-HF (Exercise Joins Education, Combined Therapies to Improve Outcomes in Newly Discharged HF patients) trial showed that baseline FI was not associated with the 1-year composite outcome of all-cause mortality or all-cause hospitalization for patients in a CR programme. These differences may be attributable to the 1) relatively small sample size of the EJECTION-HF study versus the HF-ACTION and the current study (278[26] versus 2,130[132] and 3,371 in the current study), 2) shorter follow-up time for outcome (1 year[26]

versus 2.9 years[132] and 5 years in the current study), and 3) exclusive recruitment of patients discharged from the hospital due to heart failure in the EJECTION-HF study. In addition, two CR studies in Japan also showed that admission frailty (abbreviated frailty phenotype[128], 19-item FI[148]) was associated with the composite of all-cause mortality and CVD hospitalization.[128,148]

To our knowledge, we are the first to demonstrate that admission frailty status in a CR setting was associated with the number of all-cause and CVD hospital visits, all-cause days in hospital, and all-cause ED visits over a 5-year follow-up (Table 4.2 and Figure 4.4). Our work adds to a body of literature which shows that FI scores predict the number of hospital admissions and days in hospital in a nursing home setting,[161] community-dwelling populations,[162] and adult home-care patients.[163] Indeed, a greater burden of frailty at CR admission translates to more time spent in care facilities and thus greater use of healthcare resources.

Overall, these results outline the importance of considering the degree of frailty in the CR setting as opposed to viewing frailty as present or absent.[7] Not only was frailty important for understanding the risk of several long-term outcomes, but incremental differences in admission frailty levels represented valuable information for understanding long-term clinical outcomes (Table 4.2). In addition, the significant association of CR admission frailty status with both all-cause and CVD outcomes, independent of several prognostic factors such as sex, age, referring diagnosis, education, employment, smoking status, and marital status, positions frailty as a key indicator of both overall and cardiovascular health. Indeed, the pathophysiology of frailty and CVDs are intertwined[72–76,164] in ageing, physical inactivity, accumulation of chronic conditions, and inflammation

- all of which results in reduced physiological reserves and ability to respond to stressors. Upon admission to CR, the frailest patients are predisposed to health complications which, in combination with CVDs and a diminished ability to recover from their disease, results in poor long-term outcomes demonstrated by our findings.

4.4.3 FI Change and 5-Year Outcomes

We are the first to show that FI improvements during a 12-week CR programme were associated with delayed time to all-cause hospitalization independent of admission FI (Table 4.2 and Figure 4.4). This is consistent with data showing that a one-point increase in the frailty phenotype was related to a 2.1% greater rate of hospital usage in older adults.[165] Our study, along with others,[128,132,148] outline the prognostic value of frailty status at CR admission. Indeed, if high frailty burdens equate to reduced physiological reserves and heightened vulnerability to stressors, then reductions in the frailty burden should translate into greater multi-system resilience. Such changes may reflect improvements in overall health, physical function, and quality of life. Patients whose health status changed during CR may experience corresponding changes in their healthcare use patterns – greater improvements in frailty may delay the patient's next hospitalization. Even so, FI changes were not associated with the total number of hospitalizations, hospital days, and ED visits due to any cause during the 5-year follow-up (Table 4.2). While greater improvements in frailty may delay the next all-cause hospitalization, the frequency of healthcare usage over 5 years was not dependent on frailty changes. Readmittances to hospitals may be inevitable for patients with CVDs who require follow-up visits as part of routine care for their condition. For instance, severely frail older adults who received comprehensive geriatric assessments and early

rehabilitation had lower rates of rehospitalization than usual care 1-month after discharge, but not 3-months after discharge.[166]

FI changes were also not associated with mortality, regardless of cause. These findings are inconsistent with longitudinal studies in community-dwelling populations which have shown that increases in FI were associated with greater mortality risk.[149,167,168] However, these differences may be due to the duration over which FI changes took place. Stolz et al.[167] and Shi et al.[149] used 1-year changes and Thompson et al.[168] used 4.5-year changes; here we used 12-week change from CR. Significant results with mortality may be partially driven by the increasing trend of FIs over time that are typically seen in older adults.[169–171] In addition, as frailty is dynamic and likely susceptible to measurement errors,[167] a longer interval between frailty measures may offer more stable estimates which can be explored through frequent, long-term serial assessments of frailty status during and after completion of CR.

Our observation that incremental frailty changes in a 12-week CR programme only informs the risk of all-cause hospitalization, but not other long-term outcomes, suggests that a more nuanced approach is required when evaluating frailty changes in relation to long-term outcomes. To better understand the relationship between FI change during CR and long-term outcomes, future studies need to consider if FI changes were due to a combination of the beneficial effects of a multicomponent CR programme, natural trajectory of illness, changes to CVD treatment, or due to a new CVD or other diagnosis that could either acutely increase their FI or prove fatal. Clinical trials show that exercise and multi-component interventions similar to CR can reduce frailty levels;[79,172] a number of cohort studies show that frailty improved during CR.[26–30] In

addition, patients who recently received treatment for CVD (percutaneous coronary interventions and coronary artery bypass graft) exhibit U-shaped frailty trajectories,[160] meaning they improve initially but worsen after 6-months post-treatment which is consistent with our population where 66.7% of patients improved in frailty during CR (Table S4.4). However, we did not monitor longer-term change in frailty as in the mentioned study. In this CR population, the dynamism and reactivity of frailty to multiple factors that may improve or reduce frailty after people complete CR can obscure the interpretation about the relationship between FI change during CR and long-term outcomes.

4.4.4 Feasibility of Frailty Assessments in CR

Whether frailty assessments can be feasibly implemented in CR is an important area of inquiry. The National Health Service in England employs an algorithm to calculate an electronic frailty index (eFI) automatically for primary care patients using routinely collected data.[173] The eFI aids physicians to make clinical decisions, allowing for more individualized treatment plans and management strategies. Routine frailty assessments like the eFI in CR could allow healthcare decision makers to better understand the cost-benefit when designing and funding future CVD care programmes.[174,175] Machine learning approaches to identify frailty are also emerging in Canadian primary care.[176] Machine learning algorithms can take advantage of the constantly evolving big data climate to accurately estimate frailty in ways that traditional statistical models cannot. Future researchers could monitor developments in machine learning and make efforts to integrate such practices to CR. These efforts may help

improve the frailty case definition in the CR context which can promote better quality indicator reporting, quality improvements, and surveillance of patient health.

4.4.5 Limitations

Our study has several limitations. First, the DAD and NACRS databases only contained hospital and ED data from one of four areas within Nova Scotia Health thus missing data of visits in hospitals and emergency departments from three regions. Second, there were large numbers of missing data (17.6%; 593/3,371) for the exercise sessions attended variable in the objective 1 sample, thus we were not able to control for any dose-response effect of CR exercise training on long-term outcomes for objective 1. Third, it was unclear exactly how long patients waited from their automatic CR referral to CR admission as referral date was not available. However, a report on a similar CR population (n=4,443 from 1999-2012) in Halifax, NS indicated that the median time from referral to enrolment was 27 days.[177] Fourth, although we found some significant 2-way interactions between admission frailty, frailty change, and referring diagnosis, (Table S4.8) we were unable to explore each diagnosis independently further due to low sample sizes in each diagnosis category which only worsens when using the lower sample sizes from DAD and NACRS. Fifth, our study was not a randomized trial. However, while a true control group might be informative for understanding frailty changes caused by CR, it would be unethical as usual care for CVD populations involve referral to CR.

Lastly, the FI used in the current study contained 25 items, 5 fewer than the minimum recommended by standard procedures.[48] At 30 items or more, the estimates of mortality are more stable. Even so, the creators of the FI reported that a minimum of 20 items may be acceptable[178] and that estimates are only unstable when there are fewer than

10 items.[48] Despite this, a FI with a greater number of items may yield different results, particularly for the FI change models as FI change calculations are affected by variance in two points of FI measures as opposed to only one in the admission FI models.

4.4.6 Conclusion

Here, we highlight the importance of frailty status at admission of a CR programme for informing the 5-year risk of mortality, hospitalization, and ED visit, as well as the total number of hospital visits, hospital days, and ED visits over 5 years post-CR. In addition, incremental frailty improvements during CR were related to a lower risk of hospitalization regardless of admission frailty status. Future work should investigate the benefits of targeting frailty reductions as an additional component of CR.

4.5 Tables and Figures

4.5.1 Tables

Table 4.1. Admission characteristics of people who attend cardiac rehabilitation by admission FI.

	Full Sample	**Frailty Levels**				
		<0.2	0.2-0.3	0.3-0.4	0.4-0.5	0.5+
N (%)	3,371 (100)	529 (15.7)	872 (25.9)	964 (28.6)	650 (19.3)	356 (10.6)
Age, mean (SD; range)	61.9 (10.7; 21-94)	62.2 (10.7; 21-93)	62.0 (10.8; 23-88)	62.7 (10.6; 26-90)	60.8 (10.9; 30-94)	60.7 (9.8; 35-86)
Sex, n male (%)	2,503 (74.2)	424 (80.2)	681 (78.1)	724 (75.1)	439 (67.5)	235 (66.0)
Education, n (%)						
Less than Grade 12	709 (21.0)	66 (12.5)	149 (17.1)	202 (21.0)	171 (26.3)	121 (34.0)
Grade 12/GED	605 (17.9)	93 (17.6)	153 (17.6)	195 (20.2)	111 (17.1)	53 (14.9)
Technical College	1073 (31.8)	157 (29.7)	263 (30.2)	296 (30.7)	232 (35.7)	125 (35.1)
Bachelor's Degree	626 (18.6)	126 (23.8)	196 (22.5)	173 (18.0)	85 (13.1)	46 (12.9)
Post-Graduate Education	358 (10.6)	87 (16.5)	111 (12.7)	98 (10.2)	51 (7.9)	11 (3.1)
Employment, n (%)						
Long-Term Disability	223 (6.6)	13 (2.5)	30 (3.4)	54 (5.6)	72 (11.1)	54 (15.2)
Unemployed	89 (2.6)	13 (2.5)	16 (1.8)	26 (2.7)	21 (3.2)	13 (3.7)
Part-Time	186 (5.5)	27 (5.1)	61 (7.0)	56 (5.8)	32 (4.9)	10 (2.8)
Full-Time	712 (21.1)	137 (25.9)	224 (25.7)	181 (18.8)	112 (17.2)	58 (16.3)
Retired	1538 (45.6)	254 (48.0)	398 (45.6)	453 (47.0)	279 (42.9)	154 (43.3)
Other	623 (18.5)	85 (16.1)	143 (16.4)	194 (20.1)	134 (20.6)	67 (18.8)
Smoking Status, n (%)						
Non-Smoker	997 (29.6)	224 (42.3)	267 (30.6)	265 (27.5)	163 (25.1)	78 (21.9)
Former Smoker	2,007 (59.5)	264 (49.9)	508 (58.3)	607 (63.0)	407 (62.6)	221 (62.1)
Current Smoker	367 (10.9)	41 (7.8)	97 (11.1)	92 (9.5)	80 (12.3)	57 (16.0)
Marital Status, n (%)						
Divorced/Separated	308 (9.1)	35 (6.6)	66 (7.6)	84 (8.7)	72 (11.1)	51 (14.3)
Widowed	226 (6.7)	20 (3.8)	62 (7.1)	67 (7.0)	50 (7.7)	27 (7.6)

Single	256 (7.6)	32 (6.1)	63 (7.2)	68 (7.1)	56 (8.6)	37 (10.4)
Married/Living with a Partner	2,581 (76.6)	442 (83.6)	681 (78.1)	745 (77.3)	472 (72.6)	241 (67.7)
Referring Diagnosis, n (%)						
Coronary Artery Disease	900 (26.7)	122 (23.1)	208 (23.9)	266 (27.6)	183 (28.2)	121 (34.0)
Percutaneous Coronary Intervention	516 (15.3)	80 (15.1)	141 (16.2)	132 (13.7)	104 (16.0)	59 (16.6)
Cardiac Surgery	629 (18.7)	119 (22.5)	193 (22.1)	178 (18.5)	95 (14.6)	44 (12.4)
Heart Failure	222 (6.6)	23 (4.4)	48 (5.5)	57 (5.9)	60 (9.2)	34 (9.6)
Myocardial Infarction	955 (28.3)	158 (29.9)	241 (27.6)	289 (30.0)	183 (28.2)	84 (23.6)
Other	149 (4.4)	27 (5.1)	41 (4.7)	42 (4.4)	25 (3.9)	14 (3.9)
Year of CR Admission, n (%)						
2005-2008	949 (28.1)	155 (29.3)	232 (26.6)	253 (26.2)	190 (29.2)	119 (33.4)
2009-2012	1,533 (45.5)	227 (42.9)	384 (44.0)	464 (48.1)	293 (45.1)	165 (46.4)
2013-2015	889 (26.4)	147 (27.8)	256 (29.4)	247 (25.6)	167 (25.7)	72 (20.2)
Exercise Sessions Attended, % (SD)	79.5 (27.4)	84.6 (22.6)	81.7 (25.7)	80.72 (26.7)	73.9 (30.4)	70.2 (32.78)
Admission FI, mean (SD)	0.34 (0.13)	0.15 (0.04)	0.26 (0.03)	0.35 (0.03)	0.45 (0.03)	0.57 (0.03)

FI = frailty index, SD = standard deviation.

Table 4.2. Association between admission FI, FI change, and outcomes measures up to 5 years after cardiac rehabilitation admission.

Outcome	Cause	**Admission FI** Per 0.01 greater admission FI		**FI Change** Per 0.01 improvement in FI	
		HR or SHR (CI)		HR or SHR (CI)	
Time to Mortality (n = 3,371)	All-Cause	**1.02 (1.01,1.04)**		0.98 (0.96, 1.01)	
	CVD	**1.03 (1.02,1.05)**		0.97 (0.94, 1.01)	
Time to First Hospitalization (n = 2,422)	All-Cause	**1.02 (1.01,1.02)**		**0.99 (0.98,0.99)**	
	CVD	**1.02 (1.01,1.02)**		1.00 (0.99,1.01)	
Time to First ED Visit (n = 1,602)	All-Cause	**1.01 (1.00,1.01)**		0.99 (0.98,1.01)	
		IRR (CI)	OR (CI)	IRR (CI)	OR (CI)
Number of Hospitalizations (n = 2,422)	All-Cause	**1.02 (1.01,1.03)**	**1.02 (1.02,1.03)**	0.99 (0.98,1.01)	**0.98 (0.97,0.99)**
	CVD	**1.02 (1.00,1.04)**	**1.02 (1.01,1.03)**	0.99 (0.96,1.02)	1.00 (0.98,1.02)
Number of Hospital Days (n = 2,422)	All-Cause	**1.01 (1.01,1.03)**	**1.02 (1.02,1.03)**	0.98 (0.97,1.01)	**0.98 (0.97,0.99)**
	CVD	1.01 (0.99,1.02)	**1.02 (1.01,1.03)**	1.00 (0.97,1.03)	1.00 (0.98,1.02)
Number of Times in ED (n = 1,602)	All-Cause	**1.02 (1.02,1.03)**	1.00 (0.99,1.01)	0.99 (0.98,1.01)	0.98 (0.96,1.01)

Outcomes correspond to 0.01 greater admission FI or FI improvement (+0.01 change in FI indicates improvement in FI from admission to completion of cardiac rehabilitation). All models were adjusted for sex, age, referring diagnosis, education, employment, smoking status, marital status, year of cardiac rehabilitation. The admission FI model was also adjusted for completion of cardiac rehabilitation status and the FI change model for admission FI score and exercise sessions attended. There were no significant three-way and two-way interactions. Bolded text represents significance at < 0.05. CI = 95% confidence interval, CVD = cardiovascular disease, ED = emergency department, FI = frailty index, HR = hazard ratio, IRR = incidence rate ratio, OR = odds ratio, SHR = sub-distributional hazard ratio.

4.5.2 Figures

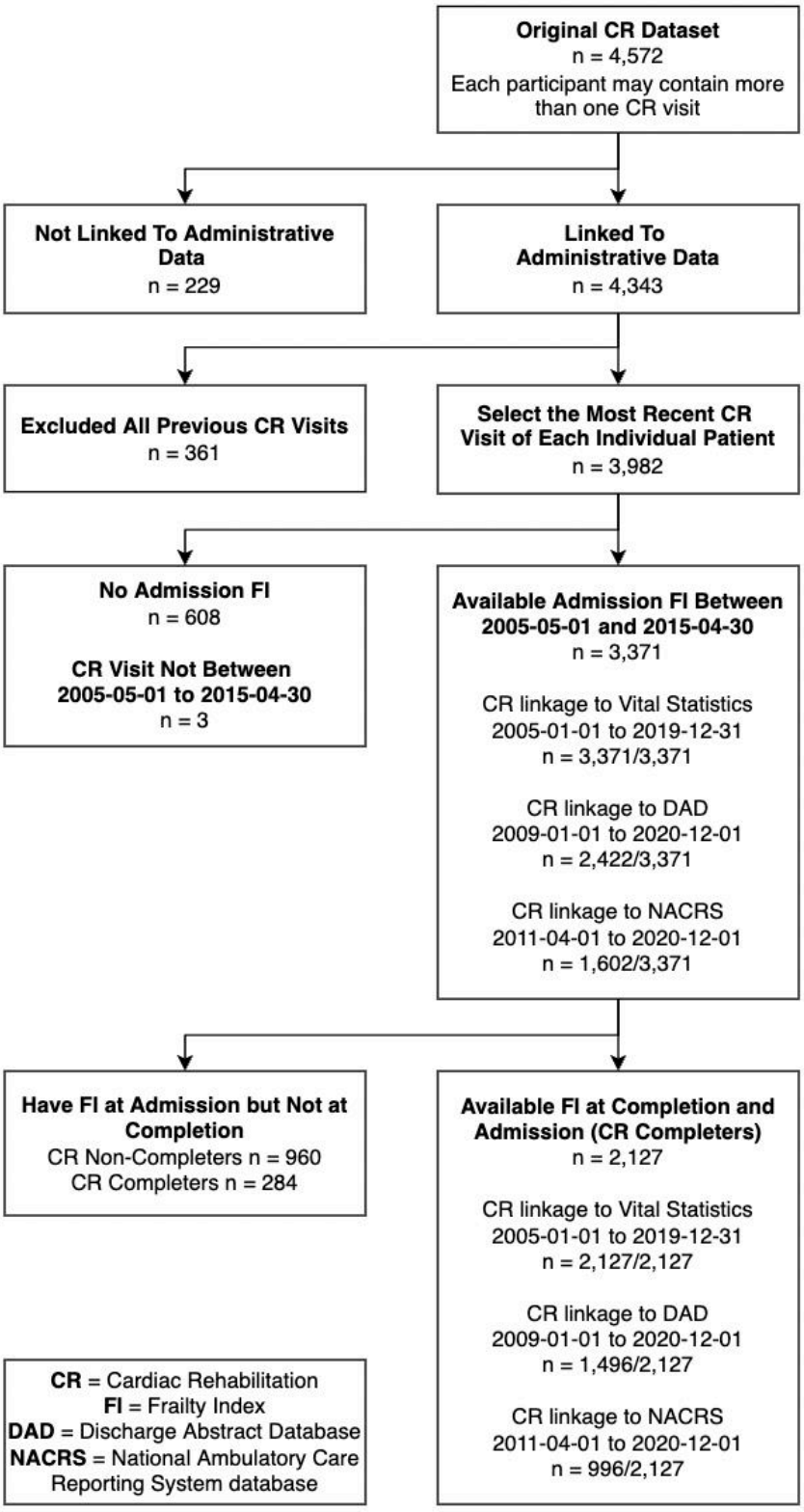

Figure 4.1. Flowchart of participants.

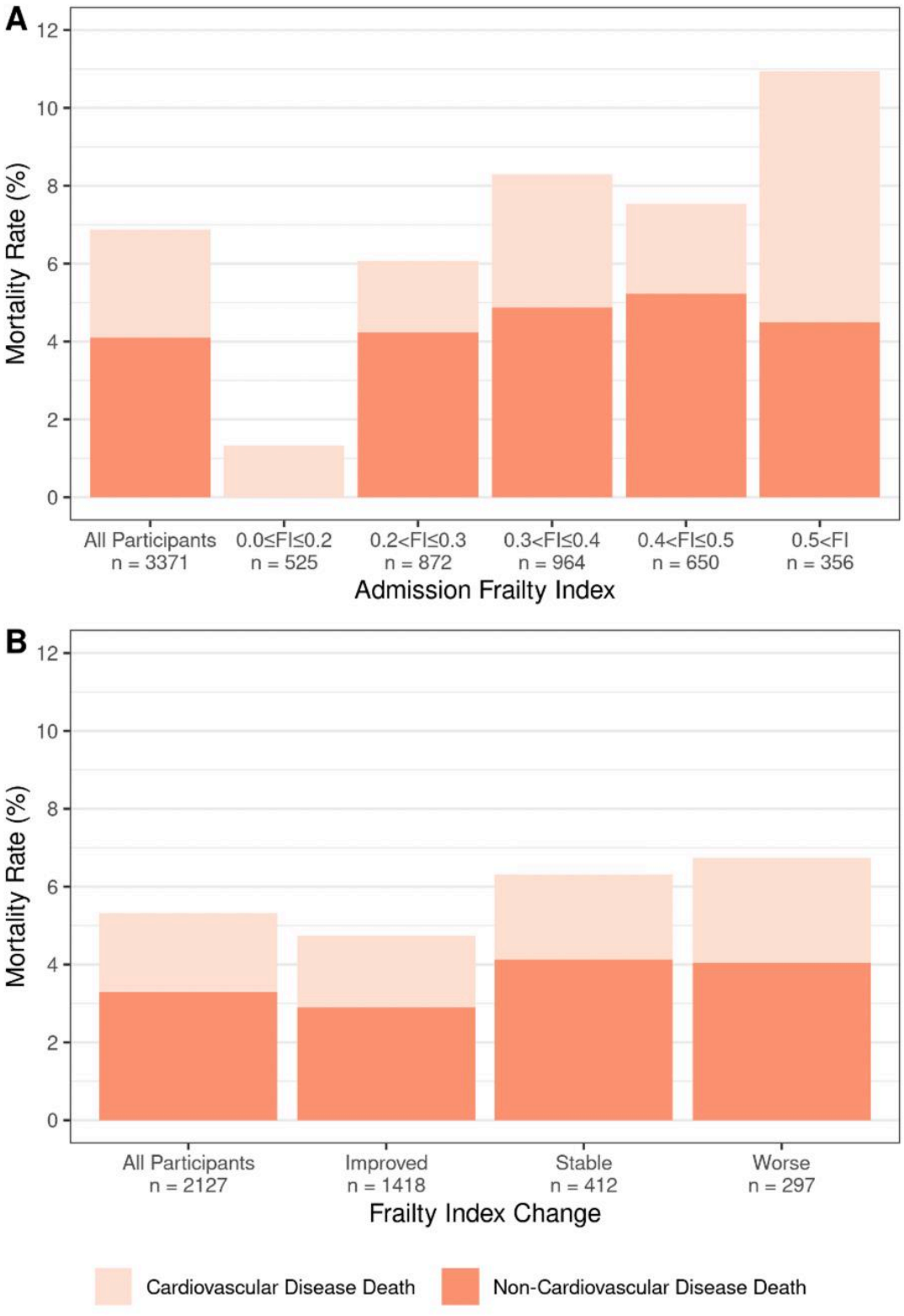

Figure 4.2. Mortality rates by A) admission frailty index and B) frailty index change. Improvement - frailty index decreased by at least 0.03; stable - frailty index changed by

less than 0.03, worsened - frailty index increased by at least 0.03 during cardiac rehabilitation.

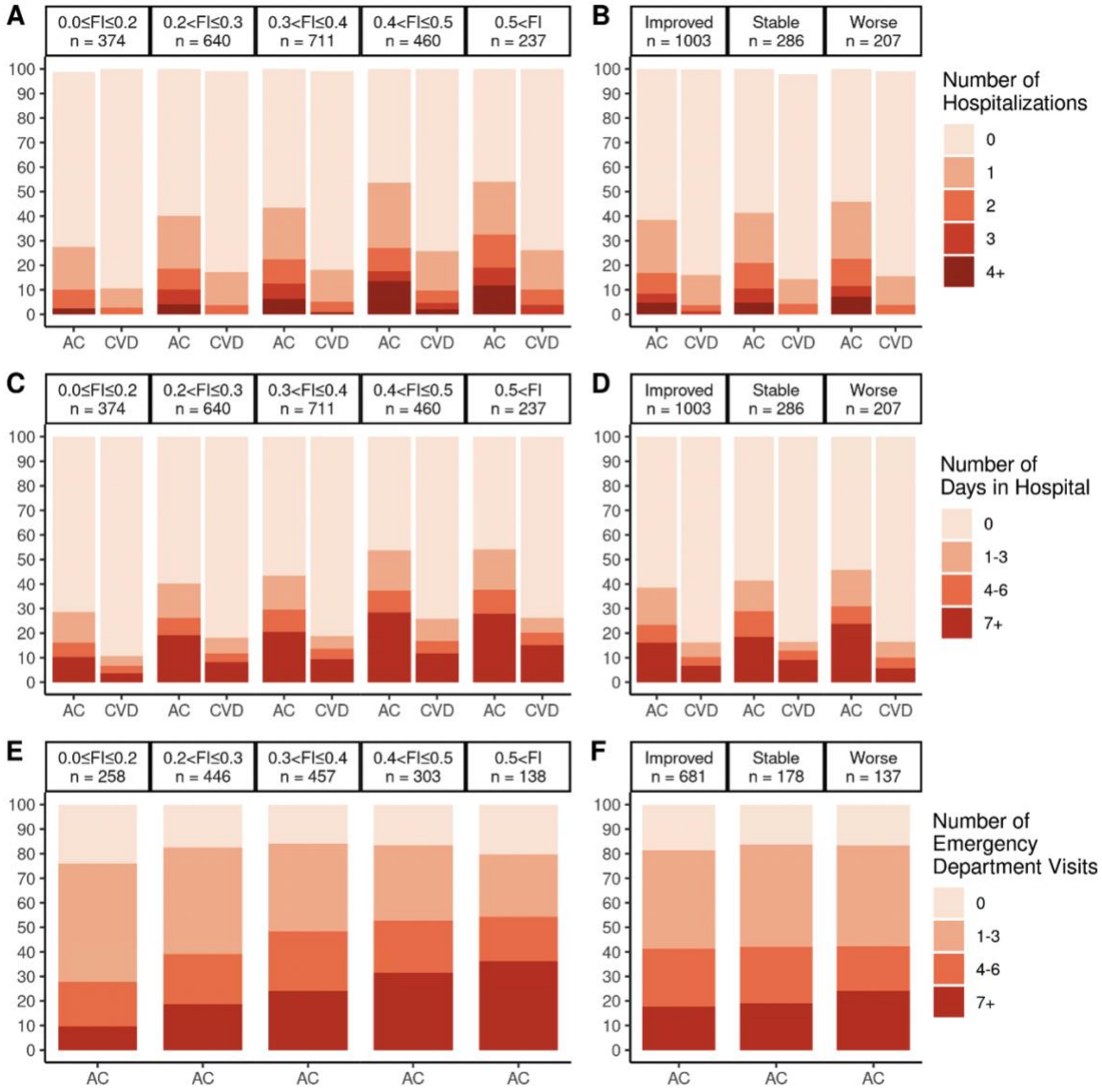

Figure 4.3. Total number of hospitalizations, hospital days, and emergency department visits by admission frailty index (panels A, C, E) and by frailty index change categories (panels B, D, F). Improvement - frailty index decreased by at least 0.03; stable - frailty index changed by less than 0.03, worsened - frailty index increased by at least 0.03 during cardiac rehabilitation. AC = all-cause, CVD = cardiovascular disease.

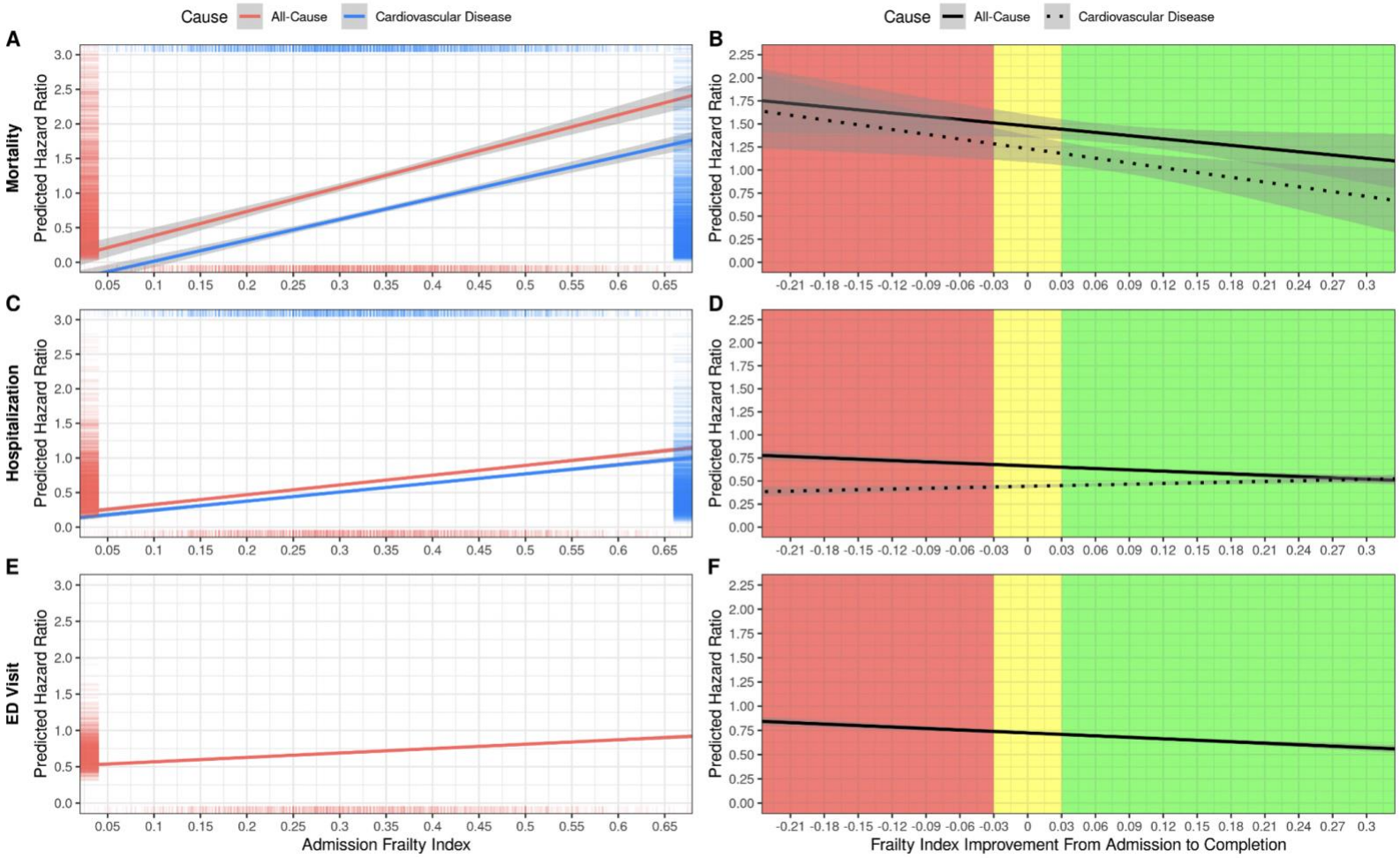

Figure 4.4. Predicted hazard ratios for risk of mortality (panels A and B), hospitalization (panels C and D), and ED visit (panels E and F) by frailty index score at cardiac rehabilitation admission (panels A, C, and E) and improvement during cardiac rehabilitation

(panels B, D, and F). Admission frailty index was a significant predictor of all-cause and cardiovascular disease risk of mortality, hospitalization, and emergency department visit ($p<0.001$). Frailty index improvement was a significant predictor of all-cause risk of hospitalization ($p=0.016$) but not for all other outcomes. Panels A, C, and E contains 'rug' plots which visualize the distribution of predicted hazard ratios and admission frailty index scores. The red, yellow, and green areas indicate clinically important worsening, stable, and improvement in frailty index score during cardiac rehabilitation on panels B, D, and F. Grey bands represent 95% confidence intervals. All models were adjusted for sex, age, referring diagnosis, education, employment, smoking status, marital status, and year of cardiac rehabilitation. The admission frailty index model was also adjusted for completion of cardiac rehabilitation status and the frailty index improvement model for admission frailty index score and percent of exercise sessions attended. ED = Emergency Department.

4.6 Supplementary Materials

4.6.1 Expanded Methods

4.6.1.1 Participants and Setting

This study used de-identified data of patients entering a CR programme from the Cardiac Rehabilitation Database. This database contains information from participants who previously enrolled in the CR programme from 1995 to 2015. Data from 2005 to 2015 was used for the current project due to the lack of information required to construct the FI in the data from 1995 to 2004. The Cardiac Rehabilitation Database recorded information on a patient's medical history, life satisfaction, physical and mental quality of life, laboratory variables including bloodwork and blood pressure, and health behaviors during CR attendance. It is housed within the Nova Scotia Health Hearts and Health in Motion CR programme located at the Mumford Professional Center in Halifax, NS. All participants consented for their data to be entered into a database and to be collected and used for research purposes. Participants were not excluded based on age. All participants experienced an adverse cardiovascular event (e.g., a heart attack, cardiac surgery, or heart failure) prior to their CR referral. Patients were automatically referred if they were recently an inpatient at the QEII hospital in the Central Zone due to heart-related conditions. Otherwise, a family physician or another health care professional would refer the patient to the CR programme.

4.6.1.2 Cardiac Rehabilitation

From 2005 to 2015, the programme experienced an expansion to the CR team and an increase in the number of classes offered per week to increase the capacity of the programme. In addition, the programme location moved from NS Rehabilitation to the

Mumford Professional Center in 2009. These changes allowed the CR programme to reduce wait times thus enrolling more patients.

4.6.1.3 Frailty Index Information

The FI included 25 variables in multiple domains: cardiovascular biomarkers (triglycerides, total, low-density lipoprotein, and high-density lipoprotein cholesterol, fasting blood glucose, systolic and diastolic blood pressure, resting pulse rate, pulse pressure, and mean arterial pressure) and symptoms (New York Heart Association functional class), quality of life according to the SF-36 questionnaire in physical, mental, and general health domains, cardiovascular fitness from an exercise stress test, body composition according to body mass index, waist circumference, bioelectrical impedance (percentage fat mass and percentage lean mass), and diet as determined by the use of the Food Frequency Questionnaire. Variables were recoded so to have scores that were either binary (0 = no deficit present, 1 = deficit present) or ordinal (e.g., New York Heart Association functional class increased in 0.33 increments: 0, 0.33, 0.66, and 1). Once all variables were recoded, the FI was calculated by dividing the sum of the deficits present in the patient by the total number of deficits considered. For example, if someone had 5 out of a possible 25 deficits, their FI score was 0.2. Higher scores indicate higher frailty levels. Any patients who were missing at least 30% of variables were excluded from the study.[156]

4.6.2 Supplementary Tables

Table S4.1. Frailty index variables used at cardiac rehabilitation admission and completion.

#	Variable	Coding	Frequency, n (%)
1	Obesity (BMI)	0: 18.5-25.0 0.5: 25.1-29.9 1: <18.5 or >30	0: 618 (18.3) 0.5: 1,294 (38.4) 1: 1,420 (42.1) Missing: 39 (1.2)
2	Waist circumference	Female: 0: <=88 cm, 1: >88 cm Male: 0: <=102 cm, 1: >102 cm	0: 1,349 (40) 1: 1,834 (54.4) Missing: 188 (5.6)
3	SF-36 Physical Function component score	0: >80 0.25: 60-80 0.5: 40-59 0.75: 20-39 1: <20	0: 807 (23.9) 0.25: 851 (25.2) 0.5: 758 (22.5) 0.75: 650 (19.3) 1: 297 (8.8) Missing: 8 (0.2)
4	SF-36 Role-physical component score	0: >80 0.25: 60-80 0.5: 40-59 0.75: 20-39 1: <20	0: 594 (17.6) 0.25: 216 (6.4) 0.5: 291 (8.6) 0.75: 471 (14) 1: 1,767 (52.4) Missing: 32 (0.9)
5	SF-36 Bodily Pain component score	0: >80 0.25: 60-80 0.5: 40-59 0.75: 20-39 1: <20	0: 923 (27.4) 0.25: 851 (25.2) 0.5: 892 (26.5) 0.75: 541 (16) 1: 151 (4.5) Missing: 13 (0.4)
6	SF-36 General Health component score	0: >80 0.25: 60-80	0: 662 (19.6) 0.25: 1,133 (33.6)

		0.5: 40-59 0.75: 20-39 1: <20		0.5: 863 (25.6) 0.75: 533 (15.8) 1: 143 (4.2) Missing: 37 (1.1)
7	SF-36 Energy component score	0: >80 0.25: 60-80 0.5: 40-59 0.75: 20-39 1: <20		0: 225 (6.7) 0.25: 720 (21.4) 0.5: 1,104 (32.7) 0.75: 847 (25.1) 1: 462 (13.7) Missing: 13 (0.4)
8	SF-36 Role-emotional component score	0: >80 0.25: 60-80 0.5: 40-59 0.75: 20-39 1: <20		0: 1,690 (50.1) 0.25: 270 (8) 0.5: <=5 (<=0.5) 0.75: 528 (15.7) 1: 868 (25.7) Missing: 10 (0.3)
9	SF-36 Mental Health component score	0: >80 0.25: 60-80 0.5: 40-59 0.75: 20-39 1: <20		0: 1,314 (39) 0.25: 1,131 (33.6) 0.5: 674 (20) 0.75: 190 (5.6) 1: 43 (1.3) Missing: 19 (0.6)
10	Change in health in the past year	0: Much better; somewhat better; same 0.5: Somewhat worse 1: Much worse		0: 2,025 (60.1) 0.5: 1012 (30) 1: 314 (9.3) Missing: 20 (0.6)
11	Percent body fat	Female: 0: <35.6% 0.33: 35.6-40.9% 0.66: 41.0-45.4% 1: >45.4%	Male: 0: <24.3% 0.33: 24.3-28.6% 0.66: 28.7-33.4% 1: >33.4%	0: 722 (21.4) 0.33: 701 (20.8) 0.66: 701 (20.8) 1: 688 (20.4) Missing: 559 (16.6)

12	Percent lean muscle mass	Female: 0: >17.3% 0.33: 15.9-17.3% 0.66: 14.6-17.2% 1: >14.6%	Male: 0: >20.4% 0.33: 19.1-20.4% 0.66: 17.9-19.0% 1: <17.9%	0: 721 (21.4) 0.33: 688 (20.4) 0.66: 694 (20.6) 1: 681 (20.2) Missing: 587 (17.4)
13	Food Frequency Score	0: >80 0.25: 60-80 0.5: 40-59 0.75: 20-39 1: <20		0: 290 (8.6) 0.25: 2603 (77.2) 0.5: 113 (3.4) 0.75: <=5 (<=0.5) 1: <=5 (<=0.5) Missing: 360 (10.7)
14	Systolic blood pressure	0: 90-140 mmHg 1: <90 or >140 mmHg		0: 2,953 (87.6) 1: 391 (11.6) Missing: 27 (0.8)
15	Diastolic blood pressure	0: 60-90 mmHg 1: <60 or >90 mmHg		0: 3,094 (91.8) 1: 245 (7.3) Missing: 32 (0.9)
16	Resting heart rate	0: 60-99 bpm 1: <60 or >99 bpm		0: 2,620 (77.7) 1: 703 (20.9) Missing: 48 (1.4)
17	Mean arterial pressure	0:70-110 mmHg 1: <70 or <110 mmHg		0: 3,139 (93.1) 1: 197 (5.8) Missing: 35 (1.0)
18	Pulse pressure	0: 30-60 mmHg 1: <30 or >60 mmHg		0: 2,506 (74.3) 1: 830 (24.6) Missing: 35 (1.0)
19	Total cholesterol	0: <=6.2 mmol/L 1: >6.2 mmol/L		0: 2,863 (84.9) 1: 153 (4.5) Missing: 355 (10.5)
20	High density lipoprotein	0: >= 1.03 mmol/L 1: <1.03 mmol/L		0: 1,355 (40.2) 1: 1,665 (49.4)

			Missing: 351 (10.4)
21	Low density lipoprotein	0: 0.98-3.36 mmol/L 1: <0.98 or >3.36 mmol/L	0: 2,402 (71.3) 1: 609 (18.1) Missing: 360 (10.7)
22	Triglycerides	0: <1.67 mmol/L 1: >=1.67 mmol/L	0: 2,083 (61.8) 1: 912 (27.1) Missing: 376 (11.2)
23	Fasting blood glucose	0: 3.9-6.1 mmol/L 1: <3.9 or >6.1 mmol/L	0: 1,604 (47.6) 1: 1,081 (32.1) Missing: 686 (20.4)
24	NYHA functional class	0: No shortness of breath 0.33: Some shortness of breath 0.66: Moderate shortness of breath 1: Major shortness of breath	0: 1,334 (39.6) 0.33: 512 (15.2) 0.66: 332 (9.8) 1: 29 (0.9) Missing: 1,164 (34.5)
25	Peak metabolic equivalents (METs)	0: >=5 METs 1: <5 METs	0: 1,843 (54.7) 1: 365 (10.8) Missing: 1,163 (34.5)

BMI = Body Mass Index, SF-36 = 36-Item Short Form Health Survey, NYHA = New York Heart Association

Table S4.2. Outcomes and associated databases.

Outcome	Cause	Dataset
Time to first hospitalization after CR*	All-cause	DAD
Time to first hospitalization after CR*	CVD	DAD
Total number of hospitalizations**	All-cause	DAD
Total number of hospitalizations **	CVD	DAD
Total number of hospital days**	All-cause	DAD
Total number of hospital days **	CVD	DAD
Time to first ED visit after CR*	All-cause	NACRS
Total number of ED visits**	All-cause	NACRS
Time to mortality*	All-cause	Vital Statistics
Time to mortality*	CVD	Vital Statistics

CR = cardiac rehabilitation, CVD = cardiovascular disease, DAD = Discharge Abstract Database, ED = emergency department, NACRS = National Ambulatory Care Reporting System. *Outcome censored at 5 years post-CR, **sum for 5-years of follow-up post-CR.

Table S4.3. Admission characteristics of people who did and did not complete cardiac rehabilitation with and without valid FI change scores at both admission and completion.

	Completers With Valid FI Change Objective 1 (n=2,127)	**Completers Without Valid FI Change** (n=284)	**Non-Completers** (n=960)
Age, mean (SD; range)	62.7 (10.4; 21-94)	62.7 (11.6; 32-90)	60.0 (10.8; 23-93)
Sex, n male (%)	1,586 (74.6)	222 (78.2)	695 (72.4)
Education, n (%)			
Less than Grade 12	401 (18.9)	56 (19.7)	252 (26.2)
Grade 12/GED	381 (17.9)	50 (17.6)	174 (18.1)
Technical College	693 (32.6)	80 (28.2)	300 (31.2)
Bachelor's Degree	429 (20.2)	54 (19.0)	143 (14.9)
Post-Graduate Education	223 (10.5)	44 (15.5)	91 (9.5)
Employment, n (%)			
Long-Term Disability	99 (4.7)	25 (8.8)	99 (10.3)
Unemployed	37 (1.7)	≤5 (≤0.05)	48 (5.0)
Part-Time	117 (5.5)	16 (5.6)	53 (5.5)
Full-Time	408 (19.2)	71 (25.0)	233 (24.3)
Retired	1,067 (50.2)	123 (43.3)	348 (36.2)
Other	399 (18.8)	45 (15.8)	179 (18.6)
Smoking Status, n (%)			
Non-Smoker	671 (31.6)	100 (35.2)	226 (23.5)
Former Smoker	1,275 (59.9)	162 (57.0)	570 (59.4)
Current Smoker	181 (8.5)	22 (7.8)	164 (17.1)
Marital Status, n (%)			
Divorced/Separated	159 (7.5)	27 (9.5)	122 (12.7)
Widowed	133 (6.2)	20 (7.0)	73 (7.6)
Single	143 (6.7)	22 (7.8)	91 (9.5)
Married/Living with a Partner	1,692 (79.6)	215 (75.7)	674 (70.2)
Referring Diagnosis, n (%)			

Coronary Artery Disease	577 (27.1)	76 (26.8)	247 (25.7)
Percutaneous Coronary Intervention	319 (15.0)	33 (11.6)	164 (17.1)
Cardiac Surgery	423 (19.9)	64 (22.5)	142 (14.8)
Heart Failure	127 (6.0)	24 (8.4)	71 (7.4)
Myocardial Infarction	598 (28.1)	75 (26.4)	282 (29.4)
Other	83 (3.9)	12 (4.2)	54 (5.6)
Year of CR Admission, n (%)			
2005-2008	631 (29.7)	55 (19.4)	263 (27.4)
2009-2012	946 (44.5)	132 (46.5)	455 (47.4)
2013-2015	550 (25.9)	97 (34.1)	242 (25.2)
Exercise Sessions Attended, % (SD)	89.5 (12.8)	81.2 (16.9)	26.2 (27.1)
Admission FI			
Mean (SD)	0.32 (0.12)	0.34 (0.12)	0.37 (0.14)
FI≤0.2, n (%)	384 (18.0)	40 (14.1)	105 (10.9)
0.2<FI≤0.3, n (%)	593 (27.9)	76 (26.8)	203 (21.1)
0.3<FI≤0.4, n (%)	635 (29.9)	79 (27.8)	250 (26.0)
0.4<FI≤0.5, n (%)	363 (17.1)	59 (20.8)	228 (23.8)
0.5≤FI, n (%)	152 (7.2)	30 (10.6)	174 (18.1)
FI Change (Admission to Completion)			
Mean (sd)	-0.07 (0.09)	-	-
Worsened by more than 0.03, n (%)	297 (14.0)	-	-
Stable (changed less than 0.03), n (%)	412 (19.4)	-	-
Improved by more than 0.03, n (%)	1,418 (66.7)	-	-

A valid FI change was defined as availability of a FI score at both cardiac rehabilitation admission and completion. FI = frailty index, SD = standard deviation.

Table S4.4. Admission characteristics of cardiac rehabilitation completers (n=2,217) by FI change categories.

	Improved (n=1,418)	**Stable** (n=412)	**Worsened** (n=297)
Age, mean (SD; range)	62.3 (10.2)	63.8 (10.7)	63.0 (10.5)
Sex, n male (%)	1148 (81.0)	316 (76.7)	228 (76.8)
Education, n (%)			
Less than Grade 12	250 (17.6)	93 (22.6)	58 (19.5)
Grade 12/GED	248 (17.5)	73 (17.7)	60 (20.2)
Technical College	473 (33.4)	131 (31.8)	89 (30.0)
Bachelor's Degree	299 (21.1)	67 (16.3)	63 (21.2)
Post-Graduate Education	148 (10.4)	48 (11.7)	27 (9.1)
Employment, n (%)			
Long-Term Disability	56 (4.0)	27 (6.6)	16 (5.4)
Unemployed	22 (1.6)	7 (1.7)	8 (2.7)
Part-Time	70 (4.9)	28 (6.8)	19 (6.4)
Full-Time	285 (20.1)	61 (14.8)	62 (20.9)
Retired	698 (49.2)	224 (54.4)	145 (48.8)
Other	287 (20.2)	65 (15.8)	47 (15.8)
Smoking Status, n (%)			
Non-Smoker	436 (30.8)	132 (32)	103 (34.7)
Former Smoker	860 (60.7)	245 (59.5)	170 (57.2)
Current Smoker	122 (8.6)	35 (8.5)	24 (8.1)
Marital Status, n (%)			
Divorced/Separated	97 (6.8)	37 (9.0)	25 (8.4)
Widowed	85 (6.0)	30 (7.3)	18 (6.1)
Single	88 (6.2)	29 (7.0)	26 (8.8)
Married/Living with a Partner	1148 (81.0)	316 (76.7)	228 (76.8)
Referring Diagnosis, n (%)			
Coronary Artery Disease	351 (24.8)	130 (31.6)	96 (32.3)
Percutaneous Coronary Intervention	214 (15.1)	60 (14.6)	45 (15.2)
Cardiac Surgery	302 (21.3)	75 (18.2)	46 (15.5)

Heart Failure	79 (5.6)	23 (5.6)	25 (8.4)
Myocardial Infarction	420 (29.6)	106 (25.7)	72 (24.2)
Other	52 (3.7)	18 (4.4)	13 (4.4)
Year of CR Admission, n (%)			
2005-2008	415 (29.3)	126 (30.6)	90 (30.3)
2009-2012	609 (43.0)	193 (46.8)	144 (48.5)
2013-2015	394 (27.8)	93 (22.6)	63 (21.2)
Exercise Sessions Attended, % (SD)	90.2 (12.8)	88.7 (12.6)	87.2 (13.0)
Admission FI, mean (SD)	0.34 (0.12)	0.28 (0.13)	0.28 (0.12)
FI Change (Admission to Completion), mean (SD)	-0.08 (0.04)	0.00 (0.02)	0.12 (0.06)

FI = frailty index, SD = standard deviation.

Table S4.5. Outcomes of people who attend cardiac rehabilitation.

	Full Sample Objective 1	**Completers With Valid FI Change** Objective 2	**Completers Without Valid FI Change**	**Non-Completers**
Mortality				
Total Sample	3,371	2,127	284	960
Proportions, n (%)				
Alive	3,139 (93.1)	2,014 (94.7)	262 (92.2)	863 (89.9)
All-Cause Death	232 (6.9)	113 (5.3)	22 (7.8)	97 (10.1)
CVD Related Death	94 (2.8)	43 (2.0)	8 (2.8)	43 (4.5)
Non-CVD Related Death	138 (4.1)	70 (3.3)	14 (4.9)	54 (5.6)
Total Number of Hospitalizations				
Total Sample	2,422	1,496	229	697
All-Cause, mean (SD)	1.0 (1.7)	0.8 (1.4)	1.1 (1.6)	1.3 (2.2)
Proportions, n (%)				
0	1,374 (56.7)	897 (60.0)	128 (55.9)	349 (50.1)
1	526 (21.7)	323 (21.6)	40 (17.5)	163 (23.4)
2	230 (9.5)	138 (9.2)	23 (10.0)	69 (9.9)
3	121 (5.0)	61 (4.1)	16 (7.0)	44 (6.3)
4+	171 (7.1)	77 (5.2)	22 (9.6)	72 (10.3)
CVD-Related, mean (SD)	0.3 (0.8)	0.2 (0.6)	0.3 (0.8)	0.4 (1.0)
Proportions, n (%)				
0	1,951 (80.6)	1,252 (83.7)	178 (77.7)	521 (74.8)
1	320 (13.2)	176 (11.8)	33 (14.4)	111 (15.9)
2	104 (4.3)	46 (3.1)	13 (5.7)	45 (6.5)
3	30 (1.2)	16 (1.1)	≤5 (≤0.05)	10 (1.4)
4+	17 (0.7)	6 (0.4)	≤5 (≤0.05)	10 (1.4)
Total Number of Days in Hospital				
Total Sample	2,422	1,496	229	697
All-Cause, mean (SD)	7.3 (22.3)	5.4 (16.4)	10.2 (26.6)	10.5 (30.2)
Proportions, n (%)				

0	1,374 (56.7)	897 (60.0)	128 (55.9)	349 (50.1)
1-3	350 (14.4)	217 (14.5)	26 (11.3)	107 (15.3)
4-6	194 (8.0)	118 (7.9)	15 (6.6)	61 (8.8)
7+	504 (20.8)	264 (17.6)	60 (26.2)	180 (25.8)
CVD-Related, mean (SD)	2.3 (9.2)	1.8 (8.1)	2.9 (9.3)	3.2 (11.1)
Proportions, n (%)				
0	1,951 (80.6)	1,252 (83.7)	178 (77.7)	521 (74.8)
1-3	149 (6.2)	83 (5.6)	15 (6.6)	51 (7.3)
4-6	100 (4.1)	55 (3.7)	10 (4.4)	35 (5.0)
7+	222 (9.2)	106 (7.1)	26 (11.3)	90 (12.9)
Total Number of Times in ED				
Total Sample	1,602	996	157	449
All-Cause, mean (SD)	4.6 (5.8)	4.2 (5.4)	5.5 (5.9)	5.2 (6.4)
Proportions, n (%)				
0	291 (18.2)	178 (17.9)	28 (17.8)	85 (18.9)
1-3	609 (38.0)	403 (40.5)	48 (30.6)	158 (35.2)
4-6	339 (21.2)	227 (22.8)	35 (22.3)	77 (17.1)
7+	363 (22.7)	188 (18.9)	46 (29.3)	129 (28.7)

A valid FI change was defined as availability of a FI score at both cardiac rehabilitation admission and completion. CVD = cardiovascular disease, ED = emergency department, FI = Frailty Index, SD = standard deviation.

Table **S4.6.** Association between admission FI and outcomes measures during the 5-year follow-up after cardiac rehabilitation.

Outcome	Cause	Order of FI	HR or SHR (CI) Per 0.01 greater admission FI	
Time to Mortality (n = 3,371)	All-Cause	Linear	**1.02 (1.01,1.04)**	
		Quadratic	**1.00 (1.00,1.00)**	
		Cubic	**1.00 (1.00,1.00)**	
	CVD	Linear	**1.03 (1.02,1.05)**	
Time to First Hospitalization (n = 2,422)	All-Cause	Linear	**1.02 (1.01,1.02)**	
		Quadratic	**1.00 (1.00,1.00)**	
	CVD	Linear	**1.02 (1.01,1.02)**	
		Quadratic	**1.00 (1.00,1.00)**	
Time to First Emergency Department Visit (n = 1,602)	All-Cause	Linear	**1.00 (1.00,1.01)**	
		Quadratic	**1.00 (1.00, 1.00)**	
			IRR (CI)	OR (CI)
Number of Hospitalizations (n = 2,422)	All-Cause	Linear	**1.02 (1.01,1.03)**	**1.02 (1.02,1.03)**
	CVD	Linear	**1.02 (1.00,1.04)**	**1.02 (1.01,1.03)**
Number of Hospital Days (n = 2,422)	All-Cause	Linear	**1.01 (1.00,1.02)**	**1.02 (1.02,1.03)**
	CVD	Linear	1.01 (0.99,1.02)	**1.02 (1.01,1.03)**
Number of Times in ED (n = 1,602)	All-Cause	Linear	**1.02 (1.02,1.03)**	1.00 (0.99,1.01)

Outcomes correspond to 0.01 greater in admission FI. All models adjusted for sex, age, referring diagnosis, education, employment, smoking status, marital status, year of cardiac rehabilitation. There were no significant three-way and two-way interactions. Bolded text represents significance at < 0.05. The first, second, and third model tested the linear, quadratic, and cubic relationships. Results were presented for all statistically significant model. If no models were statistically significant, the linear model was presented. CI = 95% confidence interval, CVD = cardiovascular disease, ED = emergency department, HR = hazard ratio, IRR = incidence rate ratio, OR = odds ratio, SHR = sub-distributional hazard ratio.

Table S4.7. Association between FI change during cardiac rehabilitation and outcomes measures during the 5-year follow-up after cardiac rehabilitation.

Outcome	Cause	Order of FI	HR or SHR (CI) Per 0.01 improvement in FI during CR	
Time to Mortality	All-Cause	Linear	0.98 (0.96, 1.01)	
(n = 2,127)	CVD	Linear	0.97 (0.94, 1.01)	
Time to First Hospitalization	All-Cause	Linear	**0.99 (0.98,0.99)**	
(n = 1,496)	CVD	Linear	1.00 (0.99,1.02)	
Time to First Emergency Department Visit	All-Cause	Linear	0.99 (0.98,1.00)	
(n = 996)	All-Cause	Quadratic	**1.00 (1.00, 1.00)**	
			IRR (CI)	OR (CI)
Number of Hospitalizations	All-Cause	Linear	0.99 (0.97,1.01)	**0.98 (0.97,0.99)**
(n = 1,496)	CVD	Linear	0.99 (0.96,1.02)	1.00 (0.98,1.02)
Number of Hospital Days (n = 1,496)	All-Cause	Linear	0.98 (0.97,1.00)	**0.98 (0.97,0.99)**
	CVD	Linear	1.00 (0.97,1.03)	1.00 (0.98,1.02)
	CVD	Cubic	**1.00 (1.00,1.00)**	1.00 (1.00,1.00)
Number of Times in ED	All-Cause	Linear	0.99 (0.98,1.00)	0.98 (0.96,1.00)
(n = 996)	All-Cause	Quadratic	**1.00 (1.00,1.00)**	1.00 (1.00,1.00)

Outcomes correspond to 0.01 greater FI improvement (+0.01 change in FI indicates improvement in FI from admission to completion of cardiac rehabilitation). All models were adjusted for admission FI, sex, age, referring diagnosis, education, employment, smoking status, marital status, year of cardiac rehabilitation, and percent exercises sessions attended. There were no significant three-way and two-way interactions. Bolded text represents significance at < 0.05. The initial, second, and third model tested the linear, quadratic, and cubic relationships, respectively. Results were presented for the linear model and the highest order model that was statistically significant. CI = 95% confidence interval, CVD = cardiovascular disease, ED = emergency department, HR = hazard ratio, IRR = incidence rate ratio, OR = odds ratio, SHR = sub-distributional hazard ratio.

Table S4.8. Two-way interaction of FI at cardiac rehabilitation admission and FI change with age, sex, and referring diagnosis for 5-year outcomes.

Outcome	Cause	Variable with Significant 2-Way Interaction with Admission FI	Variable with Significant 2-Way Interactions with FI Change
Mortality	AC	None	None
	CVD	None	Referring Diagnosis (Other)
Hospitalization	AC	Referring Diagnosis (MI)	None
	CVD	Referring Diagnosis (PCI)	None
Emergency Department Visit	AC	None	None
Number of Hospital Visits	AC	None	Referring Diagnosis (PCI)
	CVD	None	Referring Diagnosis (PCI)
Number of Hospital Days	AC	Referring Diagnosis (PCI)	Referring Diagnosis (PCI, MI, Other)
	CVD	None	None
Number of Emergency Department Visits	AC	None	Referring Diagnosis (PCI)

Interactions were significant when alpha < 0.05. There were no significant interactions between age, sex, and exercise sessions attended with admission frailty and frailty change during cardiac rehabilitation. All models were adjusted for sex, age, referring diagnosis, education, employment, smoking status, marital status, year of cardiac rehabilitation. The admission frailty index model was also adjusted for completion of cardiac rehabilitation status and the frailty index improvement change model for admission frailty index score and exercise sessions attended. The percent exercise sessions attended by admission frailty was not checked. AC = all-cause, CVD = cardiovascular disease, FI = frailty index, PCI = percutaneous coronary intervention, MI = myocardial infarction, Other = other CVDs.

Table S4.9. All coefficients of cox regression and Fine-Gray (survival) models for admission frailty index analyses.

Covariate	Mortality		Hospitalization		ED Visit
	All-cause	CVD	All-cause	CVD	All-cause
Admission Frailty Index (per 0.01)	1.02 (1.01,1.04)	1.03 (1.02,1.05)	1.02 (1.01,1.02)	1.02 (1.01,1.02)	1.01 (1.00,1.01)
Sex: Female	0.52 (0.37,0.74)	1.05 (1.02,1.08)	0.94 (0.81,1.09)	0.70 (0.57,0.87)	1.21 (1.06,1.39)
Age	1.06 (1.04,1.08)	0.59 (0.35,0.98)	1.03 (1.02,1.04)	1.03 (1.01,1.04)	1.01 (1.00,1.02)
Ref. Diagnosis: Coronary Artery Disease	Reference	Reference	Reference	Reference	Reference
Ref. Diagnosis: Percutaneous Coronary Intervention	1.21 (0.74,1.95)	0.95 (0.42,2.16)	0.72 (0.59,0.88)	0.72 (0.55,0.95)	0.94 (0.80,1.11)
Ref. Diagnosis: Cardiac Surgery	1.42 (0.93,2.18)	1.31 (0.65,2.66)	0.90 (0.74,1.08)	0.80 (0.61,1.04)	1.01 (0.85,1.20)
Ref. Diagnosis: Heart Failure	4.47 (2.97,6.71)	5.83 (3.16,10.75)	1.59 (1.27,2.00)	2.12 (1.62,2.79)	1.46 (1.13,1.90)
Ref. Diagnosis: Myocardial Infarction	1.36 (0.92,2.02)	1.43 (0.76,2.70)	0.89 (0.75,1.06)	0.87 (0.69,1.11)	1.02 (0.87,1.20)
Ref. Diagnosis: Other	2.03 (1.10,3.75)	1.43 (0.45,4.58)	1.09 (0.83,1.44)	0.82 (0.54,1.24)	1.10 (0.86,1.41)
Education: Less than Grade 12	Reference	Reference	Reference	Reference	Reference
Education: Grade 12/GED	1.30 (0.87,1.92)	0.93 (0.50,1.74)	0.99 (0.81,1.20)	0.80 (0.61,1.06)	1.00 (0.84,1.20)
Education: Technical College	1.09 (0.77,1.56)	0.86 (0.50,1.51)	1.05 (0.89,1.24)	1.01 (0.81,1.27)	0.95 (0.81,1.12)
Education: Bachelor's Degree	1.08 (0.71,1.65)	0.90 (0.45,1.78)	0.96 (0.79,1.18)	0.95 (0.72,1.25)	0.95 (0.80,1.14)
Education: Post-Graduate Education	1.10 (0.66,1.84)	0.78 (0.31,1.94)	1.02 (0.80,1.29)	0.89 (0.64,1.24)	0.90 (0.73,1.12)
Employment: Long-Term Disability	Reference	Reference	Reference	Reference	Reference
Employment: Unemployed	0.70 (0.23,2.12)	1.57 (0.37,6.69)	0.64 (0.40,1.04)	0.46 (0.21,1.02)	0.66 (0.40,1.08)
Employment: Part-Time	1.00 (0.46,2.17)	0.92 (0.23,3.64)	0.80 (0.56,1.15)	0.82 (0.49,1.36)	0.56 (0.41,0.78)
Employment: Full-Time	0.59 (0.30,1.15)	1.01 (0.35,2.86)	0.77 (0.57,1.02)	0.79 (0.53,1.18)	0.56 (0.43,0.74)
Employment: Retired	0.95 (0.52,1.75)	1.11 (0.38,3.29)	0.82 (0.62,1.09)	1.00 (0.68,1.48)	0.66 (0.51,0.86)
Employment: Other	0.62 (0.31,1.23)	0.88 (0.30,2.56)	0.85 (0.64,1.14)	0.97 (0.65,1.45)	0.68 (0.52,0.90)
Smoking Status: Non-Smoker	Reference	Reference	Reference	Reference	Reference
Smoking Status: Former Smoker	1.18 (0.86,1.63)	0.87 (0.52,1.44)	1.02 (0.89,1.18)	1.04 (0.86,1.27)	1.02 (0.91,1.16)
Smoking Status: Current Smoker	1.77 (1.09,2.90)	0.99 (0.45,2.15)	0.85 (0.66,1.09)	1.17 (0.85,1.60)	0.81 (0.64,1.02)
Marital Status: Divorced/Separated	Reference	Reference	Reference	Reference	Reference
Marital Status: Widowed	1.19 (0.66,2.13)	1.04 (0.44,2.42)	0.99 (0.73,1.33)	0.87 (0.58,1.31)	0.96 (0.73,1.27)
Marital Status: Single	1.15 (0.62,2.15)	0.84 (0.35,2.00)	1.00 (0.74,1.37)	0.92 (0.61,1.37)	1.19 (0.90,1.57)
Marital Status: Married/Living with a Partner	0.90 (0.57,1.43)	0.58 (0.30,1.12)	1.01 (0.81,1.25)	0.86 (0.64,1.14)	1.12 (0.92,1.36)
Year of Cardiac Rehabilitation	0.94 (0.89,0.99)	0.97 (0.89,1.06)	0.91 (0.88,0.94)	0.94 (0.89,0.98)	1.01 (0.96,1.06)
Completed Cardiac Rehabilitation	0.54 (0.41,0.71)	0.53 (0.34,0.83)	0.69 (0.60,0.79)	0.61 (0.51,0.73)	0.88 (0.77,1.01)

Coefficients are hazard ratio (HR) for all-cause mortality and sub-distributional hazard ratios (SHR) for all other outcomes. The logistic regression portion of the hurdle model was omitted. CVD = cardiovascular disease, ED = emergency department.

Table S4.10. All coefficients of negative binomial hurdle models for admission frailty index analyses.

Covariate	Number of Hospitalizations		Number of Hospital Days		Number of ED Visits
	All-cause	CVD	All-cause	CVD	All-cause
Admission Frailty Index (per 0.01)	1.02 (1.01,1.03)	1.02 (1.00, 1.04)	1.02 (1.01,1.03)	1.01 (1.00,1.02)	1.02 (1.02,1.03)
Sex: Female	0.96 (0.74,1.24)	1.34 (0.87,1.99)	1.02 (0.79,1.32)	1.23 (0.85,1.77)	0.97 (0.85,1.11)
Age	1.01 (1.00,1.03)	1.01 (0.98,1.04)	1.04 (1.02,1.05)	1.03 (1.01,1.05)	1.10 (1.02,1.19)
Ref. Diagnosis: Coronary Artery Disease	Reference	Reference	Reference	Reference	Reference
Ref. Diagnosis: Percutaneous Coronary Intervention	0.81 (0.56,1.16)	1.37 (0.78,2.40)	0.60 (0.41,0.87)	0.68 (0.41,1.11)	0.79 (0.66,0.94)
Ref. Diagnosis: Cardiac Surgery	0.84 (0.59,1.19)	0.69 (0.36,1.33)	0.77 (0.54,1.10)	0.88 (0.54,1.45)	0.81 (0.68,0.98)
Ref. Diagnosis: Heart Failure	1.44 (0.94,2.22)	1.65 (0.93,2.94)	1.69 (1.04,2.74)	1.66 (0.94,2.91)	1.18 (0.91,1.53)
Ref. Diagnosis: Myocardial Infarction	0.78 (0.57,1.06)	1.09 (0.66,1.80)	0.78 (0.57,1.08)	1.03 (0.68,1.58)	0.79 (0.66,0.94)
Ref. Diagnosis: Other	0.80 (0.48,1.33)	0.66 (0.22,1.95)	1.07 (0.63,1.81)	1.22 (0.56,2.69)	0.95 (0.74,1.22)
Education: Less than Grade 12	Reference	Reference	Reference	Reference	Reference
Education: Grade 12/GED	0.97 (0.66,1.41)	0.85 (0.43,1.67)	0.89 (0.59,1.33)	0.93 (0.55,1.58)	0.96 (0.79,1.17)
Education: Technical College	1.25 (0.91,1.71)	1.22 (0.75,1.98)	1.05 (0.74,1.47)	1.09 (0.71,1.68)	1.04 (0.88,1.23)
Education: Bachelor's Degree	1.26 (0.87,1.82)	1.25 (0.69,2.26)	1.00 (0.67,1.48)	1.02 (0.61,1.71)	0.78 (0.64,0.96)
Education: Post-Graduate Education	0.90 (0.56,1.44)	1.14 (0.52,2.54)	0.69 (0.43,1.10)	0.88 (0.46,1.68)	0.77 (0.61,0.98)
Employment: Long-Term Disability	Reference	Reference	Reference	Reference	Reference
Employment: Unemployed	0.72 (0.29,1.78)	NA	1.10 (0.44,2.72)	1.19 (0.30,4.64)	0.76 (0.49,1.19)
Employment: Part-Time	0.54 (0.28,1.04)	0.17 (0.04,0.83)	0.41 (0.21,0.80)	0.76 (0.29,1.98)	0.77 (0.55,1.07)
Employment: Full-Time	0.67 (0.42,1.09)	0.47 (0.25,0.92)	0.59 (0.36,0.99)	0.65 (0.34,1.98)	0.67 (0.52,0.88)
Employment: Retired	0.81 (0.50,1.30)	0.44 (0.23,0.85)	0.90 (0.54,1.49)	0.75 (0.40,1.25)	0.89 (0.68,1.15)
Employment: Other	0.60 (0.37,0.98)	0.45 (0.23,0.87)	0.62 (0.37,1.04)	0.71 (0.37,1.43)	0.65 (0.50,0.85)
Smoking Status: Non-Smoker	Reference	Reference	Reference	Reference	Reference
Smoking Status: Former Smoker	1.07 (0.83,1.38)	1.15 (0.74,1.78)	1.03 (0.80,1.33)	0.91 (0.64,1.30)	0.97 (0.85,1.11)
Smoking Status: Current Smoker	1.30 (0.82,2.06)	1.65 (0.88, 3.09)	1.33 (0.83,2.13)	1.64 (0.88,3.04)	1.05 (0.82,1.34)
Marital Status: Divorced/Separated	Reference	Reference	Reference	Reference	Reference
Marital Status: Widowed	0.57 (0.33,0.97)	0.57 (0.21,1.56)	0.58 (0.32,1.03)	0.84 (0.40,1.76)	0.91 (0.66,1.24)
Marital Status: Single	1.29 (0.76,2.19)	1.96 (0.93,4.14)	1.17 (0.66,2.08)	2.18 (1.06,4.50)	1.47 (1.09,1.96)
Marital Status: Married/Living with a Partner	0.74 (0.51,1.07)	1.09 (0.61,1.94)	0.60 (0.48, 0.90)	1.21 (0.75,1.95)	1.09 (0.88,1.36)
Year of Cardiac Rehabilitation	0.82 (0.69,0.97)	0.75 (0.51,1.09)	1.24 (1.03,1.48)	1.11 (0.87,1.43)	1.10 (0.97,1.25)
Completed Cardiac Rehabilitation	0.77 (0.60,0.98)	0.66 (0.50,0.88)	0.73 (0.56,0.96)	0.81 (0.58,1.15)	0.89 (0.78,1.02)

All coefficients are incident rate ratios (IRR). The logistic regression portion of the hurdle model was omitted. CVD = cardiovascular disease, ED = emergency department. NA indicates subgroups with too little sample size to generate coefficients.

Table S4.11. All coefficients of cox regression and Fine-Gray (survival) models for frailty index change analyses.

Covariate	Mortality		Hospitalization		ED Visit
	All-cause	CVD	All-cause	CVD	All-cause
Frailty Index Change (per 0.01 improvement)	0.98 (0.96,1.01)	0.97 (0.94,1.01)	0.99 (0.98,0.99)	1.00 (0.99,1.01)	0.99 (0.98,1.01)
Admission Frailty Index	1.03 (1.01,1.05)	1.05 (1.02,1.08)	1.02 (1.01,1.03)	1.02 (1.01,1.03)	1.01 (0.99,1.01)
Sex: Female	0.40 (0.23,0.69)	0.48 (0.21,1.11)	1.00 (0.83,1.22)	0.69 (0.51,0.93)	1.24 (1.04,1.47)
Age	1.08 (1.05,1.11)	1.07 (1.02,1.12)	1.03 (1.02,1.05)	1.03 (1.01,1.05)	1.01 (1.00,1.02)
Ref. Diagnosis: Coronary Artery Disease	Reference	Reference	Reference	Reference	Reference
Ref. Diagnosis: Percutaneous Coronary Intervention	1.98 (1.00,3.94)	1.60 (0.44,5.86)	0.71 (0.55,0.92)	0.67 (0.45,1.00)	1.06 (0.86,1.31)
Ref. Diagnosis: Cardiac Surgery	1.64 (0.87,3.07)	2.75 (0.96,7.89)	0.91 (0.72,1.16)	0.70 (0.48,1.02)	1.09 (0.88,1.35)
Ref. Diagnosis: Heart Failure	6.53 (3.54,12.02)	8.91 (3.25,24.39)	1.34 (0.96,1.86)	1.95 (1.30,2.93)	1.36 (0.97,1.92)
Ref. Diagnosis: Myocardial Infarction	1.75 (0.96,3.20)	1.50 (0.48,4.62)	0.97 (0.77,1.22)	1.06 (0.76,1.49)	1.12 (0.91,1.38)
Ref. Diagnosis: Other	3.72 (1.59,8.70)	4.61 (1.05,20.21)	1.06 (0.73,1.54)	1.01 (0.59,1.75)	1.12 (0.80,1.57)
Education: Less than Grade 12	Reference	Reference	Reference	Reference	Reference
Education: Grade 12/GED	1.17 (0.64,2.15)	1.09 (0.36,3.25)	0.99 (0.75,1.29)	0.82 (0.55,1.22)	1.14 (0.91,1.42)
Education: Technical College	1.38 (0.81,2.35)	1.15 (0.49,2.71)	1.12 (0.89,1.40)	1.04 (0.76,1.44)	0.99 (0.81,1.22)
Education: Bachelor's Degree	1.35 (0.74,2.47)	1.79 (0.67,4.79)	0.99 (0.75,1.30)	0.97 (0.66,1.42)	0.90 (0.72,1.12)
Education: Post-Graduate Education	1.00 (0.45,2.22)	1.38 (0.39,4.91)	1.11 (0.81,1.52)	0.86 (0.54,1.38)	0.84 (0.64,1.10)
Employment: Long-Term Disability	Reference	Reference	Reference	Reference	Reference
Employment: Unemployed	NA	NA	0.58 (0.24,1.42)	0.68 (0.19,2.41)	1.26 (0.59,2.67)
Employment: Part-Time	1.01 (0.33,3.07)	0.57 (0.08,3.96)	0.58 (0.34,0.99)	0.58 (0.26,1.29)	0.44 (0.27,0.70)
Employment: Full-Time	0.58 (0.21,1.64)	0.74 (0.17,3.30)	0.75 (0.48,1.16)	0.69 (0.37,1.28)	0.53 (0.36,0.79)
Employment: Retired	0.62 (0.24,1.58)	0.47 (0.10,2.25)	0.64 (0.42,0.98)	0.77 (0.43,1.39)	0.56 (0.38,0.81)
Employment: Other	0.45 (0.15,1.29)	0.58 (0.12,2.70)	0.75 (0.48,1.16)	0.75 (0.40,1.40)	0.58 (0.39,0.87)
Smoking Status: Non-Smoker	Reference	Reference	Reference	Reference	Reference
Smoking Status: Former Smoker	1.25 (0.80,1.98)	1.06 (0.48,2.34)	0.99 (0.83,1.18)	0.92 (0.71,1.19)	1.09 (0.94,1.27)
Smoking Status: Current Smoker	1.60 (0.72,3.55)	1.97 (0.65,5.97)	0.72 (0.48,1.06)	0.94 (0.56,1.57)	0.65 (0.47,0.90)
Marital Status: Divorced/Separated	Reference	Reference	Reference	Reference	Reference
Marital Status: Widowed	0.58 (0.23,1.46)	0.58 (0.15,2.23)	0.81 (0.54,1.21)	0.60 (0.33,1.09)	0.73 (0.51,1.04)
Marital Status: Single	1.40 (0.58,3.39)	1.34 (0.39,4.67)	0.90 (0.58,1.38)	0.73 (0.40,1.34)	1.12 (0.79,1.58)
Marital Status: Married/Living with a Partner	0.61 (0.32,1.17)	0.40 (0.16,1.01)	0.85 (0.64,1.14)	0.68 (0.46,1.00)	1.03 (0.81,1.32)
Year of Cardiac Rehabilitation	0.90 (0.83,0.97)	0.92 (0.80,1.04)	0.90 (0.86,0.95)	0.93 (0.87,0.99)	0.97 (0.92,1.04)
Percent Exercise Sessions Attended	1.00 (0.99,1.02)	1.00 (0.98,1.02)	1.00 (0.99,1.01)	1.00 (0.99,1.01)	1.00 (0.99,1.00)

Coefficients are hazard ratio (HR) for all-cause mortality and sub-distributional hazard ratios (SHR) for all other outcomes. The logistic regression portion of the hurdle model was omitted. CVD = cardiovascular disease, ED = emergency department. NA indicates subgroups with too little sample size to generate coefficients.

Table S4.12. All coefficients of negative binomial hurdle models for frailty index change analyses.

Covariate	Number of Hospitalizations		Number of Hospital Days		Number of ED Visits
	All-cause	CVD	All-cause	CVD	All-cause
Frailty Index Change	0.99 (0.98,1.01)	0.99 (0.96,1.02)	0.98 (0.97,1.01)	1.00 (0.97,1.03)	0.99 (0.98,1.01)
Admission Frailty Index	1.02 (1.01,1.04)	0.92 (0.65,1.30)	1.02 (1.01,1.04)	1.01 (0.99,1.03)	1.03 (1.02,1.03)
Sex: Female	0.86 (0.60,1.22)	0.96 (0.56,1.66)	1.06 (0.75,1.50)	1.40 (0.81,2.41)	0.97 (0.81,1.15)
Age	1.21 (0.99,1.48)	1.02 (0.99,1.04)	1.30 (1.08,1.57)	1.18 (0.84,1.67)	1.12 (1.01,1.24)
Ref. Diagnosis: Coronary Artery Disease	Reference	Reference	Reference	Reference	Reference
Ref. Diagnosis: Percutaneous Coronary Intervention	0.76 (0.46,1.25)	0.81 (0.35,1.89)	0.60 (0.37,0.96)	0.37 (0.18,0.76)	0.78 (0.62,0.98)
Ref. Diagnosis: Cardiac Surgery	0.83 (0.54,1.28)	0.55 (0.20,1.47)	0.84 (0.55,1.28)	0.59 (0.29,1.21)	0.78 (0.62,0.99)
Ref. Diagnosis: Heart Failure	1.13 (0.63,2.05)	1.67 (0.84,3.31)	1.04 (0.56,1.96)	1.12 (0.47,2.65)	0.98 (0.68,1.42)
Ref. Diagnosis: Myocardial Infarction	0.74 (0.49,1.12)	0.91 (0.50,1.66)	0.93 (0.62,1.38)	1.09 (0.61,1.94)	0.86 (0.68,1.08)
Ref. Diagnosis: Other	0.42 (0.19,0.95)	0.24 (0.03,1.84)	0.88 (0.43,1.78)	1.05 (0.35,3.11)	0.88 (0.62,1.24)
Education: Less than Grade 12	Reference	Reference	Reference	Reference	Reference
Education: Grade 12/GED	1.24 (0.74,2.08)	0.62 (0.20,1.91)	1.31 (0.78,2.19)	0.84 (0.41,1.75)	0.99 (0.77,1.28)
Education: Technical College	1.34 (0.87,2.05)	1.56 (0.80,3.02)	1.21 (0.79,1.85)	1.43 (0.80,2.59)	1.15 (0.93,1.44)
Education: Bachelor's Degree	1.74 (1.07,2.81)	1.50 (0.70,3.20)	1.69 (1.05,2.74)	1.30 (0.63,2.67)	0.91 (0.70,1.17)
Education: Post-Graduate Education	0.94 (0.50,1.77)	1.26 (0.42,3.74)	0.77 (0.43,1.40)	1.01 (0.41,2.54)	0.93 (0.68,1.27)
Employment: Long-Term Disability	Reference	Reference	Reference	Reference	Reference
Employment: Unemployed	0.32 (0.05,2.00)	NA	0.28 (0.07,1.19)	0.23 (0.03,1.71)	0.54 (0.26,1.10)
Employment: Part-Time	0.46 (0.17,1.22)	NA	0.22 (0.09,0.57)	0.35 (0.07,1.82)	0.81 (0.50,1.31)
Employment: Full-Time	0.68 (0.34,1.38)	0.45 (0.18,1.12)	0.60 (0.28,1.26)	0.77 (0.26,2.29)	0.79 (0.53,1.18)
Employment: Retired	0.85 (0.43,1.69)	0.55 (0.23,1.30)	0.95 (0.46,1.95)	1.02 (0.39,2.70)	0.99 (0.68,1.45)
Employment: Other	0.61 (0.30,1.23)	0.46 (0.19,1.10)	0.60 (0.29,1.27)	0.82 (0.29,2.35)	0.80 (0.54,1.19)
Smoking Status: Non-Smoker	Reference	Reference	Reference	Reference	Reference
Smoking Status: Former Smoker	1.26 (0.90,1.75)	1.13 (0.65,1.97)	1.09 (0.80,1.49)	1.10 (0.68,1.77)	1.01 (0.85,1.20)
Smoking Status: Current Smoker	1.47 (0.74,2.90)	1.25 (0.53,2.97)	1.49 (0.76,2.92)	1.29 (0.52,3.25)	1.13 (0.79,1.61)
Marital Status: Divorced/Separated	Reference	Reference	Reference	Reference	Reference
Marital Status: Widowed	0.49 (0.24,1.02)	0.63 (0.18,2.21)	0.93 (0.45,1.93)	1.97 (0.68,5.68)	0.92 (0.59,1.42)
Marital Status: Single	1.62 (0.76,3.47)	1.46 (0.52,4.11)	2.30 (1.05,5.04)	2.98 (0.90,9.90)	1.55 (1.03,2.32)
Marital Status: Married/Living with a Partner	0.65 (0.38,1.10)	0.89 (0.41,1.95)	1.10 (0.64,1.89)	2.00 (0.97,4.13)	1.11 (0.83,1.50)
Year of Cardiac Rehabilitation	0.70 (0.56,0.89)	0.72 (0.49,1.06)	1.06 (0.84,1.35)	1.32 (0.93,1.87)	1.18 (0.99,1.41)
Percent Exercise Sessions Attended	0.99 (0.98,1.00)	1.00 (0.97,1.02)	1.00 (0.98,1.01)	0.99 (0.97,1.01)	1.00 (0.99,1.01)

All coefficients are incident rate ratios (IRR). The logistic regression (odds ratio) portion of the hurdle model was omitted. CVD = cardiovascular disease, ED = emergency department. NA indicates subgroups with too little sample size to generate coefficients.

4.6.3 Supplementary Figures

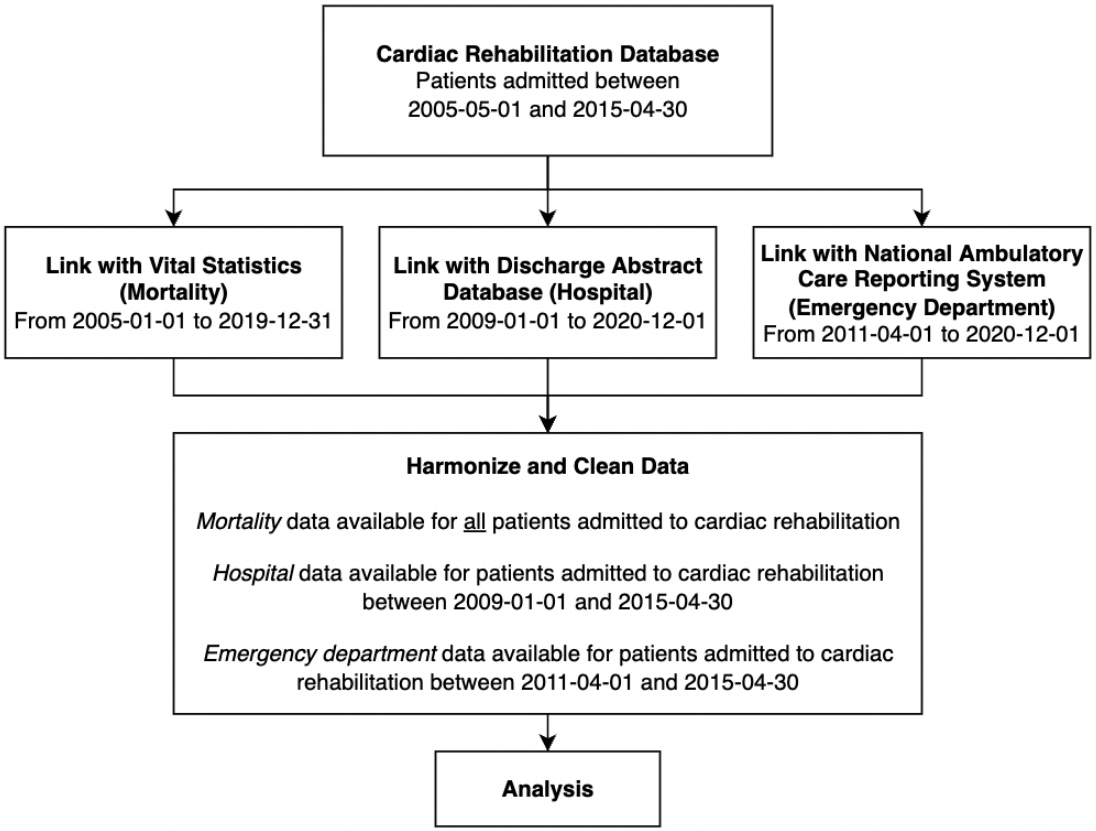

Figure S4.1. Data linkage procedure.

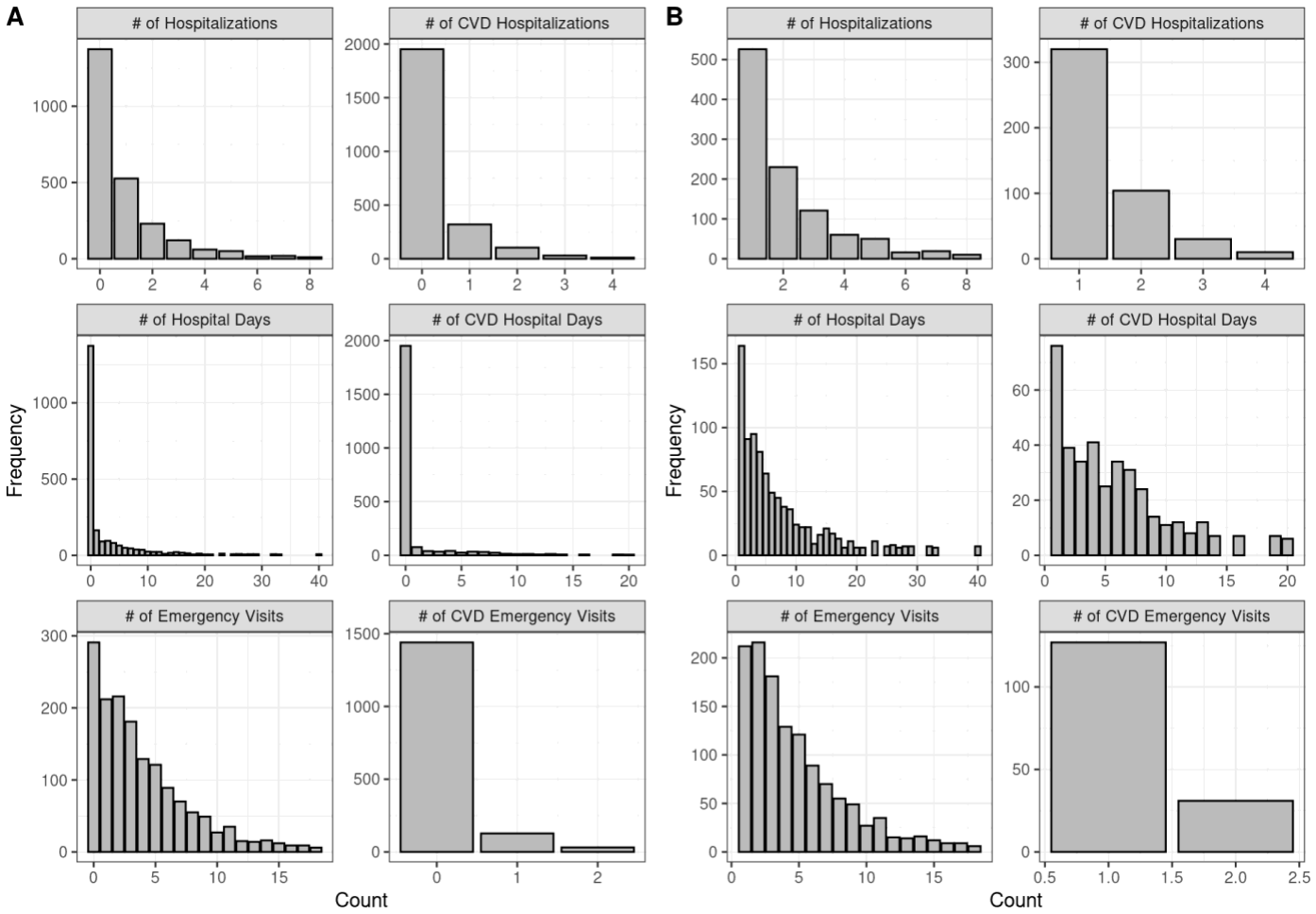

Figure S4.2. Distribution of total of number of hospitalizations, hospital days, and emergency department visits over a 5-year follow-up due to all-causes and CVD causes. Panel A includes zero counts and panel B excludes zero counts. CVD = cardiovascular disease.

Chapter 5 Discussion

5.1 Thesis Summary

The high prevalence of frailty in CR is concerning for the long-term health of patients who live with CVD. This thesis examined the relationship between frailty status on admission to CR, frailty changes that take place during CR, and 5-year health outcomes. The objectives were to 1) examine the association between admission frailty and mortality, hospitalizations, and emergency department visits due to all-causes and CVDs over a 5-year follow-up period in CR patients and 2) investigate the association between frailty changes with said outcomes (Chapter 4). When comparing admission FI and FI changes during CR, the limited ability of FI changes to predict long-term outcomes was surprising (Table 5.1).

Table 5.1. Summary of the associations between admission frailty and frailty changes with 5-year outcomes.

	Higher frailty at cardiac rehabilitation admission	**Greater frailty improvement from cardiac rehabilitation admission to completion**
All-cause mortality risk	↑↑	X
CVD mortality risk	↑↑↑	X
All-cause hospitalization risk	↑↑	↓
CVD hospitalization risk	↑↑	X
All-cause ED visit risk	↑	X
Number of all-cause hospital visits	↑↑	X
Number of CVD hospital visits	↑↑	X
Number of all-cause hospital days	↑	X
Number of CVD hospital days	X	X
Number of all-cause ED visits	↑↑	X

CVD = cardiovascular disease, ED = emergency department. Each arrow represent one percent change in risk per 0.01 greater admission frailty index or frailty index improvement during cardiac rehabilitation. Red arrows = greater risk, green arrows = lower risk.

5.1.1 Results Summary

The high frailty burden in patients who attended the current CR programme is likely related to the majority of the population being older, previously, or currently smoking, and having CVD diagnoses. The finding that current frailty status predicts outcomes means that a patient's physiological resilience may be important to various aspects of their future health. Indeed, patients who are more susceptible to injury and stressors may face greater complications which require use of inpatient and emergency medicine resources. Alongside having to address the burdens of multiple interacting health problems, lengthy and frequent hospital and emergency department visits are additional direct contributors to diminished quality of life for patients living with frailty.[179] For instance, primary characteristics of long hospital stays include social isolation, lack of exercise, and prolonged bed rest[180] add to the cycle of rapid physiological decline which ultimately result to premature death. Such health implications motivate action and investment to mitigate the effects of frailty on patients who attend CR.

In addition, our finding that FI changes were limited for long-term outcomes prediction when compared to admission FI is curious. If high frailty burdens are related to poor outcomes, then reductions in frailty should also manifest as better outcomes especially when considering that frailty may be reversibility. [27,77–84] However, the performance of FIs as a tool to measure changes in health is still a topic of extensive inquiry. In people who attend CR, we need to consider at which intervals to measure changes in frailty. It is possible that the current FI is not well-suited to capture short-term changes in frailty.

5.1.2 Admission Frailty and 5-Year Outcomes

Objective 1 of Chapter 4 demonstrated that most patients enter CR with mild to severe levels of frailty (Table 4.1). Importantly, greater frailty burden was related to worse 5-year health outcomes. Frailer patients at CR admission had greater 5-year risks of mortality and hospitalization due to all-causes and CVDs, and ED visits due to all-causes. In addition, frailer patients visited and spent more days in hospitals due to all-causes and CVDs and visited emergency departments more often due to all-causes (Table 4.2 and Figure 4.4).

First and foremost, our results emphasized the importance of considering the degree of frailty in the CR setting as opposed to viewing frailty as a dichotomy.[7] Specifically, incremental differences in admission frailty levels represented valuable information for understanding long-term clinical outcomes. Importantly, the significant association of CR admission frailty status with both all-cause and CVD outcomes, independent of many prognostic factors such as sex, age, referring diagnosis, education, employment, smoking status, and marital status, positions frailty as a key indicator of both overall and cardiovascular health. Indeed, frailty and CVDs are rooted[72–76,164] in ageing, physical inactivity, accumulation of chronic conditions, and inflammation, all of which results in diminished physiological reserves and impairment in recovery. Upon admission to CR, the frailest patients were predisposed to health complications which, in combination with CVDs and a reduced ability to recover from their disease, resulted in poor long-term outcomes.

5.1.3 Frailty Changes and 5-Year Outcomes

The identification of frailty as a key determinant of long-term health outcomes in CR ought to be followed with assessments of frailty changes and its impact on health outcomes. Objective 2 of Chapter 4 demonstrated that patients whose frailty improved during CR had a lower 5-year risk of all-cause hospitalization, but not with other outcomes (Table 4.2 and Figure 4.4). If high frailty burdens means reduced physiological reserves and greater vulnerability to stressors, then reductions in the frailty burden should mean greater resilience. Subsequently, frailty improvements should reflect improvements to overall health, physical function, and quality of life and thus better long-term outcomes. Patients whose health status changed during CR may experience corresponding changes in their healthcare use patterns – greater improvements in frailty may delay the patient's next hospitalization. However, FI changes were not associated with the total number of hospitalizations, hospital days, and ED visits due to any cause during the 5-year follow-up (Table 4.2). While greater improvements in frailty may delay the next all-cause hospitalization, the frequency of healthcare usage over 5 years was not dependent on frailty changes. Readmittances to hospitals may be inevitable for many patients with CVDs who require follow-up visits as part of routine care for their condition. For instance, older adults with severe frailty who received comprehensive geriatric assessments and early rehabilitation had lower rates of rehospitalization than usual care 1-month after discharge, but not 3-months after discharge.[166]

Our observation that incremental frailty changes in a 12-week CR programme only informs the risk of all-cause hospitalization, but not other long-term outcomes, suggests that greater nuance is required when evaluating frailty changes in relation to

long-term outcomes. Future research should consider if FI changes were due to a combination of the beneficial effects of a multicomponent CR programme, natural trajectory of illness, changes to CVD treatment, or due to a new CVD or other diagnosis that could either acutely increase their FI or prove fatal. Clinical trials show that exercise and multi-component interventions similar to CR can reduce frailty levels;[79,172] a number of cohort studies show that frailty improved during CR.[26–30] In addition, patients who recently received treatment for CVD (percutaneous coronary interventions and coronary artery bypass graft) exhibit U-shaped frailty trajectories,[160] meaning they improve initially but worsen after 6-months post-treatment which is consistent with our population where 66.7% of patients improved in frailty during 12-week CR (Table S4.4). In this CR population, the dynamism and reactivity of frailty to multiple factors that may improve or reduce frailty after people complete CR can obscure interpretations about the relationship between FI change during CR and long-term outcomes.

Moreso, the interval in which frailty change was measured may have not been long enough to capture stable frailty changes. Several longitudinal studies in community-dwelling populations which showed that FI change was a significant predictor of mortality[149,167,168] used 1-year changes or 4.5-year changes, longer than our 12-week change. As frailty is dynamic and likely susceptible to measurement errors,[167] a longer interval between frailty measures may offer more stable estimates which can be explored through frequent, long-term serial assessments of frailty status during and after completion of CR.

In addition, sensitivity analyses (Chapter 4, Section 4.3.5) further questions the utility of 12-week frailty changes for predicting long-term outcomes. The exclusion of

PCIs from the CR population mitigated the significant association between frailty changes and all-cause hospitalization. However, the change in p-value (p=0.072 without PCI, p=0.014 with PCI) may have been due to the loss of 18.1% of the sample (271/1,496) in the all-cause hospitalization model.

5.1.4 Domains Captured by the Frailty Index

The FI used in the current study captured several domains that have been shown to be associated with frailty including cardiovascular biomarkers,[181] physical[182] and mental[182] well-being, body composition,[183] and cardiovascular fitness. Other domains not fully captured in this FI include chronic conditions, cognition, social vulnerability, functional status, and medication use. Although this FI did not capture every health domain that is related to frailty, this method it is still robust when measuring frailty as physiological systems are interconnected and thus redundant – deficits in one physiological system may manifest as deficits in another system.

Other CR studies which used an FI measured similar domains as the FI in the current study. Pandey et al.[132] also included various cardiovascular biomarkers, quality of life, but additionally chronic conditions and sleep. Mudge et al.[26] notably included activities of daily living, comorbidities, cognition, and sleep. For future frailty research in CR, FIs should ideally capture multiple health domains so that sensitivity analyses can be conducted to assess the performance when predicting outcomes. For instance, the current study would benefit from sensitivity analyses to remove CVD-related items from the FI. For clinical practice, considering the feasibility of measuring frailty with an FI is of great importance. The task of measuring many health domains for understanding frailty may

require retraining and addition of frailty experts in CR – any decision to invest in additional resources may require investigation into cost-benefits of such policy changes.

5.2 Strengths

The current study contains a long follow-up of several outcomes in a relatively large CR population. To our knowledge, our study had the largest sample when reporting frailty prevalence and frailty changes during CR. In addition, our study sample had the longest (5-year) follow-up for five separate outcomes which were also specific to all-causes or to CVDs. The breadth of relevant health outcomes that we considered enabled comparisons of the frailty implications on outcomes in the same population.

5.3 Limitations

The study from Chapter 4 has several limitations. First, the DAD and NACRS databases only contained hospital and ED data from the Central Zone of the Nova Scotia Health thus missing data of visits in hospitals and emergency departments in the more rural Eastern, Northern, and Western zones. This limitation in data may have caused an under-estimation of the frequency of hospital and emergency department usage. Thus, the burden of frailty on patients in regard to frequent healthcare use may be greater than data we reported. Second, there were large numbers of missing data (17.6%; 593/3,371) for exercise sessions attended in the objective 1 sample (n=3,371), thus we were not able to control for any dose-response effect of CR exercise training on long-term outcomes. As the majority of the objective 1 sample completed CR and thus attended a greater proportion of exercise sessions, the relationship between frailty and long-term outcomes may have been over-estimated. Third, it was unclear exactly how long patients waited from their CR referral to CR admission as referral date was not available. However, a

report on a similar CR population (n=4,443 from 1999-2012) in Halifax, NS indicated that the median time from referral to enrolment was 27 days.[177] Even so, having a more precise account of the wait time would allow for better understanding of whether frailty changes during CR were due to the CR programme or due to illness trajectory. Lastly, although we found significant 2-way interactions between admission frailty, frailty change, and referring diagnosis, (Table S4.8) we were unable to explore each diagnosis independently further due to low sample sizes in each diagnosis category which only worsens when using the lower sample sizes from DAD and NACRS. Each referring diagnoses may exhibit distinct frailty trajectories, therefore the frailty burden on long-term outcomes may be greater in myocardial infarction and heart failure when compared to percutaneous coronary intervention.

The FI used in the current study contained 25 items, 5 fewer than the minimum recommended by standard procedures.[48] At 30 items or more, the estimates of mortality are more stable. Even so, the creators of the FI reported that a minimum of 20 items may be acceptable[178] and that estimates are unstable when there are fewer than 10 items.[48] In addition, the FI contained a large number of deficits related to CVD (12/25). Typically, sensitivity analyses would be performed removing all items related to CVD to assess the performance of the FI to predict outcomes. In this case, removing CVD related items would result in too few FI items – any estimates of outcomes would be unstable and have little value for interpretation.

5.4 Research Implications

Our findings highlight the importance of frailty status at CR admission for mortality, hospital use, and ED use, motivating further research to identify whether CR is

more beneficial to people with certain frailty levels. Given that frailty modifies the efficacy of an exercise intervention performed by patients with chronic heart failure,[132] it is plausible that patients who live with a greater degree of frailty would derive more benefit than patients who live with lower-frail from a full CR programme. In addition, our results are unique to the Halifax, NS CR population. Even though many CR programs follow similar guidelines, the heterogeneity across CR programs across countries motivate a harmonized analysis with other CR datasets to confirm the impact of frailty across different populations and settings. Furthermore, the frailty benefits from a CR programme may extend beyond the intervention period. Successful changes to behaviour, including better nutrition and more frequent exercise, can have lasting impacts on patients and their frailty trajectories post-CR. Therefore, future trials aiming to investigate frailty changes or target frailty should implement frequent follow-ups to measure frailty. In addition, the frequency and length of hospitalization and ED visits is a crude proxy for healthcare costs. Future research should investigate the impact of frailty and frailty changes on actual healthcare costs. For example, the CR data here can be linked with the Nova Scotia Medical Services Insurance billing data. This information would be valuable for healthcare policy makers looking to understand the financial burden of frailty in CR. Lastly, while our study was informative, it was not a randomized trial hence causal inferences were not able to be made for the relationship between frailty and long-term outcomes. While implementing a true control group would be valuable for understanding frailty changes caused by CR, it may be unethical as usual care for CVD populations involve referral to CR. Future research could implement propensity score

matching to emulate a control group, recruiting patients who were referred to CR but opted to not enrol in the programme.

5.5 Clinical Implications

The result that higher admission frailty levels in CR predicts greater frequency of healthcare use could be of interest to healthcare policy decision makers. CR is cost-effective[184] and reduces healthcare use due to illness. Where healthcare resources are limited, targeted recruitment and retention of people who attend CR with frailty may be a cost-effective strategy to reduce the burden on healthcare systems caused by frequent and lengthy hospitalizations and ED visits. The cost of a CR programme in NS (~$1,500) is fractional compared to the cost of a standard hospital stay in Canada ($7,619) and in NS ($7,238).[185,186] It is of interest to many stakeholders, including clinicians, governments, patients, and Canadian tax payers that frail CVD populations – who are more likely to drop out of CR[27] – receive the benefits of CR.

Arguably more important than cost-saving is the potential to improve the quality of life of patients, especially those who are in the most need. Frailer patients living with CVD have worse outcomes but at the same time underutilize CR.[187] Strategies should aim to routinize the assessment of frailty in CR and train staff to recognize the presence and degree of frailty in CR patients. Understanding admission frailty levels and the risks associated with frailty could empower staff to engage in tailored protocols that support patients to complete CR. Indeed, assessing and tracking the frailty status of CR patients may provide more personalization to CR treatments; frailty status-based adjustments to physical activity, nutritional, and pharmacologic treatments can ensure that patients receive the most suitable care for their needs. Lastly, while frailty assessments were

originally designed for older adults, research has shown that they also apply for middle-aged and younger adults with chronic conditions such as CR patients. Thus, the inclusion of frailty assessments in CR has the potential to improve care for all patients.

5.6 Conclusion

This thesis highlights the importance of frailty status at admission of a CR programme for informing the 5-year risk of mortality, hospitalization, and ED visit, as well as the total number of hospital visits, hospital days, and ED visits over 5 years post-CR. In addition, incremental frailty improvements during CR were related to a lower risk of hospitalization regardless of admission frailty status. Future work should investigate the benefits of targeting frailty reductions as an additional component of CR.

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