COMPARING VIRTUAL AND CENTER BASED CARDIAC REHABILITATION ON CHANGES IN FRAILTY

by

Evan MacEachern

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Table of Contents

List of Tables

List of Figures

Abstract

Background: Cardiac rehabilitation (CR) is the standard of care for the secondary prevention of cardiovascular disease (CVD). Healthcare providers delivering CR contend with an ageing CVD patient population who accumulate other age associated health problems. Frailty defines health in ageing and is associated with adverse outcomes in adults and people with CVD. Evidence suggests patients who complete center-based CR can reduce their frailty level, with the greatest improvements observed in the most severely frail patients. CR is also offered virtually, whereby patients receive their care remotely. Yet, whether virtual CR can improve patient frailty has not been studied. Here, we seek to better understand the influence of virtual CR on frailty change.

Objectives: The purpose of this thesis was to (1) compare changes in frailty from CR admission to completion in patients who enrolled in center-based or virtual CR, and (2) determine if admission frailty was associated with changes in cardiovascular biomarkers in both program models. I hypothesized (1) virtual CR would be associated with similar frailty improvements as in center-based CR, and (2) frailer participants at CR admission would observe the greatest improvement in frailty and cardiovascular biomarkers.

Methodology: This is secondary analysis of the Hearts and Health in Motion CR database consisted of 132 participants who completed virtual (n=58) and center-based CR (n=74) from August 2021 to April 2022. Participants' CR program allocation was determined by CR staff. Low-to-moderate risk participants were preferentially allocated to virtual CR, while center-based CR included patients who were deemed low, moderate, or high risk. CR programs were 6-to-10-weeks in duration (center-based and virtual CR, respectively), which included exercise therapy, and education on exercise safety, nutritional guidance, medication management, and cardiovascular risk factor reduction. Frailty was measured using a 65-item frailty index. ***Analysis****:* Frailty changes from CR admission to completion were analyzed using a two-way, mixed analysis of variance, comparing virtual versus center-based CR programs. Changes to cardiovascular health indicators were analyzed using linear regression. All analyses adjusted for exercise attendance, and age, sex, and cardiovascular biomarkers at admission. Simple slope analyses examined *a priori* admission frailty*CR program type interactions on frailty change and cardiovascular biomarkers.

Results: From 132 participants (age 64.5±10.5, 63.6% male), center-based (0.14±0.003) versus virtual CR participants (0.07±0.003) had higher admission frailty. We observed no main effect of CR model on frailty change. Frailer virtual participants at admission (FI=0.20-0.25) observed greater frailty improvements (-3.810 [-7.360,-0.251], p=.034) and reductions in triglyceride (-0.766 [-1.508,-0.025], p=0.04) and cholesterol (-0.660 [-1.229,-0.092], p=.021) compared to frailer center-based CR participants.

Conclusions: While our main analysis showed that both program models did not change frailty, frailer participants at CR admission were associated with greater frailty change and change to some CVD biomarkers in the virtual program.

List of Abbreviations Used

ANOVA	Analysis of variance
CLSA-FI	Canadian Longitudinal Study on Ageing Frailty Index
CR	Cardiac rehabilitation
CVD	Cardiovascular disease
EFS	Edmonton Frail Scale
FI	Frailty index
FICVD	CLSA-FI including cardiovascular biomarkers
HDL-cholesterol	High density lipoprotein cholesterol
HF	Heart failure
HRQOL	Health related quality of life
IADLs	Instrumental activities of daily living
LDL-cholesterol	Low density lipoprotein
METs	Metabolic equivalents
MICE	Multiple Imputation by Chained Equations
NSH	Nova Scotia Health (Authority)
OS	Oxidative stress
RCT	Randomized controlled trial
RPE	Rate of perceived exertion
TAVI	Transcatheter aortic valve implantation
6MWD	6-minute walk distance

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CHAPTER 1: Introduction

Cardiovascular diseases (CVDs) are among the leading causes of death and hospitalization in Canada [1] and around the world [2]. The prevalence of CVD increases with increasing age, from approximately 40% in those aged 40-59 years, to 70-75% in persons aged 60-79 years, and to 79-86% among those aged 80 years or older [3]. CVD patients are also tasked with managing age-associated health problems, which may be unrelated to their CVD, that increase their risk of experiencing subsequent adverse health outcomes [4]. Manifestations of an individual's accumulating health deficits can be described as frailty, which represents a subjective measure of health in relation to age [5].

Frailty is defined as a state which affects multiple physiological systems and provides a lens to an individual's overall health status [6]. Frailty considers an individual's variability in health and functional status relative to their age [7], and reflects an individual's biological age, rather than chronological age. As such, frailty allows for health comparisons among age matched peers [8, 9]. Frailty causes a reduction in physiological reserve due to accumulating health problems throughout the lifespan, thereby compromising the ability to recover from stressors (e.g., falls) [5, 6]. Importantly, CVD and frailty appear to have a bi-directional association, such that CVD can lead to worsening frailty, and vice-versa [10, 11]. The co-occurrence of frailty and CVD will heighten the risk for rapid health deficit accumulation, resulting in greater vulnerability to failing health [12], morbidity [13, 14], and mortality [15].

Currently, the gold standard for the secondary prevention of CVD is cardiac rehabilitation (CR) [16]. CR programs are typically delivered in a hospital or out-patient clinic setting [16] to provide regular exercise training, education on cardiovascular risk

factor reduction (i.e., education on exercise safety, nutrition, medication management, smoking behaviours, lifestyle modifications), and psychosocial support [16, 17]. These core components of CR are guided by a multidisciplinary healthcare team (e.g., cardiologist or physician, nurse, physiotherapist, dietician, program lead) who facilitate baseline assessments at CR admission, prescribe exercise regimes, provide education materials and counseling, and supervise the on-site portions of CR classes [16]. Despite evidence from the literature supporting the benefits of center-based CR to improve cardiovascular health, only one third of eligible patients choose to enroll [16, 18, 19]. Furthermore, research demonstrates CR patients with higher degrees of frailty at CR admission are less likely to complete CR [17, 20], despite evidence suggesting frailer CR participants stand to gain the greatest benefit, in terms of frailty and cardiovascular improvements, should they complete CR [4, 12, 14, 17, 21, 22].

As a strategy to increase enrollment, eligible "low-to-moderate CVD risk" patients have been offered home-based or virtual-based CR programs as an alternative to center-based care [23-25]. The virtual CR model uses the same core components as center-based CR; however, they are delivered to the patient remotely at home [23-25]. Virtual CR is facilitated through use of the internet, telephone, or smart devices to monitor patients' progression throughout their program [24, 26, 27]. Virtual CR has demonstrated non-inferior, and in some cases, significant improvements in CR health outcomes in "low-to-moderate CVD risk" participants, as compared to center-based CR [24, 27]. Virtual CR has the potential to increase patient enrollment by alleviating issues of transportation and accessibility to a healthcare center, bridging the gap for eligible patients to receive CR services.

Provided that center-based CR can improve CVD and frailty, and virtual CR can improve cardiovascular health similarly as in center-based CR, we propose that virtually delivered CR has the potential to improve frailty to a similar extent as center-based CR. To date, there are no studies investigating the impact of virtual CR on changes in frailty in CVD patients. Moreover, there are no studies comparing virtual versus center-based CR on changes in frailty level, and the association between admission frailty levels and change in cardiovascular biomarkers in virtual CR participants is unknown. This knowledge gap must be addressed to understand the impact of virtual-based CR on improving patient frailty levels and to compare its efficacy with center-based CR programs.

In this thesis, we address the existing knowledge gap by comparing changes in frailty level, as measured using an accumulation of deficits frailty index (FI), between CR participants who enrolled in center-based or virtual CR programs. Secondly, we examined associations between admission frailty level, CR model type, and changes to cardiovascular biomarkers over the course of CR. This thesis is divided into a literature review (Chapter 2), objectives, hypothesis, and methodology (Chapter 3), a manuscript (Chapter 4), and a general discussion (Chapter 5). Chapter 2 examines previously published work related to frailty and CR, including a systematic review of 25 research studies including 9,358 participants from 8 different countries. Chapter 4 describes our study's research and clinical implications, our sample's demographics, and our study's results, which are complemented by tables and figures. Chapter 5 discusses our findings, summarizes our limitations and challenges, and provides recommendations for future research.

CHAPTER 2: Literature Review

2.1. Cardiovascular Disease

CVD remains one of the global leaders of mortality (estimated mortality of 17.9 million, annually) [2], and disproportionately impacts the lives of older adults [3, 10]. Canadian data estimates that the number of Canadians aged 80+ will increase by approximately 3-fold, from 1.6 million to 4.7 million by 2068 [28]. This is important, as the Canadian government reports those aged 80+ have the greatest prevalence and burden of multiple CVDs [29]. North American data shows the prevalence of CVD, including hypertension, coronary heart disease, heart failure (HF), and stroke, increases linearly with age [30], from approximately 40% in persons aged 40-59 years, to 70-75% in persons aged 60-79 years, and to 79-86% among those aged 80 years or older [3]. Therefore, the overall prevalence and burden of CVD is expected to escalate over the next 45 years due to an increasingly ageing population [28].

CVD accounts for approximately 1 in every 4 deaths in Canada, trailing only behind cancer as the leading national cause of mortality [31]. CVD further contributes to patient burden concerning treatment and hospitalization [32]. Canadian incidence rates of CVD hospitalization are notably highest in the Maritime provinces [1]. Specifically, Newfoundland and Labrador, New Brunswick, Nova Scotia, and Prince Edward Island top the nation with CVD hospitalization rates of 1105, 960, 816, and 574 per 100,000 people, respectively [1]. Moreover, a 2018 report stated Nova Scotia and Newfoundland are the provinces with the highest prevalence of ischemic heart disease (9.7%) and greatest incidence of myocardial infarction (2.3%) in the nation, respectively [29]. Together, the impact of CVD in Canada, specifically in the Maritime provinces, advocates for health

interventions focussed on reducing cardiovascular risk factors to improving the health of Canadians in their later years.

2.1.2. What is Cardiovascular Disease?

The cardiovascular system is made up of the heart and supporting vasculature (e.g., arteries, veins, and smooth muscle tissues) which work to circulate blood and supply the peripheral organs and tissues with oxygen, minerals, and nutrients [33]. CVDs occur when pathological abnormalities affect the structure or function of the circulatory system [33]. An example of CVD is atherosclerosis, which is the result of plaque build-up in blood vessels, leading to increases blood pressure (hypertension) and decreased supply of blood to peripheral organs and tissues [33]. A key component to the development of CVD, specifically in atherosclerosis, is inflammation [34]. Endothelial damage caused by atherosclerosis will increase production of pro-inflammatory cytokines leading to inflamed vascular endothelial tissue [34]. Atherosclerosis has also been associated with oxidative stress, which creates a toxic cellular environment, and therefore speeds up 'cellular ageing', resulting in reduced resistance to stress or damage [34, 35]. These alterations, due to CVD, contributes to decreased function of the heart and/or the vasculature supplying blood to organs throughout the body [33].

There are several different pathologies that fall under the umbrella of CVD. These include, but are not limited to, HF, atrial fibrillation, acute coronary syndromes, heart attack, stable or unstable angina, arterial revascularization, stroke, transient ischemic attack, or peripheral vascular disease caused by atherosclerosis [36]. The various number of CVDs are due to many contributing risk factors, including non-modifiable risk factors such as genetics (i.e., family history of CVD) [37], age [37], and sex, such that CVD

impacts males at a younger age [38], and females are more impacted by the effects of smoking and diabetes on CVD development [38]. Female sex has also been associated with sex-specific risk factors, such as hypertensive disorders of pregnancy and early menarche [38]. In addition, modifiable lifestyle factor have been associated with greater CVD risk, such that cigarette smoking [39], greater volume of inactivity [33], and poor dietary habits [33, 39] were each associated with the development of CVD. Furthermore, the prevalence of CVD differs among levels of education, income, and socioeconomic status [40-42], such that lower levels of education and lower socioeconomic status were more strongly associated with developing CVD and CVD risk factors [40, 41]. The association between low income and CVD were observed in both high-income [42] and low-medium income countries [40].

2.1.3. Ageing and CVD

Older adults have a greater risk of experiencing health-related decline as compared to younger adults [43]. As such, the expression of greater functional impairment [44], greater frailty levels [45], and the co-existence of chronic health conditions [46], including CVD, is more prevalent as people age. To mitigate the impact of age-related declines in health, today's healthcare systems manage medical procedures (e.g., cardiac surgery), medication prescriptions, and lifestyle and behaviour interventions (e.g., CR) designed to increase survival and health span of older adults [16, 47, 48]. These improvements in healthcare have come to fruition, as more CVD patients are surviving their initial acute cardiovascular events, as compared to previous decades [48]. This means, however, many people are now living with CVD for a longer duration, requiring long term management of their CVD condition [48]. Importantly, CVDs will seldomly act in isolation, meaning the

typical CVD patient will have multiple health problems associated with ageing which will also require management [49]. Here, the expression of an individual's accumulated health deficits over the lifespan can describe an individual's level of frailty [49].

2.2. Frailty

In 2013, Clegg and colleagues defined frailty as, "a state of increased vulnerability to poor resolution of homoeostasis after a stressor event, which increases the risk of adverse outcomes, including falls, delirium, and disability" [50]. Frailty hinders one's ability to respond or recover from stressors put on the body to a greater extent than non-frail counterparts [51] and is associated with an increased vulnerability of falls, disability, poor health, dependency, and mortality [52]. Furthermore, frailty has been associated with negatively impacting physical and mental health, based on systematic review and meta-analytic evidence from six different countries [53]. Negative influences on physical and mental health can manifest as difficulty with multiple activities of daily living, thus challenging the ability to live independently [51]. More severely frail individuals have a greater susceptibility to developing disease, and will experience worse outcomes of that disease, compared to more robust contemporaries [4]. Systematic review and meta-analytic evidence from 31 studies and 158,764 participants demonstrated that frailty was associated with a 1.8 to 2.3-fold increased risk of mortality and 1.2 to 1.8-fold increased risk of hospitalization in older male and female community dwellers, respectively [51].

The prevalence of frailty is more common as age increases [4, 54]. Systematic review and meta-analytic evidence from 1.7 million participants found that among individuals in their 50's, 60's, 70's, 80's, and 90+, global estimates of high degrees of frailty were 11%, 16%, 20%, 31%, and 51%, respectively [54]. However, frailty is a

dynamic state of health, and variable across age, meaning that changes in frailty status, expressed as improvements or losses to various domains of health, can influence the physiological reserve of multiple body systems [6, 55].

2.2.1. How is Frailty Measured?

Although research on frailty has increased over the last 20 years, there remains no consensus on which tool should be used to measure frailty. A review from 2016 reported 67 different frailty instruments have been used to assess frailty, nine of which were highly cited [56], and novel instruments continue to be developed to meet the needs of different populations. The most commonly used assessment instruments are the frailty phenotype [57] and the frailty index [5]. While many new tools have been introduced, other frailty tools are generally developed in line with these two models since emerging in the early 2000's.

Introduced by Fried and colleagues, the frailty phenotype views frailty as a syndrome of physical frailty, characterized by the presence or absence of five signs and symptoms pertaining to an individual's physical and metabolic status [57, 58]. The five criteria of the frailty phenotype include self-reported levels of physical inactivity, unintentional weight loss, and exhaustion, and measures of muscle weakness and slow gait speed [57]. Meeting three or more of the frailty phenotype criteria is indicative of frailty, one or two items is suggestive of pre-frailty, and meeting zero of the five criteria is considered robust [57]. Many variations of the frailty phenotype have been created to meet the needs of specific clinical settings and participants who are undergoing assessment [59]. Still, the frailty phenotype prevails as one of the leading tools used for clinical frailty assessment and research. A systematic review and meta-analysis by O'Caoimh and

colleagues, including 62 countries and 1.7 million participants aged 50+ across the world, reports the estimated prevalence of frailty and pre-frailty using the frailty phenotype is 12% and 42%, respectively [54].

Mitnitski and Rockwood's accumulation of deficits model views frailty as a state, rather than a syndrome, that is multifactorial in nature and representative of variability in health among adults [5]. The accumulation of deficits model assumes that the more health deficits a person has, the frailer that person is [60]. To account for health deficits, a FI is created using a guidelines-based approach [5, 49, 60]. These guidelines recommend that variables can be included in a FI if the deficits 1) are associated with health status, 2) generally increase in prevalence with older age, 3) do not saturate too early in life (i.e., everyone 50+ presents with the health deficit, such as cataracts), 4) cover a range of system functions, and 5) the items do not change if using a repeat assessment on the same sample [60]. The FI is used to count health deficits pertaining to physical and cognitive health, presence of chronic diseases, disabilities, and laboratory abnormalities [5, 58]. The FI provides a ratio score of deficits present divided by the total number of deficits considered [60]. For example, if a person presents with 10 of 40 deficits considered, that persons FI score would be 10/40 = 0.25. FI scores with higher ratios indicate higher levels of frailty [5]. The FI should ideally include at least 30 items; however, the more items that are included in the FI, the more precise the estimates with prevalence and risk for adverse health outcomes are [5]. Thus, the accumulation of deficits model for a FI permits flexibility in the variables used, and generalizability among different populations. The aforementioned systematic review and meta-analysis by O'Caoimh and colleagues

estimated, in persons aged 50 and over, comparisons of "frail" and "pre-frail" prevalence using the accumulation of deficits model were 24% and 49%, respectively [54].

While previous literature has advocated for the frailty phenotype and the FI to accurately predict adverse health outcomes [61], evidence from O'Caoimh and colleagues indicates there are prevalence differences of frailty based on the operationalization of the frailty assessment in use [54]. We believe that using a FI to assess frailty eliminates certain "ceiling and floor" effects as compared to the frailty phenotype, permitting greater discrimination of the lower and higher ends of the FI to be determined. Moreover, the FI provides an eye to which health concerns (i.e., cognition, cardiovascular health) are contributing more severely to an individual's frailty level based on deficit responses found within the index. For example, if an individual has many deficits in cardiovascular health, and few deficits in cognition, their cardiovascular health may be a greater contributor to their frailty level. For these reasons, this study used the accumulation of deficits (i.e., FI) approach to assess frailty.

2.3. Frailty and CVD

Many patients with CVD are impacted by frailty [3, 4, 12, 15, 17, 62-64]. Frailty predisposes individuals to more severe CVD outcomes, such as alterations in structure and function of the heart [62, 64] and greater risk of CVD mortality and CVD hospitalization [65, 66]. Systematic review evidence from 30 cross-sectional and case-series studies, including 96,841 participants, reported mortality rates were 2.5 to 3.5-fold greater among frail CVD patients as compared to non-frail counterparts [67]. Furthermore, systematic review evidence from 2009 examined the association between CVD and frailty among 54,250 community dwellers from 9 different studies and found frail community dwellers

status was associated with a two-to-threefold increase in the prevalence of CVD as compared with non-frail counterparts [12]. Additional systematic review and meta-analytic evidence from 26 observational and interventional studies including 6,896 patients with HF - a severe consequence of CVD - report one in every two HF patients were frail [6]. Accordingly, a series of systematic review and meta-analytic evidence indicates that frail individuals were more likely to have atrial fibrillation [62], arterial stiffness [63], and hypertension [68], each aligning with the findings of Afilalo and colleagues in 2009 [12]. The suggested co-occurrence of CVD and frailty may bias individuals toward accelerated health deficit accumulation, highlighting the need for interventions which can treat CVD and frailty simultaneously to be prioritized for those with exacerbated CVD conditions due to frailty, and vice-versa.

2.3.1. The Link Between Frailty and CVD

The origins of frailty and CVD are mutually complex due to numerous pathways that contribute to their existence. Even so, frailty and CVD share several overlapping risk factors, including genetic, biological (e.g., inflammation) [52, 69], behavioural (e.g., physical inactivity) [4, 70], physiological (e.g., cognitive impairment) [71, 72], and psychological factors (e.g., social well-being) [73]. Furthermore, systematic review evidence from 23 longitudinal studies including 119,503 participants pointed to sociodemographic contributions, such that lower education level, lower income, and lower socioeconomic positioning were significantly associated with both frailty and CVD [73].

Biological factors, such as inflammatory and immune responses, similarly impact frailty and cardiovascular health, suggesting a link between the two health concerns [34]. In fact, a systematic review and meta-analysis on 32 studies and 23,910 participants

identified several immune and inflammatory blood biomarkers that were significantly associated with frailty [52]. Soysal and colleagues found higher concentrations of white blood cells, fibrinogen, and pro-inflammatory cytokines c-reactive protein and interleukin-6 were associated with frail community dwellers, compared with pre-frail or robust peers [52]. Another theory broadening the association between frailty and CVD is oxidative stress (OS) [34, 35]. OS occurs when there is decreased cellular antioxidant enzymatic activity, which contaminates the cellular environment, thus increasing 'ageing' at the cellular level (i.e., declining resistance to stress or damage) [35]. Cellular ageing stimulated by OS will negatively impact an individual's physiological resilience over time, by impacting muscles (i.e., smooth muscle of the vasculature, working muscles for mobility), bones, and the immune system [35].

2.4. Managing Frailty

Properly managing frailty can prolong independence, increase longevity, and improve quality of life and functional mobility [74]. A recent scoping review suggests key strategies to managing frailty involve multicomponent and multidisciplinary lead interventions [74]. Indeed, exercise interventions which focussed on aerobic, balance and coordination, or resistance-based training showed improved mobility, walking speed, strength, and overall physical performance in community-dwellers living with frailty [74], which is indicative of improved frailty by certain frailty definitions [57, 75]. Furthermore, evidence suggests nutrition supplementation aided frail community-dwellers to improve their physical performance and muscle strength [74, 76]. Lastly, reviewing and managing medications in acute hospital care was associated with improved frailty outcomes for frail hospitalized patients [74]. While managing frailty is the most successful when including

an exercise training component [76], multicomponent interventions which accompany exercise therapy with nutrition and medication management, as well as education and consulting, may optimize the management of frailty in community-dwelling and hospitalized individuals [74, 76].

2.5. Cardiac Rehabilitation

The current gold standard for the treatment and secondary prevention of CVD is CR [16, 48]. The extensive, multidisciplinary, evidence-informed approach of CR implements behaviour change therapy consisting of exercise therapy, education on nutritional guidance, medication management, CVD education, and psycho-social support to manage CVD (Table 1) [16, 77, 78]. Based on North American, European, and Asian CR guidelines, CR is delivered and supervised by a multidisciplinary team, including a cardiologist, nurse, physiotherapist, dietician, and other supporting CR staff (e.g., program lead) [16, 17]. CR programs are typically 12-weeks in duration [16], although, programs may range from six weeks to six months [48, 79-81]. On occasion, CR may be extended with additional follow-up periods of up to 36 months [16]. Exercise therapy is the cornerstone to CR [16]. Exercise sessions in CR typically occur 1-3 times per week, with a focus on aerobic and resistance type of exercises [16, 17]. Depending on the CR program, balance and flexibility exercises may be included to improve participants' mobility and functional capacity [16]. The duration, frequency, and intensity of exercise sessions are subject to variability across different programs [16]. However, a systematic review and meta-analysis on 63 RCTs, including a sample of 14,486 CR participants, reported exercise sessions are most often 10-90 minutes in duration and performed at the Borg Scale rate of perceived exertion of 11-15, or 50-85% of maximal heart rate [16].

Table 1. Core components of cardiac rehabilitation[a]

CR Core Component	Facilitated by	Volume	Material Covered
Patient Assessment	Multi-disciplinary led[b]	Assessments may occur at various time points (i.e., admission, completion, throughout).	Graded exercise stress test (i.e., METs), blood lipids, blood sugars, quality of life measures
Exercise Training	Physiotherapist, exercise physiologist	1-3 times weekly, 10-90 minutes in duration	Exercise safety, aerobic and resistance exercises, warm-up and cool-down, monitoring heart rate and rate of perceived exertion
Nutrition Education	Dietician	Weekly, bi-weekly, up to 60 minutes in duration	Healthy food options, controlling blood sugars and lipids, and alcohol intake
Medication Education	Nurse, family doctor	Weekly, bi-weekly, up to 60 minutes in duration	Recommendations on medication changes, altering doses, frequencies
Risk Factor Education	Multi-disciplinary led[b]	Weekly, 10 minutes-3 hours in duration	Lifestyle behaviour change, weight management, smoking status, sedentary behaviour
Psycho-Social Support	Multi-disciplinary led[b]	Weekly, duration based on subjective needs	Guidance on program progression, question and answer opportunities, expectations of the CR program

[a]Table characteristics drawn from North American Guidelines on CR [16]. [b]Multidisciplinary healthcare team lead by nurse, physiotherapist, dietician, cardiologist or physician, and supporting staff (e.g., program lead).

Education material provided in CR is delivered by the multidisciplinary CR staff in group-based sessions, one-to-one sessions, or a combination of the two [82]. Education sessions may occur face-to-face (most frequent), over the telephone, using the internet, home visits (least frequent), or a combination of methods [82, 83]. Due to the various methods of delivery, the 'dose' of education in CR (i.e., frequency and duration) varies substantially among programs [82]. However, a systematic review from 2014 indicated the

average number of education sessions in CR is 6, with a range of 10 minutes to 3 hours per session [83]. Delivery of education in CR is facilitated through group discussions, lectures and presentations, and question and answer periods [83]. Systematic review evidence from 42 studies (23 randomized controlled trials, 7 quasi-experimental, 6 cross-sectional, 5 cohort, and 1 mixed study design) with 16,079 participants from 11 countries and 3 continents identified the focus of education in CR pertains to CVD risk factor reduction, medication management, smoking cessation, nutritional guidance, exercise safety, behaviour change strategies, and returning to one's day-to-day activities [83]. Furthermore, education is supplemented by providing participants with information about general CVDs, updates on participants' on-going health condition, and how they are progressing through their program [82, 84].

The psychosocial component of CR refers to social support and psychological counselling for individuals who feel unwell following their cardiac event, or anxiety toward starting CR [84]. Psychosocial support is a multidisciplinary led initiative, with each healthcare professional available to discuss questions or concerns regarding the core components of CR or an individual's health status [83]. Psychosocial support includes counselling on relaxation techniques, self-management strategies, stress and anxiety management, and social and emotional support [83]. Psychosocial counselling is offered by the CR healthcare team throughout the program or upon CR discharge [83].

Participation in CR has proven to reduce the risk of experiencing an adverse cardiovascular event, improve cardiovascular risk factors [84], improve functional status (i.e., aerobic fitness, muscular strength), survival, and contribute to a healthier psychosocial well-being [18, 85]. A systematic review and meta-analysis of 63 randomized controlled

trials (RCTs), including 14,486 participants, reported individuals who attended CR reduced their cardiovascular mortality by 25% and secondary hospitalization by 18% when compared to people who did not receive CR [16]. Additionally, Anderson and colleagues identified health related quality of life (HRQOL) was improved in 66% (14/21) of studies that included HRQOL as an outcome of interest [16]. Altogether, CR represents a thorough management strategy toward to the treatment and secondary prevention of CVD, and too, a promising multicomponent healthcare intervention which may lend to improvements in frailty [83, 84].

2.5.1. How is Cardiac Rehabilitation Delivered?

The most common setting of CR delivery is through hospital or out-patient clinics, which is an extension of one's hospital care following an acute cardiovascular event [16]. However, during the COVID-19 pandemic in Canada, Moulson and colleagues [23] recommended CR programs must adapt to offer home-based or virtual programs to properly provide rehabilitation services to CVD patients while respecting public health guidelines (i.e., social distancing) [23, 25]. The literature on virtual-based CR programs identifies virtual care is typically designed for patients who, based on their admission risk-stratification assessment (i.e., patient medical history, orthopaedic limitations, exercise stress test results), are deemed clinically stable and are considered "low-to moderate risk" patients [23, 86]. Therefore, the typical participant demographics of virtual-based CR programs will contrast with traditional center-based CR programs, which are accommodating of patients who are considered "low, moderate, or high-risk" at CR admission [23, 86].

Countries in North America, Europe, and Asia, employ the same core components for virtual CR as center-based CR [77], including education on exercise safety, medication management, nutrition guidance, and psychosocial supports [78]. Consultations in virtual CR occur regularly as in center-based CR, however, the virtual model permits remotely monitored rehabilitation [78]. Most often, education consultations are facilitated using the internet (i.e., video conferencing, websites), telephone, or a combination of the two [25]. Therefore, the virtual model of CR differs from traditional CR in terms of supervision, whereby virtual CR participants would not receive regular supervision, monitoring, or access to their healthcare team during exercise sessions [77]. Virtual CR relies on technologies such as mobile devices (i.e., smart phone), wearable technology (i.e., heart rate monitors), or self-reports (i.e., during video conferencing with healthcare team) to monitor care throughout the virtual program [24, 25].

Additionally, virtual CR contrasts with center-based CR when prescribing physiotherapist recommended exercise programs. In virtual CR, participants will consult with their CR physiotherapist to create individualized exercise prescriptions, which can be completed with equipment or resources available to them at home or surrounding community [23, 26]. Therefore, exercise prescriptions may include home-based exercise activity (e.g., body weight resistance exercise) or outdoor recreational activities in surrounding areas (e.g., walking in public parks, bicycle trails) [23, 24]. Reasonably, the unsupervised nature of virtual CR autonomizes its participants to govern exercise prescriptions with their day-to-day schedule, overcoming the scheduling barriers associated with center-based CR enrolment [26, 78]. Regular consultations with virtual participants' healthcare team warrants a guided progression through CR, ensuring patient

safety and comfort throughout the program. In sum, the literature supports virtual-based CR as a safe, feasible, and promising alternative to traditional center-based care, enabling eligible "low-to-moderate risk" CVD patients to receive rehabilitation services and improve their health when center-based programs are inaccessible [77, 87-89].

2.5.2. How Effective is Virtual Cardiac Rehabilitation?

Systematic review and meta-analytic evidence from nine RCTs suggested virtual CR can improve blood lipids [77], blood pressure [77], morbidity, and mortality when compared to traditional center-based CR, demonstrating non-inferiority in "low-to-moderate risk" patients [24, 25, 77, 90]. An additional systematic review and meta-analysis on 1189 participants from 11 RCTs reported that virtual CR is at least as effective, if not more effective than center-based CR for improving cardiovascular risk factors and functional capacity in "low-to-moderate risk" patients [24]. Virtual CR was also associated with greater physical activity and program adherence when compared to center-based CR [24, 25], and that patients' HRQOL was improved following the completion of virtual CR [25].

Certain advantages of virtual versus center-based CR relate to issues of accessibility, transportation, commuting, and in-person scheduling at a health care center, which are more challenging for center-based CR programs [24, 26, 91, 92]. The virtual model allows for CR to reach a greater proportion of eligible patients with geographic inequities, such as those living rurally or outside the area of health-centers [24, 27]. Additionally, Dinesen and colleagues suggested virtual CR offers increased relatedness with health care providers, whereby participants perceived healthcare providers in new roles, such as coaches, providing motivation and encouragement throughout participants'

more autonomous virtual intervention [89]. Furthermore, Spindler and colleagues report stronger interaction with program materials and decision making within interventions was observed in virtual CR participants [88]. Through self-management, participants' perceived control and self-efficacy for managing their health was enhanced, thus providing greater regulation over one's rehabilitation intervention and care [88]. Dinesen and colleagues did not investigate these outcomes in center-based CR participants.

However, virtual CR is not without its limitations. A potential disadvantage to virtual CR is safety concerning higher risk patients due to the lack of standardization across virtual-based CR programs [86]. The lack of standardization in virtual CR makes novel evidence and advocacy difficult to generalize across different populations. As well, programs are typically implemented among "low-to-moderate risk" CVD patients, which introduces biases when interpreting the results of virtual CR interventions. Despite these limitations, virtual CR bolsters the core components of center-based CR while alleviating common barriers to enrollment and program adherence [77]. Therefore, virtually modelled interventions enable eligible CR participants to adopt healthy behaviours into their daily, home-based routine, and are not restricted to a hospital or healthcare setting [93].

2.6. Cardiac Rehabilitation and Frailty

Based on the multifactorial nature of CR programs, evidence suggests CR may be appropriate to target both improvements in cardiovascular and frailty outcomes. As such, there is a growing body of literature that aims to understand frailty in CR [4, 12, 14, 17, 22, 94, 95]. However, previously published evidence on frailty and CR has not been synthesized to understand its role for patients, healthcare providers, and healthcare systems delivering CR programs to patients. Therefore, we undertook a systematic

review to map the current body of literature pertaining to CR and frailty to better understand how frailty has been used as an outcome measure, a predictor of experiencing health outcomes, or as a characteristic of the study sample among CR participants.

To be included in this review, articles were required to measure or focus on specific dimensions of frailty in participants enrolling in CR (i.e., using frailty as an outcome measure in CR, using frailty as a predictor of health outcomes, or using frailty to describe the study's sample). Our review included observational studies (including cohort and case– control studies) which investigated frailty among CR participants. Studies employing methodology to capture quantitative data were included to consider different aspects of frailty in CR participants. Articles were included if they were: published between 2000-2021, written in the English language, and involved human participants. For this review, we excluded randomized controlled trial study designs. We also excluded articles if they did not use a recognized frailty tool to capture frailty.

To identify relevant literature, databases Embase, CINAHL, and Medline were searched from 2000- 2021. Key terms used to search each database were: frail* OR fragil* AND (cardiac OR heart OR coronary OR cardiovascular) NEAR/3 (rehabilitation OR therapy OR nursing). A total of 1395 articles were identified from the database searches, from which, 321 articles were removed as duplicates. Two independent reviewers screened the remaining 1074 articles (Embase: 618, Medline: 289, CINAHL: 167), of which, 110 met the criteria for full-text review. Fifteen publications of original research published between 2017-2021 and 10 abstracts published between 2011-2021 were included. In total, 25 research studies including 9,358 participants were retrieved pertaining to frailty and CR. A flow diagram depicting these results is shown in Figure 1.

Of the 25 studies included in this review, 12 were based in Japan [13, 14, 66, 96-104], three in Canada [17, 105, 106], and one each from the United Kingdom [107], USA [94], Australia [22], Germany [108], Brazil [109], and Columbia [110]. The remaining 4 studies did not disclose the location of the sample [111-114]. Study designs consisted of retrospective cohort studies (n=14) [13, 15, 17, 20, 22, 66, 94, 97, 99, 101, 103, 109, 113, 114] and prospective cohort studies (n=11) [14, 96, 100, 102, 104, 106-108, 110-112]. Mean age was reported in 18 studies [13-15, 17, 66, 94, 96, 97, 99, 100, 102-104, 107-109, 111, 114]. Mean age from 7,044 participants included in our review was 73.5 years old. The proportion of male and female participants was reported in 18/25 studies [13-15, 17, 22, 94, 96, 97, 99, 100, 102-104, 107-109, 113, 114]. Two studies reported a greater proportion of female participants, whereby samples consisted of 52.2% [108] and 73.3% [96] female CR participants [113], respectively, while one study consisted exclusively of female CR participants (100%) [113]. The remaining 7 studies did not report on sex distribution within their sample [20, 66, 101, 106, 110-112].

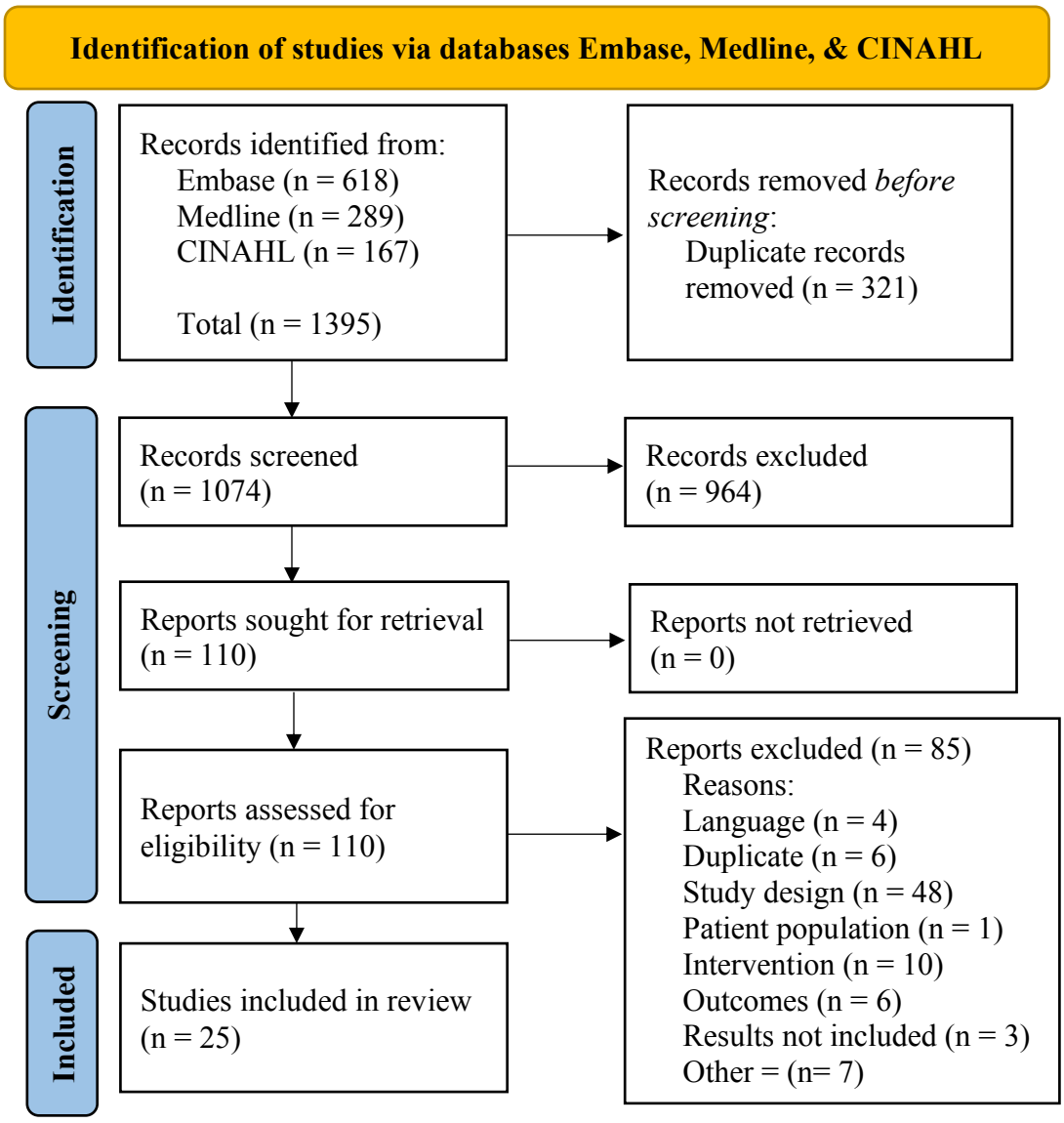

Figure 1. PRISMA flow diagram of systematic review search results.

Our systematic review included studies which evaluated frailty on patients experiencing HF (n=4) [13, 22, 66, 96], transcatheter aortic valve implantation (TAVI) (n=2) [108, 114], cardiac surgery (n=1) [99], and general CVD/coronary artery disease (n=11) [14, 15, 17, 20, 95, 97, 100, 102, 109, 111, 112]. The remaining 7 studies did not specify their samples referring diagnoses to CR [100, 101, 104, 106, 107, 110, 113].

The most widely used frailty tools from this review were the frailty phenotype (n=9) [57], the FI (n=6) [5], and the Kihon Checklist (n=6) [14]. The latter is a version of the FI

using 25 items and has been primarily used in Japan-based cohorts [115]. Two studies assessed frailty using both the frailty phenotype and the accumulation of deficits model (FI) [20, 112], two studies used the Edmonton Frail Scale (EFS) [106, 109], and three studies used modified versions of the Short Physical Performance Battery [94, 111, 116]. Distinctions of frailty were often described as robust or non-frail, pre-frail, or frail and severely frail. Frailty cut-off points varied among studies depending on the frailty tool used. Unless otherwise indicated by study authors, we defined frailty as ≥0.20, pre-frailty as 0.10-0.19, and robust at <0.10 for studies using a FI.

2.6.1. Frailty Prevalence in Cardiac Rehabilitation

Seventeen studies (n = 4,580) included a frailty assessment at CR admission [14, 15, 17, 22, 94, 97, 99, 102, 103, 106-108, 112-114]. From these studies, the pooled prevalence of robust, pre-frail, and frail CR participants upon admission was 30.6%, 26.3%, and 43.1%, respectively (Table 2) [14, 15, 17, 22, 94, 97, 99, 102, 103, 106-108, 112-114]. Two studies assessed frailty in CR but did not identify when assessments took place (i.e., admission or completion of CR) [101, 110]. Based on these two studies, the pooled prevalence of robust, pre-frail, and frail CR participants was 47%, 28.7%, and 24.3%, respectively. Nozaki and colleagues (2020) reported the frailty prevalence of 387 participants solely upon discharge from CR, whereby 46.5% were considered robust and 53.5% were frail [100]. Sex differences were only discussed in three studies [13, 15, 110]; for example, Aida and colleagues estimated the prevalence of frailty in females (56%) was greater than in males (31%) [15], which aligns with previous work [67].

Table 2. Systematic review frailty prevalence at cardiac rehabilitation admission

				Frailty Prevalence			
Ref.	**Author & Year**	**Sample Size**	**Assessment Time**	**Robust**	**Pre-frailty**	**Frail**	**Frailty Assessment Tool**
[22]	Mudge et al., 2021	256	Admission	42.9%	0.0%	57.1%	41-item frailty index
[94]	Lutz et al., 2020	243	Admission	30.8%	28.8%	40.4%	Modified Frailty Phenotype
[15]	Aida et al., 2020	895	Admission	11.2%	45.5%	43.3%	Frailty Phenotype Model
[17]	Kehler et al., 2020	2322	Admission	17.8%	27.6%	54.6%	25-item frailty index
[97]	Nishitani-Yokoyama et al., 2021	102	Admission	31.3%	34.3%	34.3%	25-item Kihon Checklist
[107]	Tew et al., 2017	100	Admission	71.0%	0.0%	29.0%	Frailty Phenotype Model
[113]	Landry et al., 2018	800	Admission	0.0%	45.9%	54.1%	Frailty index
[66]	Kamiya et al., 2020	862	N/A[a]	N/A[a]	N/A[a]	N/A[a]	19-item frailty index
[112]	Cacciatore et al., 2011	240	Admission	68.8%	0.0%	31.2%	Frailty Phenotype Model, Lach's Frailty Scale, Frailty Index
[110]	Quintero-Cruz et al., 1018	35	Did not say	22.8%	54.4%	22.8%	Frailty Phenotype Model
[106]	Mathew et al., 2019	764	Admission	82.3%	17.7%	0.0%	Edmonton Frail Scale
[99]	Arai et al., 2019	78	Admission	57.7%	0.0%	42.3%	Frailty Phenotype Model
[100]	Mitsuhiro-Kunimoto et al., 2018	251	Admission	49.9%	31.0%	19.1%	25-item Kihon Checklist
[101]	Toshie Tanaka et al., 2018	31	Did not say	74.2%	0.0%	25.8%	Frailty Phenotype Model
[102]	Ushijima et al., 2020	89	Admission	11.2%	63.0%	25.8%	Frailty Phenotype Model
[96]	Kato et al., 2021	29	N/A[a]	N/A[a]	N/A[a]	N/A[a]	25-item Kihon Checklist
[114]	Eichler et al. 2015	171	Admission	50.8%	0.0%	49.2%	Pathologic Frailty Index
[111]	Henderson et al., 2017	60	N/A[a]	60.0%	0.0%	40.0%	Modified SPPB[a]
[13]	Nozaki et al., 2020	387	Discharge	46.5%	0.0%	53.5%	Modified Frailty Phenotype Model
[108]	Eichler et al., 2017	122	Admission	63.1%	0.0%	36.9%	Frailty index
[14]	Kunimoto et al., 2019	845	Admission	33.9%	31.9%	34.2%	25-item Kihon Checklist
[103]	Honzawa et al., 2020	255	Admission	29.4%	31.8%	38.8%	25-item Kihon Checklist
[104]	Kunimoto et al., 2019	182	Admission	59.9%	N/A[a]	40.1%	25-item Kihon Checklist
[20]	Kimber et al., 2018	235	N/A[a]	N/A[a]	N/A[a]	N/A[a]	Clinical frailty scale, Modified Phenotype Model, SPPB[a], Functional Frailty index
[109]	Ritt et al., 2021	51	Admission	N/A[a]	N/A[a]	N/A[a]	Edmonton Frail Scale

[a]Abbreviations: N/A, not available; SPPB, short physical performance battery.

2.6.2. Frailty Improvements in Cardiac Rehabilitation

Eichler and colleague's (2017) prospective cohort study assessed frailty using a modified FI in 122 transcatheter aortic valve implantation patients, demonstrating the prevalence of frailty was reduced by 9% (from 36.9% to 27.9%) over an average of 19.4 ± 3.1 days following a 5x/week inpatient CR intervention [108]. Eichler et al. (2017) report improvements were mainly derived from 6-minute-walk-distance (6MWD), maximum work load, and physical and mental aspects of the Short Form-12 questionnaire among frail CR participants [108].

Mudge and colleague's (2021) retrospective cohort study assessed frailty using a 41-item FI in 256 participants with HF attending a 12-week exercise and education phase II CR program [22]. Mudge and colleagues report 21% of participants improved their frailty level in CR, with the most severely frail participants observing the greatest magnitude of improvement [22]. Over a 6-month follow up period, Mudge's group reported a small, but clinically meaningful improvement in mean FI score, from 0.23 to 0.20 [22], which aligns with previously published work [117, 118].

Likewise, Kehler and colleague's (2020) retrospective cohort study assessed change in frailty from admission to completion of CR using a 25-item FI. Kehler and colleagues reported on a sample of 2,322 CR participants with mixed CVD pathologies enrolling to a 12-week phase II exercise and education CR program [17]. Kehler et al. suggested frailty levels can be improved from admission to completion of a comprehensive CR intervention in participants with various types of CVDs (e.g., coronary artery disease, percutaneous coronary intervention, myocardial infarction, cardiac surgery, HF) [17]. For example, 622 (26.8%) participants observed a minmal improvement (0.03-0.09 FI reduction), 472

(20.3%) participants observed a moderate improvement (0.09-0.15 FI reduction), 459 (19.9%) observed a large improvement (>0.15), 422 (18.1%) maintained their level of frailty, while 327 (14%) worsened over the course of CR [17]. Notably, Kehler and colleagues suggested higher admission frailty levels were associated with the greatest magnitude of improvement in frailty following CR completion [17].

Lutz and colleague's (2020) retrospective cohort study assessed frailty using a modified SPPB in 243 CVD patients with various CVD pathologies (e.g., HF, cardiac surgery, transcatheter aortic valve replacement, myocardial infarction, percutaneous coronary intervention) reporting 20% of phase II CR participants improved their level of frailty, while only 6% worsened during the exercise and education CR intervention [94]. Similarly, Ritt et al. (2021) report average EFS scores were reduced from 5.4 ± 2 at admission to 4.8 ± 1.9 at 3 month completion (p=0.034) [109]. Ritt and colleagues suggest higher EFS scores at CR admission were associated with greater chance of responding to the CR program [109]. Similiarly, Mathew and colleague's (2019) prospective cohort study assessed frailty using the EFS in 764 participants attending a comprehensive 12-week phase II CR program [106], whereby 275 (35.9%) participants experienced an improvement in EFS score, 228 (29.84%) participants experienced no change in EFS score, and 261 (34.2%) participants experienced worsening of EFS score [106]. Additionally, Mathew et al. reported 16.2% of their sample improved EFS scores by greater or equal to 1 point [106], indicative of a small, clinically meaningful improvement [117]. Aligning with the results of Mudge et al. (2021) [22], Kehler et al. (2020) [17], and Ritt et al. (2021), Mathew et al. (2019) suggest CR participants who are frailer will derive the greatest

magnitude of improvement in frailty status should they complete the center-based CR interventions [106].

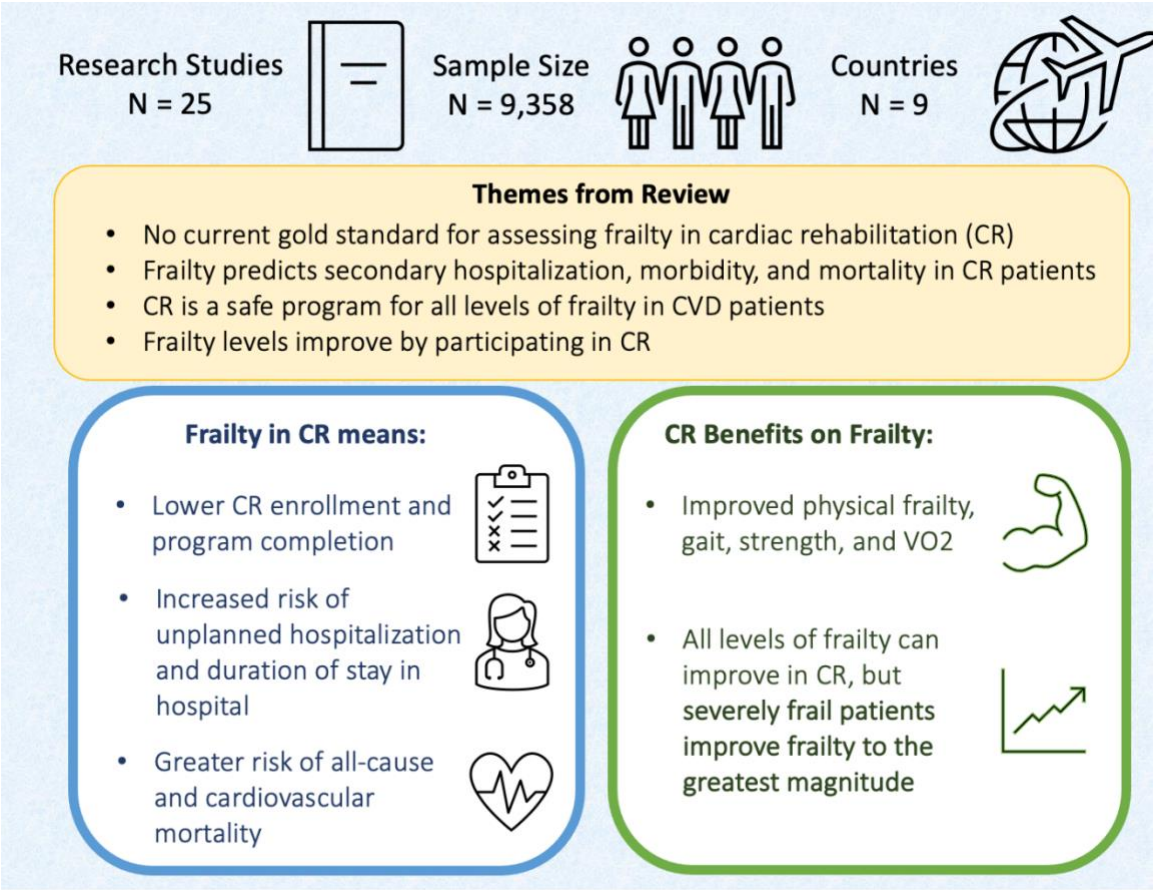

Figure 2. Graphic abstract of CR and frailty systematic review.

2.6.3. Frailty Predicting Health Outcomes in Cardiac Rehabilitation

Upon frailty assessment at CR admission, higher levels of frailty were associated with scoring low on physcial outcomes such as walking tests [14, 22, 99, 102, 103], grip strength [14, 22, 102], peak work rate [14, 102], lower extremity strength [102], lean body weight [14, 103], and functional mobilty [22].

Lutz and colleagues (2020) reported improvements in gait speed ($p=0.05$), timed-up-and-go ($p=0.007$), hand grip strength ($p<0.001$), and mean 6MWD ($p<0.001$) were observed among frail phase II CR participants [94]. Lutz and colleagues suggested

improvements in timed-up-and-go tests were more significant in the frail versus non-frail and intermediately frail groups [94]. Although, no significant differences between groups' gait speed, hand grip strength, and mean 6MWD were observed [94].

Similarly, Ushijima et al. (2019) conducted a prospective cohort study and reported gait speed (1.06 ±0.20 vs. 1.20 ±0.18 m/sec, $p<0.001$), grip strength (21.7 ±5.5 vs. 23.6 ±6.3 kg, $p=0.01$), and lower extremity strength (0.37 ±0.09 vs. 0.43 ±0.11 kgf/kg, $p=0.001$) were significantly improved among frail participants completing a 12-week phase II CR intervention [102]. Furthermore, Ushijima et al. indicate 87% of their sample who were classified as frail at admission left the frail classification upon completion of a multicomponent phase II CR intervention [102].

Similarly, Nishitani-Yokoyama and colleague's retrospective cohort study assessed frailty in 102 phase II CR participants using the 25-item Kihon Checklist [97]. Nishitani-Yokoyama et al. found higher levels of frailty upon admission assessment in CR were associated with fewer social activities (0.58 ± 0.56 vs 0.31 ± 0.55, $p=0.03$), depressive mood (2.67 ± 1.57 vs. 1.53 ± 1.70, $p<0.01$), and constipation ($p=0.01$) when compared with non-frail phase II CR participants [97].

Kunimoto and colleague's retrospective cohort study also evaluated frailty using the 25-item Kihon Checklist among 845 phase II CR participants from Japan, indicating frailty was associated with a greater prevalence of chronic kidney disease ($p<0.01$) and chronic obstructive pulmonary disease ($p=0.03$) [14]. Lastly, Honzawa and colleague's retrospective cohort study assessed frailty in 255 phase II CR participants from Japan using the 25-item Kihon Checklist [103]. Honzawa et al. found state anxiety (41.6 ± 0.9 vs. 34.9

± 1.0, $p<0.01$) and trait anxiety (45.5 ± 0.9 vs. 35.1 ± 1.1, $p<0.01$) was significantly higher among frail CR participants, compared to non-frail counterparts [103].

Several studies used frailty as a predictor of subsequent health problems, such as unplanned hospitalization, all cause mortality [15], hospital readmittance [107], hospitalization duration [13], and 5 year event-free survival [66]. Frailty was also suggested to help predict CR program enrollment [107] and program completion [17, 20, 106],

Three studies assessed hospital readmission in relation to frailty levels among CR participants [15, 66, 107]. Aida and colleague's retrospective cohort study assessed frailty using a modified version of the Frailty Phenotype on a sample of 895 Japanese CVD patients attending inpatient CR [15]. Aida et al. reported in reference to robust participants, pre-frail and frail CR participants have a 2.19 (1.00-4.79, $p<0.001$) to 3.27 (1.49-7.21, $p<0.001$) fold higher risk of subsequent CVD unplanned hospitalization, repectively [15]. Futhermore, greater frailty according to the Fried Phenotype was progressively associated with higher risk of CVD all-cause mortality, with significant differences observed between CR participants with frailty phenotype scores of zero and one ($p<0.001$) [15]. Aida et al. suggest frailty can help to predict subsequent unplanned hospitalization and all-cause mortality in Japanese CR participants [15].

Kamiya and colleague's 2020 multicenter retrospective cohort study evaulated frailty using a 19-item FI in 862 HF patients attending a five month CR intervention [66]. Kamiya et al. and found in reference to patients with an FI score of <0.21, those with FI scores of 0.21-0.31, 0.32-0.41, and >0.42, were 2.11 (1.75-2.56), 3.18 (2.59-3.90), and 3.93

(3.29-4.70) times more likely to experience a composite outcome of all-cause mortality and HR-related hospitalization over a 5-year follow-up, respectively [66].

Tew and colleague's prospective cohort study evaluated frailty in 100 cardiology patients from the Royal Infirmary of Edinburgh using the Frailty Phenotype model and the Clinical Frailty Scale [107]. Tew et al. reported frail individuals according to the Frailty Phenotype model would less frequently attend CR [107]. Furthermore, Tew et al. reported higher levels of frailty were associated with longer duration of hospitalization readmission over a 30 day follow-up period [107]. Tew and colleagues indicate frail CR participants on average spent 4 ± 7.3 days readmitted to hospital compared to 0.9 ± 2.9 days for non-frail counterparts (p=0.04) [107].

Similarly, Nozaki and colleague's retrospective cohort study of 387 HF patients from Japan evaluated frailty using a modified version of the Frailty Phenotype [13]. Nozaki et al. noted higher levels of frailty among Japanese CR participants was associated with longer duration in rising-time from bed during phase I CR [13]. Nozaki and authors suggested measuring rising-time duration in frail phase I CR participants may detect reduced physical performance associated with poor prognosis [13].

Finally, Kehler et al. [17], Mathew et al. [106], and Kimber et al. [20] each reported frailer CR participants were less likely to complete CR programs.

2.7. Knowledge Gap and Importance of Study

After systematically reviewing the body of literature concerning CR and frailty, we support the comprehensive and evidence-based contributions of CR to manage CVD, improve functional capacity, reduce cardiovascular morbidity and mortality, and improve frailty in CVD patients. However, our synthesis of the literature identifies a knowledge

gap, wherein to date, no research has examined frailty among virtual CR participants, and furthermore, no research has examined the efficacy of virtual CR to improve frailty among patients with CVDs. Therefore, we sought to strengthen what is known about the association between frailty and CR by examining frailty change in virtual versus center-based CR. Here, our study's results have implications to both research and practice. First, our study extends the body of knowledge on frailty and CR to better our understanding of alternative CR models for improving frailty among CVD patients. Second, our research determined if frailty can be effectively managed irrespective of CR delivery model. Our research will inform clinicians on proper patient allocation in CR, by identifying which model of CR (virtual or center-based) will better serve patients with greater needs, optimizing the delivery of care.

CHAPTER 3: Objectives, Hypothesis, & Methodology

3.1. Objectives

The objectives of this study were to (1) compare the changes in frailty levels from CR admission to completion in participants who enrolled in either center-based CR or virtual-based CR, and (2) determine if admission frailty affected cardiovascular biomarker changes in both program models.

3.2. Hypothesis

I hypothesized that (1) virtual versus center-based CR would be associated with similar frailty improvements; and (2) frailer participants at admission would observe the greatest improvements in frailty and cardiovascular biomarkers.

3.3. Study Design

We reported an observational study, secondary analysis of data collected as a part of routine care at the Nova Scotia Health (NSH) Hearts and Health in Motion CR program in Halifax, Nova Scotia.

3.4. Data, Participants, and Consent

This study used routinely collected data from the Hearts and Health in Motion clinical database, housed at the Mumford Professional Center in Halifax, Nova Scotia. The NSH Hearts and Health in Motion database housed all participants' data who enrolled in CR. All CR participants were referred to CR after experiencing an adverse cardiovascular event (e.g., heart attack, cardiac surgery). Here, we examined CR participant data collected from August 2021 to April 2022. Data was extracted on participants who attended virtual and center-based CR during this period. Traditionally, the Hearts and Health in Motion CR program is offered as center-based case, however, the virtual CR program was introduced

in 2020 following public health guidelines and program modifications responding to COVID-19. All patient information was de-identified. All participants from the Hearts and Health in Motion program were asked to provide informed consent to the program and allow their data to be entered into the database and to be collected and used for research purposes (90% consent rate).

3.5. Cardiac Rehabilitation Allocation

CR participants' program allocation was determined prior to CR enrollment by CR staff, pending agreement from enrolling participants. To a lesser extent, CR participants' preference of CR model (i.e., request to enrol in either virtual or center-based CR) was taken into consideration by CR staff when deciding upon participants' program allocation. To grade cardiovascular risk, the Hearts and Health in Motion staff considered patient medical history (i.e., CVD risk factor evaluation), orthopaedic limitations to exercise (i.e., limitations to exercise due to musculoskeletal programs, gait, and/or mobility limitations), clinical judgement, and required level of supervision by CR staff at CR admission. As the virtual-based CR program was novel to Hearts and Health in Motion, participants who were deemed "low-to-moderate-risk" upon admission assessment were preferentially allocated to the virtual CR program, while the center-based CR program included participants who were deemed "low, moderate, and high-risk" upon CR admission assessment. Also, all CR participants were requested to perform admission graded exercise stress testing and were referred for admission bloodwork requisitions to assist in exercise prescription and safety.

3.6. Description of the Cardiac Rehabilitation Programs

All participants were offered guidance to accessing resources (i.e., referral to stress management programs, smoking cessation programs) that were provided by NSH and the

University Health Network Cardiac College. If participants were unable to access the internet, a paper copy of instructional guidance was provided upon request. Neither program reported an adverse event occurring during exercise sessions. CR program model characteristics are described in Table 3.

3.6.1. Center-based Cardiac Rehabilitation Description

The center-based CR programs were delivered at three community-based centers. All three centers were part of the Hearts and Health in Motion CR program. These community centers were located at the Mumford Professional Center (Halifax, NS), the Zatzman Sportsplex (Dartmouth, NS), and the Cobequid Health Center (Sackville, NS). Cohorts were grouped based on program start dates and location of the programs (e.g., Cobequid Monday – A, Sportsplex Thursday – B). Center-based CR consisted of a multidisciplinary-led healthcare team, including a medical director, program lead, nurse, dietician, and physiotherapist.

Center-based CR was a group-based, 6-week program offered from August–November of 2021. All exercise sessions were supervised by a program nurse, dietician, and physiotherapist, who measured exercise adherence by CR attendance. Exercise sessions occurred once weekly for 60 minutes per session (40 minutes exercise), including a warm-up and cool-down (20 minutes). Types of exercise in center-based CR were continuous or interval aerobic exercise performed on a treadmill (20 minutes) or leg cycle or arm cycle ergometer (20 minutes). Center-based CR participants were encouraged to exercise at a self-monitored, moderate intensity of 11-13 on the Borg Rating of Perceived Exertion (RPE) scale. Exercise was progressed by increasing treadmill speed or incline, or ergometer resistance while maintaining revolution speed. Participants were also provided

with a home-based exercise guide of aerobic and resistance type exercises upon request. Group-based education with CR staff provided information on how to manage CVD risk factors through health behaviour changes to diet, exercise safety, and medication management, if needed. In the center-based program, education included up to three weekly, 60-minute, phone or Zoom video call rotation with the physiotherapist, nurse, and dietician. Education was supplemented by in-person consultations during weekly exercise sessions, for up to six additional hours of direct education time with CR staff. In total, center-based participants were eligible to receive up to nine hours of CR staff supervised education consultations. The center-based CR programs were delivered as planned.

Table 3. Description of center- and virtual-based CR[a] programs[b]

CR[a] model	**Center-based CR[a]**	**Virtual CR[a]**
Duration of program	6-weeks	9-10 weeks
Exercise component	Group-based exercise sessions which included individualized prescription based on graded exercise stress testing at CR admission and orthopaedic limitations.	Individual home-based exercise prescribed using graded exercise stress test results at CR admission, orthopaedic limitations, and availability of exercise equipment/resources to the patient.
Type of exercise	Exercises include a continuous or interval type aerobic exercise on a treadmill, leg cycle ergometer, or arm cycle ergometer.	CR physiotherapists prescribe exercise types by discussing the equipment or resources that are available on a patient-to-patient basis. Examples of exercises include walking indoors or outdoors, bicycling, recreational sport, body weight resistance training, resistance training with equipment, and flexibility or stretching exercises.

CR[a] model	Center-based CR[a]	Virtual CR[a]
Frequency & Duration	Once weekly, 60-minute exercise class, including 10 minutes of warm-up, 40 minutes of exercise time, and 10 minutes of cool-down. Participants were encouraged to reach 150 minutes of moderate-vigorous exercise per week by supplementing outside of CR.	Exercise target to meet 150 minutes of moderate-vigorous exercise per week. This exercise target could be completed in bouts of 10+ minutes of exercise throughout the week.
Education component	Up to 3, one-hour, weekly group-based phone/video call rotation from team physiotherapist, nurse, and dietician. Education sessions focussed on cardiovascular health and risk factor reduction, incorporating health behaviour changes to diet, physical activity, or medications if needed. In addition to weekly phone calls, center-based participants could interact with members of their CR team during each of their 6 exercise sessions, totalling a possible 9 hours spent with CR staff.	Up to 4, one-hour, weekly group-based phone/video call rotation from team physiotherapist, nurse, and dietician, with a group Question and Answer Zoom video session held during week 4. From week 5 to program completion, virtual participants received up to 6 weekly, 45-minute, individual phone calls, totalling a possible 8.5 hours spent with CR staff. Sessions provided education on cardiovascular health and risk factor reduction, incorporating health behaviour changes to diet, physical activity, or medications if needed.
Multidisciplinary healthcare team	Medical director, program lead, nurse, physiotherapist, dietician.	Medical director, program lead, nurse, physiotherapist, dietician.

[a]Abbreviations: CR, cardiac rehabilitation. [b]Table descriptions are from the Nova Scotia Health Hearts and Health in Motion CR Program.

3.6.2. Virtual Cardiac Rehabilitation Description

The virtual-based CR program operated for 9-10-weeks in duration depending on the time virtual participants were enrolled (i.e., Fall of 2021 programs were 9-weeks in duration; Winter of 2022 programs were 10-weeks in duration). As organized in center-

based CR, virtual cohorts were grouped based on program start date (e.g., Virtual Monday – A, Virtual Thursday – B) and consisted of a multidisciplinary-led healthcare team, including a medical director, program lead, nurse, dietician, and physiotherapist.

The Hearts and Health in Motion virtual-based CR program was an individualized, unsupervised program to be completed at home. Physiotherapists would prescribe individualized exercise regimes, targeting 150-minutes of moderate-vigorous exercise weekly, based on patient-to-patient resource availability (e.g., neighborhood walk, body-weight exercises). Exercise intensity in virtual CR was consistent with center-based CR (i.e., RPE of 11-13 on the Borg Scale). Education material provided to virtual CR participants was consistent with the center-based CR program and was facilitated by CR staff. Weekly education sessions included up to four 60-minute group-based Zoom video calls (weeks 1-4), and up to six, 45-minute, individual telephone calls (week 5 to completion), rotating between the team physiotherapist, nurse, and dietician. In total, virtual-based CR participants were eligible to receive up to 8.5 hours of direct education consultation time with their multidisciplinary CR team. During virtual consultations, physiotherapists would record exercise adherence, progressions, or modifications to prescribed exercise. Similarly, the nurses and dieticians would record any changes to managing medications or diet, which included alcohol consumption and smoking behaviours. Virtual CR was subject to interruption and modifications due to COVID-19, detailed under limitations in Chapter 5.

3.7. Frailty Index

A 65-item frailty index (FI) based on data from the Canadian Longitudinal Study on Aging (CLSA-FI) was used to identify frailty at CR admission and completion

(Appendix A). The CLSA-FI was developed in accordance with previous guidelines [60] and has been validated elsewhere [119]. CLSA-FI evaluated health status by including variables of signs, symptoms, diseases, and disability [119]. The presence of health deficits, such as diseases, were scored as 0 (deficit not present) to 1 (deficit present). Variables with three or more possible outcomes were scored on a grading scale from least to most severe based on the number of outcomes. The CLSA-FI is a ratio of the health deficits present, divided by the total number of health deficits assessed, to assign a score ranging from 0-1 (e.g., 20/65=0.31). Higher CLSA-FI scores indicate higher frailty levels. We also developed a FI for sensitivity analyses by adding 8 cardiovascular biomarkers (described below) to the CLSA-FI (FICVD).

3.8. Cardiovascular Outcomes

Cardiac biomarkers included triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol, creatine kinase, creatinine, c-reactive protein, systolic blood pressure, diastolic blood pressure, and resting pulse. Biomarkers were routinely collected in both CR models by CR staff (e.g., blood pressures) or through blood requisition (e.g., cholesterol) at admission and upon completion of CR. The FICVD did not include biomarkers creatine kinase and c-reactive protein as CR staff advised confounding factors (e.g., medication changes, illness) may have influenced patients' values over the short CR duration.

3.9. Data Collection

Routinely collected data from August 2021 to April 2022 was entered into the NSH Hearts and Health in Motion clinical database. Data was extracted on participants who attended virtual and center-based CR during this period. Prior to our data extraction for statistical analyses, all patient information was de-identified. All CR participant data on

frailty and cardiovascular health outcomes were collected at CR admission and again upon CR completion. The final cohort of CR participants included in this study enrolled in CR in January of 2022.

3.10. Primary and Secondary Outcomes

Our primary outcome was to examine change in frailty from CR admission to completion between center-based CR and virtual CR using the CLSA-FI. Secondary outcomes of this study were to examine the effect of admission frailty on changes to cardiovascular biomarkers in both program models. Cardiac biomarkers such as triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol, creatinine, c-reactive protein, systolic blood pressure, diastolic blood pressure, and resting pulse were routinely collected by CR staff at admission and upon completion. Cardiac biomarker values (triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, creatinine, c-reactive protein) were collected from laboratory blood work requisitions, while vital signs (systolic blood pressure, diastolic blood pressure, and resting pulse) were taken during graded exercise stress testing at CR admission and completion.

3.11. Analysis of Data

Analyses were performed with RStudio 2022.02.1 (RStudio, Boston, MA) and SPSS Version 27 (IBM Corp, Armonk, NY). Independent t-tests and Chi-Square tests compared differences in continuous and categorical descriptors of CR program models, respectively. A two-way mixed measures analysis of variance (ANOVA) examined frailty change from CR admission to completion in virtual versus center-based CR participants. Models were adjusted for exercise attendance and admission age, sex, triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol, creatine kinase, creatinine, c-reactive

protein, systolic blood pressure, diastolic blood pressure, and resting pulse. Follow-up simple slope analyses were performed on the CLSA-FI in RStudio 22.02.01 because pre-planned analysis revealed an interaction effect between admission frailty and CR program model on frailty change. RStudio software analyzed linear regression models to predict change in cardiovascular biomarkers from admission CLSA-FI scores, stratifying by CR program model. For individual cardiovascular biomarkers, linear regression models were adjusted for exercise attendance and admission age, sex, frailty, and other previously mentioned cardiovascular biomarkers. RStudio MICE (Multiple Imputation Chained Equations) was used to perform multiple imputation analyses to account for missing CLSA-FI and cardiovascular biomarkers. MICE imputed 1353/3407 (28.42%) missing data points on frailty and cardiovascular biomarkers, generating 100 predictive mean matching sequences. Little's Test determined our data was missing completely at random (Chi-square=836.634, degrees of freedom=965, p=.999). We completed two sensitivity analyses. First, we completed analyses by using the FICVD to measure change in frailty and CVD biomarkers with CR. Second, we performed analyses using listwise deletion, whereby only participants with complete frailty data at admission and follow up were included. Frequency of individual CLSA-FI items from our listwise deletion CR participants are found in Supplementary Table A.2. A two-sided P-value of <.05 was considered statistically significant for all analyses. FI values were multiplied by 100 to improve the interpretability of findings.

CHAPTER 4. Manuscript

Original Investigation

Full title:

Comparing Virtual and Center Based Cardiac Rehabilitation on Changes in Frailty

Short running title:

Virtual vs. Traditional Cardiac Rehab on Frailty

Authors:

Evan MacEachern[1], BKin, Nicholas Giacomantonio[2], MD, Olga Theou[1,3], PhD, Jack Quach[1], BSc, Wanda Firth[4], PDt, Ifedayo Abel-Adegbite[5], PT, D. Scott Kehler[1,3], PhD

Affiliations:

[1]School of Physiotherapy, Dalhousie University, Halifax, NS, Canada,

[2]Department of Cardiology, Dalhousie University, Halifax, NS, Canada,

[3]Division of Geriatric Medicine, Dalhousie University, Halifax, NS, Canada,

[4]Hearts and Health in Motion, Nova Scotia Health, Halifax, NS, Canada

[5]Faculty of Health, Dalhousie University, Halifax, NS, Canada

Corresponding Author:

Dr. Scott Kehler, Room 1314 QEII Health Sciences Centre - Camp Hill Veterans Memorial Building 5955 Veterans' Memorial Lane, Halifax, NS, B3H 2E1. 902-473-3363, scott.kehler@dal.ca

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Conflicts of interest:

N.G. has research grants from Pfizer Canada. The other authors have no conflicts of interest to disclose.

Structured Abstract

Purpose: Many cardiovascular disease (CVD) patients are frail. Center-based CR can improve frailty, however, whether virtual CR provides similar frailty improvements has not been examined. We compared the effect of center-based and virtual CR on frailty; and determined if admission frailty affected frailty change and CVD biomarkers.

Methods: 132 patients were allocated to virtual (n=58) and center-based CR (n=74) from August 2021-April 2022 for up to 10 weeks. Both programs provided exercise and education on nutrition, medication, exercise safety, and CVD. Frailty was measured with a 65-item frailty index (FI; scores range from 0-1; a higher score indicates a higher frailty level). The primary outcome was a change in frailty and was analyzed with a two-way mixed ANOVA. Secondary outcomes were changes in CVD biomarkers using multivariable linear regression. Analyses adjusted for age, sex, exercise attendance, and CVD biomarkers at admission (e.g., triglycerides, cholesterol). Simple slopes analyzed whether admission frailty affected frailty and CVD biomarker change by CR model type.

Results: From 132 participants (age 64.53±10.5, 63.6% male), center-based (0.14±0.003) versus virtual participants (0.07±0.003) had higher admission FIs. We observed no main effect of CR model on frailty change. Frailer virtual participants at admission (FI=0.20-0.25) observed greater frailty improvements (B-coefficient: -3.810[95% CI: -7.360,-0.251], p=.034) and reductions in triglyceride (-0.766[-1.508,-0.025], p=0.04) and cholesterol (-0.660[-1.229,-0.092], p=.021) than center-based CR participants.

Conclusions: Even though both program models did not change frailty, higher admission frailty was associated with greater frailty reductions and change to some CVD biomarkers in the virtual program.

Condensed Abstract

We compared virtual versus center cardiac rehabilitation on changes in frailty and cardiovascular biomarkers. We observed no effect of cardiac rehabilitation model on change in frailty. However, frailer virtual participants at admission showed greater frailty improvements and greater reductions in triglyceride and total cholesterol than center-based participants.

Key Perspective

What is novel?

- We are the first to compare frailty change in virtual versus center-based cardiac rehabilitation.
- This is the first study to compare virtual versus center-based cardiac rehabilitation on frailty in relation to CVD biomarker changes.

What are the clinical and/or research implications?

- Virtual cardiac rehabilitation was non-inferior to center-based cardiac rehabilitation on changes in frailty.
- Cardiac rehabilitation participants who are at least mildly frail upon admission derived the greatest improvements in frailty in the virtual cardiac rehabilitation model.
- Among mild-to-moderately frail participants, virtual cardiac rehabilitation significantly reduced some, but not all cardiovascular biomarkers, demonstrating non-inferiority to center-based cardiac rehabilitation.

4.1. INTRODUCTION

Cardiovascular diseases (CVDs) are among the leading causes of hospitalization and mortality [1, 2]. CVD disproportionately impacts older adults [3] who are more likely contend with co-occurring health problems that impact their adverse outcome risk compared to younger people [5]. Frailty describes the degree to which people accumulate these health problems with age, which results from decreased physiological reserve across multiple organ systems that increases vulnerability to worsening health [120]. Evidence suggests a bi-directional association between CVD and frailty, as they share underlying physiological processes that increase the expression of one-another [12, 120]. Patients with more severe CVD are generally frailer [4, 15, 121], and frail CVD patients experience a greater risk of mortality compared to people with CVD and lower degrees of frailty [12, 67].

Agencies that provide guidance on cardiovascular care have sought to mitigate the combined impact of frailty and CVD through cardiac rehabilitation (CR) [16]. CR is a comprehensive program for the secondary prevention of CVD [16], and is also effective for the improvement in frailty of participants [17, 22, 94, 101, 102]. CR implements behaviour change therapy consisting of nutritional guidance, medication management, CVD education, and exercise therapy to manage CVD in hospital settings, out-patient clinics, and alternatively, as virtual care [77, 78]. Virtual CR is a home-based modification of traditional CR and is facilitated using the internet or 'smart-devices' (e.g., smartphones) to remotely monitor progress and facilitate patient counseling [25]. Virtual CR has grown in popularity due to reduced center-based opportunities since the COVID-19 pandemic. Virtual CR shows similar improvements to center-based CR in managing cardiovascular

biomarkers (e.g., cholesterol) [77], exercise outcomes (e.g., VO2 peak) [87], and quality of life for people [88] with a low-moderate CVD risk [23, 86]. While virtual CR provides an opportunity to reach more people who could benefit from CR, little is known about the effect virtual CR has on frailty levels in CVD patients. Here, our objectives were to (1) compare the changes in frailty levels from CR admission to completion in patients who enrolled in either center-based CR or virtual-based CR, and (2) determine if admission frailty affects frailty changes and cardiovascular risk factors in both program models.

4.2. METHODS

This study included 317 center-based or virtual CR participants from the Hearts and Health in Motion CR program in Halifax, Nova Scotia, from August 2021-January 2022. Included participants were referred to CR following an acute adverse cardiovascular event by an automated referral system (i.e., following cardiac surgery) or healthcare professional (e.g., cardiologist). The Nova Scotia Health Research Ethics Board approved this study.

Eligible participants were adults 18-years of age or older who were referred and enrolled in CR for the secondary prevention of CVD. Participants were excluded if they withdrew from CR, cancelled participation for medical (e.g., critical illness) or personal (e.g., delayed enrollment) reasons, non-response to frailty questionnaires at either CR admission or completion, or did not have an email address.

CARDIAC REHABILITATION

Participants' CR model allocation was determined prior to enrollment by the multidisciplinary CR staff (program details are provided in Supplemental Table A.1) based on participants' preference of program model and level of supervision by CR staff deemed

necessary based on the participant's health status. Participants deemed "low-to-moderate-risk" at CR admission assessment were preferentially allocated to the virtual program, while the center-based program included "low, moderate, and high-risk" participants at admission assessment. All CR participants performed admission graded exercise stress testing for exercise prescription and safety.

Center-based CR was a group-based, 6-week program offered from August–November of 2021. Exercise sessions were supervised by a physiotherapist who measured exercise adherence by CR attendance. Exercise sessions occurred once weekly for 60 minutes per session (40 minutes exercise), including a warm-up and cool-down. Exercise types were continuous or interval aerobic exercise on a treadmill, or a leg or arm cycle ergometer (20 minutes); resistance training was not included. Participants were encouraged to exercise at a self-monitored, moderate intensity of 11-13 on the Borg Rating of Perceived Exertion (RPE) scale. Exercise was progressed by increasing treadmill speed or incline, or ergometer resistance while maintaining revolution speed. Group-based education with CR staff provided information on how to manage CVD risk factors through health behaviour changes to diet, exercise safety, and medication management if needed. Education included up to 3 weekly phone or Zoom video call rotation with the physiotherapist, nurse, and dietician, supplemented by in-person consultations during exercise sessions. Center-based CR was delivered as planned.

Virtual-based CR participants received up to 10-weeks of individualized, unsupervised programming at home. Physiotherapists prescribed 150-minutes of moderate-vigorous exercise weekly based on patient-to-patient resource availability (e.g., neighborhood walk, body-weight exercises). Exercise intensity was consistent with center-

based CR. Weekly education included up to 4 group-based Zoom video calls, and up to 6 individual telephone calls, rotating between the physiotherapist, nurse, and dietician. Physiotherapists would record adherence, progressions, or modifications to prescribed exercise. Virtual CR was subject to interruption and modifications due to COVID-19, detailed under limitations. Neither program reported an adverse event.

FRAILTY INDEX

A 65-item frailty index (FI) based on the Canadian Longitudinal Study on Aging (CLSA-FI) data was used to identify frailty at CR admission and completion (Supplemental Table A.2). The CLSA-FI was developed in accordance with previous guidelines [60] and has been validated elsewhere [119]. CLSA-FI variables included signs, symptoms, diseases, and disability [119]. The presence of health deficits, such as diseases, were scored as 0 (deficit not present) to 1 (deficit present). Variables with three or more possible outcomes were scored on a grading scale from least to most severe based on the number of outcomes. The CLSA-FI is a ratio of the health deficits present, divided by the total number of health deficits assessed, to assign a score ranging from 0-1 (e.g., 20/65=0.31). Higher CLSA-FI scores indicate higher frailty levels. We also developed a FI for sensitivity analyses by adding 8 cardiovascular biomarkers (described below) to the CLSA-FI (FICVD; Supplemental Table A.3).

CARDIOVASCULAR OUTCOMES

Cardiac biomarkers included triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol, creatine kinase, creatinine, c-reactive protein, systolic blood pressure, diastolic blood pressure, and resting pulse. Biomarkers were routinely collected in both CR models by CR staff or through blood requisition at admission and upon completion. FICVD

did not include creatine kinase and c-reactive protein as CR staff advised confounding factors (e.g., medication changes, illness) may have influenced patients' values over the course of CR.

STATISTICAL ANALYSIS

Analyses were performed with RStudio 2022.02.1 (RStudio, Boston, MA) and SPSS Version 27 (IBM Corp, Armonk, NY). Independent t-tests and Chi-Square tests compared differences in continuous and categorical descriptors of CR program models, respectively. A two-way mixed measures analysis of variance (ANOVA) examined frailty change from CR admission to completion in virtual versus center-based CR participants. Models were adjusted for exercise attendance and admission age, sex, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, creatine kinase, creatinine, c-reactive protein, systolic blood pressure, diastolic blood pressure, and resting pulse. Follow-up simple slope analyses were performed on the CLSA-FI in RStudio 22.02.01 because a pre-planned analysis revealed an interaction effect between admission frailty and CR program model. RStudio software analyzed linear regression models to predict change in cardiovascular biomarkers from admission CLSA-FI scores, stratifying by CR program model. For individual cardiovascular biomarkers, linear regression models were adjusted for exercise attendance and admission age, sex, frailty, and other previously mentioned cardiovascular biomarkers. RStudio MICE (Multiple Imputation Chained Equations) was used to perform multiple imputation analyses to account for missing CLSA-FI and cardiovascular biomarkers. MICE imputed 1353/3407 (28.4%) missing data points on frailty and cardiovascular biomarkers, generating 100 predictive mean matching sequences. Little's Test determined our data was missing completely at random (Chi-

square=836.634, degrees of freedom=965, p=.999). We completed two sensitivity analyses. First, we used the FICVD to measure change in frailty and CVD biomarkers. Second, we performed analyses using listwise deletion, whereby only participants with complete frailty data at admission and follow up were included. Frequency of individual CLSA-FI items from our listwise deletion CR participants are found in Supplementary Table A.2. A two-sided P-value of <.05 was considered statistically significant for all analyses. FI values were multiplied by 100 to improve the interpretability of findings.

4.3. RESULTS

DESCRIPTION OF PARTICIPANTS

Three hundred and seventeen participants were screened for study inclusion (Figure 3). These participants were allocated to center-based (n=165) and virtual CR (n=152) programs. Of these 317 participants, 11 were excluded for primary prevention, one personal and five medical cancellations, five with no email address, and two with clinical scheduling conflicts. An additional 24 withdrew from CR, and 137 did not respond to frailty assessments. The remaining 132 participants (mean age 64.5±10.5, range 40-90, 63.6% male) were enrolled in to virtual (n=58) or center-based (n=74) CR.

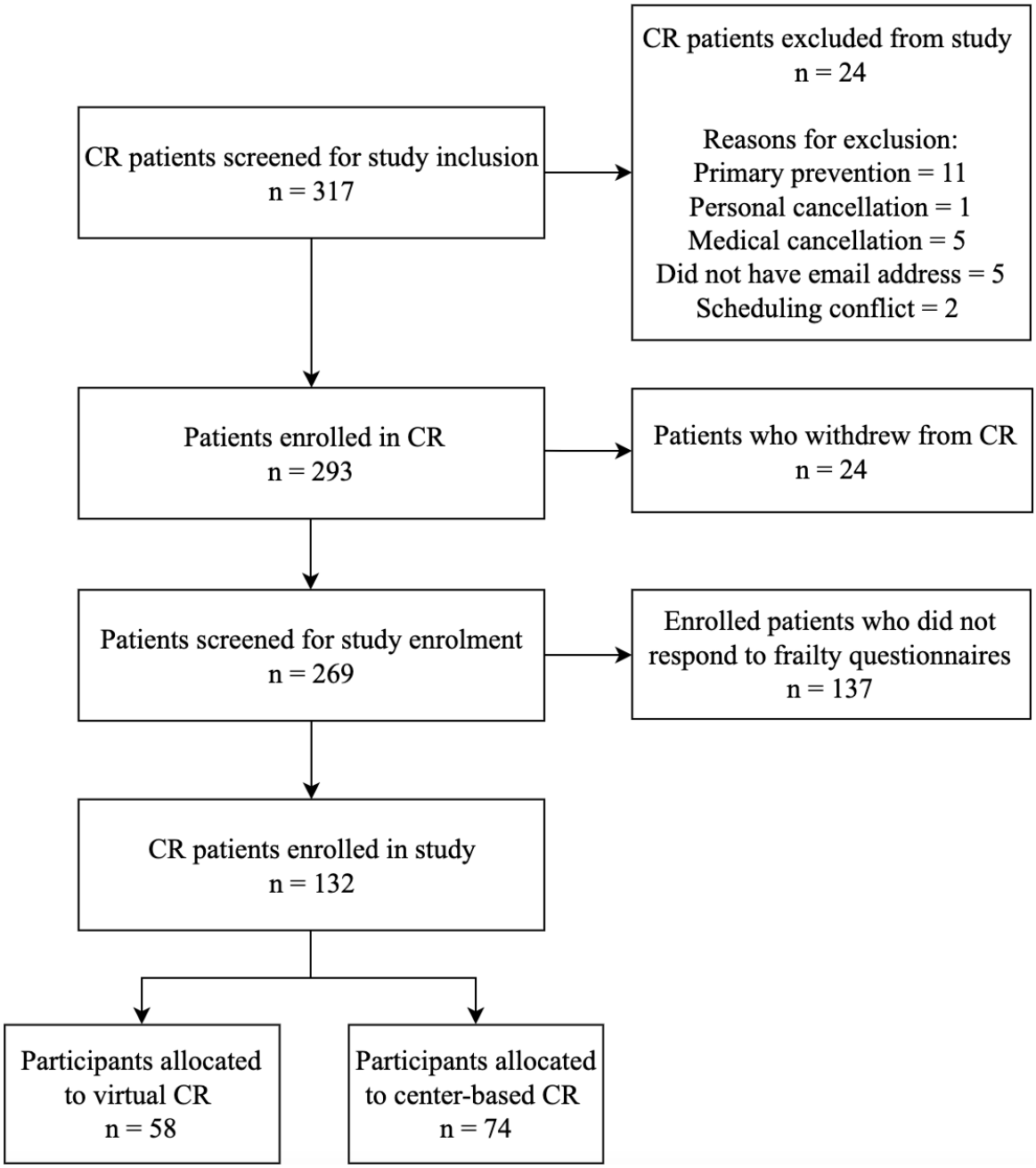

Figure 3. Flow diagram of study enrollment and CR program allocation.

Center- and virtual-based participants did not differ by sex, age, unadjusted mean admission CLSA-FI score, exercise attendance, or smoking status. A greater proportion of center-based participants had a history of stable coronary artery disease, while virtual

participants were more likely to have coronary artery bypass graft surgery and hyperlipidemia (Table 4.1).

Table 4.1. Demographic information of center-based and virtual cardiac rehabilitation participants at CR admission

Variable	**Cardiac Rehabilitation Model**		**P Value**
	Center-based	**Virtual**	
Sex			
- Male	47 (63.5%)	37 (63.7%)	.974
- Female	27 (46.5%)	21 (46.3%)	
Mean Age	63.1 ± 10.6	66.4 ± 10.1	.069
Unadjusted admission CLSA-FI[a]	0.11 ± 0.07	0.11 ± 0.06	.946
- FI <0.10	35 (47.2%)	29 (50%)	
- FI = 0.11-0.19	32 (43.2%)	24 (41.3%)	
- FI = >0.20	7 (9.4%)	5 (8.6%)	
Adjusted admission CLSA-FI[a]	0.14 ± 0.003	0.07 ± 0.003	*.001**
Exercise session attendance	88.9% ± 17.9	88.9% ± 22.2	.975
Cardiovascular biomarkers[a]			
- Triglycerides	1.76 ± 1.01	1.54 ± 0.76	.168
- Total cholesterol	3.74 ± 1.07	3.43 ± 0.76	.062
- HDL-cholesterol	1.10 ± 0.28	1.13 ± 0.24	.579
- LDL-cholesterol	1.85 ± 0.84	1.59 ± 0.65	.053
- Creatine kinase	110.15 ± 64.48	115.10 ± 75.66	.685
- Creatinine	86.65 ± 35.41	77.28 ± 15.32	.062
- C-Reactive protein	6.70 ± 16.57	4.03 ± 5.25	.240
- Systolic blood pressure	122.72 ± 19.84	125.53 ± 15.02	.371
- Diastolic blood pressure	72.19 ± 10.11	71.64 ± 9.05	.746
- Resting pulse	66.89 ± 10.82	65.45 ± 10.73	.447
Smoking Status			
- Current smoker	11 (14.8%)	8 (13.8%)	.884
- Former smoker	34 (43.6%)	24 (41.3%)	.603
- Never smoked	29 (39.1%)	22 (37.9%	.863
- Missing	2 (2.7%)	2 (3.4%)	

Variable	Cardiac Rehabilitation Model		P Value
	Center-based	Virtual	
History of CVDs[a]			
- Stable coronary artery disease	19 (24.3%)	6 (10.3%)	*.026**
- Acute coronary syndrome	9 (12.2%)	5 (8.6%)	.515
- Myocardial infarction	32 (43.2%)	30 (51.7%)	.336
- Coronary artery bypass graft	4 (5.1%)	17 (29.3%)	*.004**
- Cardiomyopathy	3 (3.8%)	2 (3.4%)	.858
- Percutaneous coronary intervention	28 (37.8%)	23 (39.7%)	.833
- Stroke	3 (3.8%)	1 (1.7%)	.442
CVD risk factors			
- Hypertension	58 (78.4%)	44 (75.8%)	.734
- Hyperlipidemia	62 (83.8%)	56 (96.5%)	*.018**
- Family history[b]	37 (50.0%)	23 (39.7%)	.239
- Diabetes	22 (29.7%)	16 (27.5%)	.789
- Inactivity	13 (17.5%)	14 (24.1%)	.357
- Obesity	13 (17.5%)	6 (10.3%)	.244
- Stress	41 (55.4%)	39 (67.2%)	.170

Data are presented as n (%) or mean ± SD from the multiple imputation dataset.

[a]Abbreviations: CLSA-FI, Canadian Longitudinal Study on Aging Frailty Index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CVD(s), cardiovascular disease(s). [b]Family History included any history of coronary artery disease in immediate family: males <55 years, females <65 years. Computed at alpha = 0.05.

CHANGE IN FRAILTY BETWEEN VIRTUAL AND CENTER-BASED CR

Admission and follow-up CLSA-FI scores after covariate adjustment were significantly higher in the center-based versus virtual CR program (Table 4.1; Figure 4A). However, frailty scores did not significantly change over time in either program model ($F(116,1)=0.477$, p=.491). After adding 8 cardiovascular biomarkers to the CLSA-FI (FICVD), frailty scores were slightly higher (Center-based: 0.159 vs 0.146; virtual: 0.084 vs 0.077) in both groups at admission (Figure 4B, Supplemental Table A.4). Center-based participants had higher frailty scores with the FICVD at admission and completion, and both groups did not change their level of frailty after completing CR ($F(116,1)=0.746$, p=0.491). Listwise deletion CLSA-FI scores were significantly higher in center-based

versus virtual CR participants, and frailty change was significantly different between CR models (F(51,1)=11.873, p=0.001; Supplemental Table A.4, Supplemental Figure 1). From admission to completion, center-based participants saw a significant CLSA-FI reduction of 0.016 (p=.018), while virtual participants saw a non-significant CLSA-FI increase of 0.006 (Supplemental Table A.4, Supplemental Figure 1).

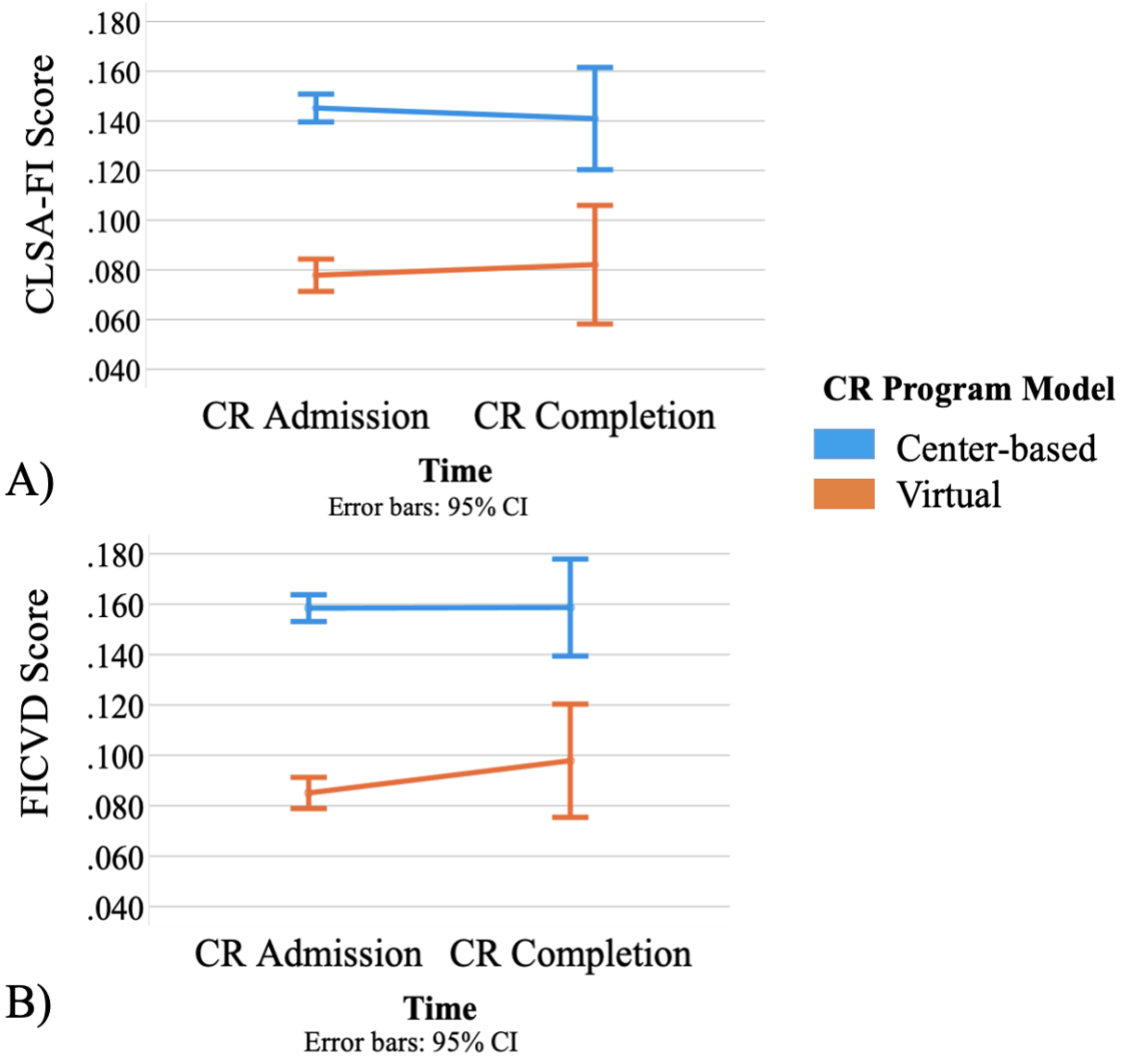

Figure 4. A) Estimated marginal means of CSLA-FI frailty scores at admission and follow-up. **B)** Estimated marginal means of FICVD frailty scores at admission and follow-up.

Frailty change from admission to completion of CR was significantly affected by admission frailty and CR model (F(118,16)=4.709, p=.002; Supplemental Table A.5). Simple slope analysis revealed at low levels of admission frailty (CLSA-FI= 0.05), frailty levels were significantly increased in virtual CR, relative to center-based CR, following the completion of CR. Frailty did not differ between CR models for CLSA-FI scores of 0.10 and 0.15. However, at mild-moderate frailty levels (CLSA-FI ≥0.20), virtual CR participants observed a greater frailty reduction compared to center-based counterparts (Figure 5, Supplemental Table A.5). For example, after centering virtual CR participants' admission CLSA-FI scores at 0.20 and 0.25, we observed corresponding beta coefficients of -3.810 (95% CI: -7.369,-0.251, p=.034) and -6.285 (-11.181,-1.390, p=.011), respectively.

Results from our FICVD sensitivity analysis were consistent with simple slope analysis using the CLSA-FI ((F(115,16)=2.105, p=.014); Figure 5B, Supplemental Table A.5) indicating that mild-moderate frailty levels at admission were associated with greater frailty reductions in frailty in the virtual program compared to center-based CR; however, frailty did not increase at FICVD scores of 0.05. Our listwise deletion analysis did not identify a significant interaction between admission frailty and CR program model on frailty change ((F(50,16)=1.603, p=0.528); Supplemental Figure 2, Supplemental Table A.5).

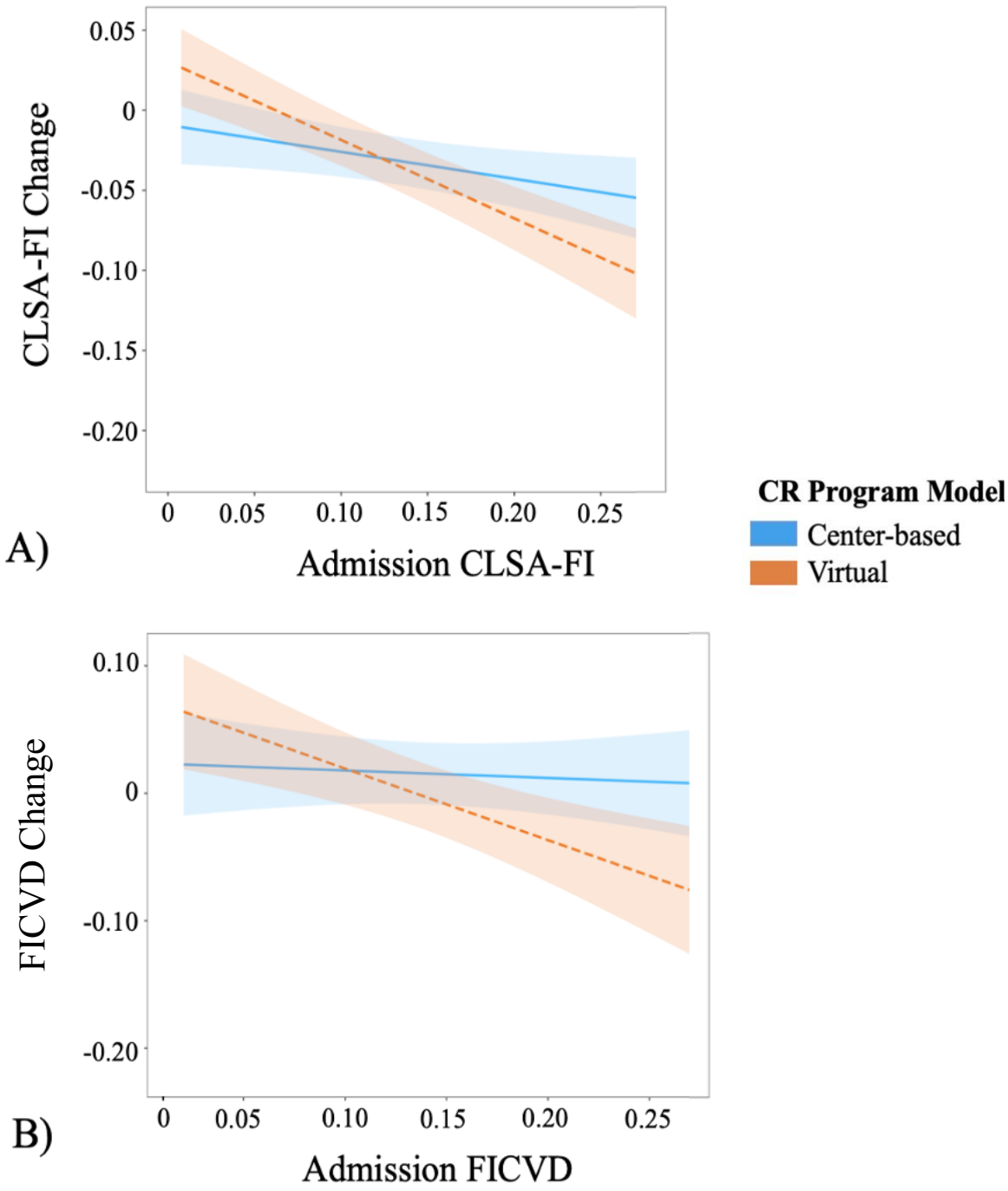

Figure 5. A) Simple slope predicting CLSA-FI change by admission frailty, stratified by CR model. **B)** Simple slope of FICVD predicting FICVD change by admission frailty, stratified by CR model.

CARDIOVASCULAR BIOMARKERS

We found no cardiovascular biomarker differences between CR models at admission, however, HDL-cholesterol was significantly higher in virtual participants at CR completion (Supplemental Table A.6). Similarly, we found admission CLSA-FI was not a significant predictor of change in cardiovascular biomarkers (Supplemental Table A.7), and admission FICVD was only predictive of increased diastolic blood pressure in the virtual compared to center-based CR group (Supplemental Table A.8). Simple slope analyses revealed significant between group differences for triglycerides and total cholesterol, such that virtual participants with higher admission CLSA-FI and FICVD (FI range = 0.20-0.25) saw greater associated reductions compared to center-based counterparts (Table 4.2, Supplemental Figure 3; Supplemental Table A.9, Supplemental Figure 4). Listwise deletion analyses revealed admission CLSA-FI was associated with increased LDL-cholesterol (B-coefficient: 0.051 [0.004,0.098], p=.033; Supplemental Table A.10), and that virtual participants significantly increased their HDL-cholesterol, LDL-cholesterol, creatine kinase, and diastolic blood pressure compared to center-based participants (Supplemental Table A.11, Supplemental Figure 5).

Table 4.2. Simple slope analyses of cardiovascular biomarker change by admission CLSA-FI[b] and CR program model interaction

Cardiovascular Biomarker	**R Square** Beta	**Beta 95% CI** Lower	Upper	**F-Statistic**	**P Value**
Simple Slope Analysis (Reference is center-based CR)					
Triglycerides	0.130	-0.001	0.099	*1.156* (116, 15)	.054
- FI = 0.05	0.210	-0.280	0.701		.392
- FI = 0.10	-0.033	-0.392	0.324		.851
- FI = 0.15	-0.277	-0.655	0.099		.143
- FI = 0.20	-0.522	-1.053	0.009		.051
- FI = 0.25	-0.766	-1.508	-0.025		*.040**

Cardiovascular Biomarker	R Square		Beta 95% CI		F-Statistic	P Value
		Beta	Lower	Upper		
Total cholesterol	0.251		-0.125	-0.017	*2.602* (116, 15)	*.009**
- FI = 0.05		0.408	-0.117	0.933		.123
- FI = 0.10		0.051	0.330	0.433		.786
- FI = 0.15		-0.304	-0.706	0.097		.132
- FI = 0.20		-0.660	-1.229	-0.092		*.021**
- FI = 0.25		-1.017	-1.811	-0.222		*.011**
HDL-cholesterol[a]	0.390		-0.015	0.024	*4.951* (116, 15)	.643
- FI = 0.05		-0.131	-0.328	0.065		.185
- FI = 0.10		-0.108	-0.252	0.036		.136
- FI = 0.15		-0.084	-0.236	0.067		.267
- FI = 0.20		-0.061	-0.275	0.152		.569
- FI = 0.25		-0.037	-0.335	0.260		.901
LDL-cholesterol[a]	0.178		-0.054	0.076	*1.683* (116, 15)	.734
- FI = 0.05		-0.409	-1.027	0.209		.188
- FI = 0.10		-0.354	-0.806	0.096		.118
- FI = 0.15		-0.300	-0.776	0.175		.209
- FI = 0.20		-0.246	-0.918	0.425		.464
- FI = 0.25		-0.192	-1.130	0.745		.682
Creatine kinase	0.135		-18.739	1.851	*1.212* (116, 15)	.104
- FI = 0.05		27.446	-72.421	127.313		.583
- FI = 0.10		-14.774	-87.629	58.080		.685
- FI = 0.15		-56.994	-134.080	20.090		.141
- FI = 0.20		-99.215	-208.194	9.763		.071
- FI = 0.25		-141.436	-293.457	10.585		.065
Creatinine	0.054		-10.558	9.447	*0.447* (116, 15)	.912
- FI = 0.05		15.163	-83.244	113.571		.758
- FI = 0.10		12.385	-60.246	85.017		.733
- FI = 0.15		9.608	-67.003	86.219		.802
- FI = 0.20		6.830	-100.248	113.909		.898
- FI = 0.25		4.052	-144.490	152.596		.956
C-Reactive protein	0.254		-1.374	1.501	*2.638* (116, 15)	.929
- FI = 0.05		-3.534	-17.556	10.488		.615
- FI = 0.10		-3.215	-13.471	7.041		.531
- FI = 0.15		-2.895	-13.718	7.925		.593
- FI = 0.20		-2.577	-17.822	12.667		.735
- FI = 0.25		-2.258	-23.496	18.979		.821

Cardiovascular Biomarker	R Square		Beta 95% CI		F-Statistic	P Value
		Beta	Lower	Upper		
Systolic blood pressure	0.185		-0.749	1.268	*1.760* (115, 16)	.607
- FI = 0.05		-6.403	-16.091	3.284		.188
- FI = 0.10		-5.105	-12.238	2.027		.154
- FI = 0.15		-3.807	-11.476	3.860		.322
- FI = 0.20		-2.509	-13.355	8.336		.644
- FI = 0.25		-1.211	-16.290	13.867		.872
Diastolic blood pressure	0.219		-0.835	0.349	*2.174* (115, 16)	.413
- FI = 0.05		2.468	-3.337	8.275		.396
- FI = 0.10		1.125	-2.975	5.484		.554
- FI = 0.15		0.040	-4.389	4.469		.985
- FI = 0.20		-1.173	-7.410	5.062		.707
- FI = 0.25		-2.388	-11.089	6.313		.584
Resting pulse	0.152		-1.731	0.387	*1.386* (115, 16)	.207
- FI = 0.05		0.125	-10.291	10.543		.980
- FI = 0.10		-3.232	-10.831	4.367		.396
- FI = 0.15		-6.589	-14.534	1.354		.099
- FI = 0.20		-9.947	-21.109	1.213		.077
- FI = 0.25		-13.305	-28.867	2.256		.089

[a]Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein. [b]CLSA-FI values were multiplied by 100 to increase interpretability of findings, corresponding beta-coefficients relate to 1-unit increases in CLSA-FI. Computed using alpha = 0.05. Model used center-based CR as the reference.

4.4. DISCUSSION

Interest regarding the impact between CVD and frailty is growing as researchers seek to better understand the coexistence of these two health concerns [122]. Here, we contribute to the literature by studying changes in frailty from CR admission to completion with center-based versus virtual CR, as was routinely implemented during COVID-19. We identified four key findings. First, center-based participants were significantly frailer than virtual participants upon CR admission. Second, frailty change did not differ between CR models in the main analysis. Thirdly, frailty change was influenced by admission frailty level and CR model, such that frailer participants at CR admission (FI≥0.20) reduced their frailty to a greater extent in virtual versus center-based CR. Fourth, admission frailty was associated with a change in some but not all cardiovascular biomarkers over the course of

virtual CR only. Here, we demonstrate that virtual CR is a reasonable alternative when center-based CR is inaccessible, enabling eligible patients to receive CR services and improve their health.

Center-based participants had significantly higher CLSA-FI and FICVD scores than virtual participants at admission (Figure 4, Supplemental Table A.4). This was expected, as participants who were deemed "low-to-moderate risk" by CR staff at admission were preferentially allocated to virtual CR. However, frailty levels were lower in our center-based sample compared to previous reports [17]. The discrepancy may relate to FI item differences or hesitancy among "higher risk" patients to enrol in CR during COVID-19. For example, previous research [17] used a 25-item FI with a greater ratio of CVD biomarkers than the CLSA-FI used here. Indeed, we observed higher FICVD versus CLSA-FI scores in both program models (Figure 4, Supplemental Table A.4), highlighting the significant contribution of CVD biomarkers on frailty among CR participants. We acknowledge participant safety remains a priority for unsupervised virtual CR programs [86, 123]. Therefore, our results support previously published literature which identify virtual-based health interventions as safe for low-to-moderate risk participants [23, 24, 86]. Yet, we did see people with mild to moderate frailty levels in virtual CR, and thus we agree with previous statements arguing for more research using virtual CR in "high-risk" participants [86].

We show that on average, frailty, as measured by the CLSA-FI and FICVD, was not significantly changed in both program models (Figure 4, Supplemental Table A.4). We anticipated that both program models would result in a lower frailty level, at least amongst people entering center-based CR, based on previous literature [17, 22, 94, 102].

Conversely, our listwise deletion analysis showed significant differences between CR models on frailty change, such that center-based participants observed a small significant decrease (FI reduction of 0.016), while virtual participants observed a small non-significant increase in frailty scores (FI increase of 0.006) from CR admission to completion (Supplemental Table A.4, Supplemental Figure 1). However, these differences were not considered a clinically meaningful change in frailty (FI threshold: ≥0.03) [117, 118]. Other studies demonstrated center-based CR was associated with improvements in frailty, however, each of those CR programs operated for a minimum of 12-weeks (range = 12-24 weeks) [17, 22, 94, 102]. Here, COVID-19 restrictions enforced capacity and duration limits in CR to address the high volume of eligible CR participants on the waitlist, resulting in shortened CR programs (i.e., Center-based = 6-weeks; Virtual = 9-10-weeks). Therefore, it is possible the limited volume of CR was insufficient to obtain similar reductions in frailty as observed in previous studies.

Although we did not identify differences in frailty change between center-based and virtual CR participants in our main analysis, simple slope analyses revealed an influence of admission frailty (CLSA-FI and FICVD), where higher frailty levels were associated with a greater magnitude of frailty reduction in participants enrolled in virtual CR (Figure 5, Supplemental Table A.5). These findings are supported by previous literature [17, 22]. Importantly, we found virtual CR participants with mild frailty levels (FI ≥0.20) improved to a greater extent than center-based counterparts (Figure 5; Supplemental Table A.5). Our sensitivity analysis evaluating FICVD change demonstrated results consistent with our main analysis, while our listwise deletion analysis revealed no between group differences (Supplemental Figure 2, Supplemental Table A.5). Despite using multiple

imputation, our results need to be interpreted with caution due to our small sample size of frailer participants at admission (Table 4.1).

Finally, other than an increase in HDL-cholesterol in virtual participants, we identified cardiovascular biomarkers were unchanged irrespective of CR model (Supplemental Table A.6). Moreover, admission CLSA-FI was not a predictor of change in cardiovascular biomarkers, and FICVD was only associated with increased diastolic blood pressure (Supplemental Tables A.7 & A.8, respectively). Our pre-planned simple slope analyses found virtual CR participants with higher admission CLSA-FI and FICVD scores saw a greater reduction in triglycerides and total cholesterol over the course of CR as compared to center-based CR (Table 4.2, Supplemental Figure 3; Supplemental Table A.9, Supplemental Figure 4, respectively). However, these changes were not observed at lower levels of admission frailty (Table 4.2, Supplemental Table A.9). Although our findings support previous work favoring virtual over center-based CR on changes in HDL cholesterol [124], triglycerides [124, 125], and total cholesterol [126], we caution our results as virtual CR programs provided 3-4 additional weeks for resolution of their acute CVD event, and based on clinical judgement of CR staff, virtual participants were considered 'lower risk' than the center-based participants.

LIMITATIONS

Our study has limitations. First, the difference between CR model duration poses a limitation to the generalizability of our findings, as these do not follow the North American guidelines of CR program duration (≥12-weeks) [16]. However, modified CR durations were necessary due to COVID-19 public health guidelines. Second, virtual CR lacked standardization across program enrollments. Depending on virtual CR participants' time

of enrollment, participants would have received different programs due to CR closures, staff redeployment, and program adjustments during COVID-19. The lack of consistency from shaping CR to address patients' needs while appreciating program interruptions among different virtual programs should be considered when interpreting the results of this study [86]. However, these challenges were anticipated nationwide [23]. Third, we used multiple imputation to generate 28.4% missing variable values. However, this level of missingness is appropriate within multiple imputation guidelines [127]. Multiple imputation provides a robust approach to missing information as missing values are generated by predictive mean matching valid responses found within the sample. Fourth, certain CLSA-FI items were not sensitive to change, meaning they could not be reversed. Thirty-five out of 65-items were reversible (e.g., difficulty with activities of daily living), whereas 30 out of 65 variables could only be accumulated (e.g., chronic diseases).

CONCLUSION

We demonstrate virtual CR is non-inferior to center-based CR on frailty change, however, frailty improvements were significantly greater in virtual participants who were frailer at admission. Admission CLSA-FI scores may also be suitable for predicting change in some cardiovascular biomarkers.

4.5. References

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4.6. Supplemental Tables Package

Supplemental Table A.1. Description of center- and virtual-based CR[a] programs[b]

CR[a] model	Center-based CR[a]	Virtual CR[a]
Duration of program	6-weeks	9-10 weeks
Exercise component	Group-based exercise sessions which included individualized prescription based on graded exercise stress testing at CR admission and orthopaedic limitations.	Individual home-based exercise prescribed using graded exercise stress test results at CR admission, orthopaedic limitations, and availability of exercise equipment/resources to the patient.
Type of exercise	Exercises include a continuous or interval type aerobic exercise on a treadmill, leg cycle ergometer, or arm cycle ergometer.	CR physiotherapists prescribe exercise types by discussing the equipment or resources that are available on a patient-to-patient basis. Examples of exercises include walking indoors or outdoors, bicycling, recreational sport, body weight resistance training, resistance training with equipment, and flexibility or stretching exercises.
Frequency & Duration	Once weekly, 60-minute exercise class, including 10 minutes of warm-up, 40 minutes of exercise time, and 10 minutes of cool-down. Participants were encouraged to reach 150 minutes of moderate-vigorous exercise per week by supplementing outside of CR.	Exercise target to meet 150 minutes of moderate-vigorous exercise per week. This exercise target could be completed in bouts of 10+ minutes of exercise throughout the week.
Education component	Up to 3, one-hour, weekly group-based phone/video call rotation from team physiotherapist, nurse, and dietician. Education sessions focussed on cardiovascular health and risk factor reduction, incorporating health behaviour changes to diet, physical activity, or medications if needed. In addition to weekly phone calls, center-based participants could interact with members of their CR team during each of their 6 exercise sessions, totalling a possible 9 hours spent with CR staff.	Up to 4, one-hour, weekly group-based phone/video call rotation from team physiotherapist, nurse, and dietician, with a group Question and Answer Zoom video session held during week 4. From week 5 to program completion, virtual participants received up to 6 weekly, 45-minute, individual phone calls, totalling a possible 8.5 hours spent with CR staff. Sessions provided education on cardiovascular health and risk factor reduction, incorporating health behaviour changes to diet, physical activity, or medications if needed.
Multidisciplinary healthcare team	Medical director, program lead, nurse, physiotherapist, dietician.	Medical director, program lead, nurse, physiotherapist, dietician.

[a]Abbreviations: CR, cardiac rehabilitation. [b]Table descriptions are from the Nova Scotia Health Hearts and Health in Motion CR Program.

Supplemental Table A.2. Frequency of 65 CLSA-FI items for CR participants at admission & follow-up

Question	Deficit	Coding	Frequency N (sample %)			
			Center-based CR responses		Virtual CR responses	
			Admission	Follow-up	Admission	Follow-up
1) Can you..	Dress and undress yourself?	0 = Yes, without help. 0.5 = Yes, with some help. 1 = No, unable to do so.	0 = 41 (97.6%) 0.5 = 1 (2.4%) 1 = 0 (0.0%)	0 = 41 (97.6%) 0.5 = 1 (2.4%) 1 = 0 (0.0%)	0 = 25 (100.0%) 0.5 = 0 (0.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 0.5 = 0 (0.0%) 1 = 0 (0.0%)
	Take care of your own appearance?	0 = Yes, without help. 0.5 = Yes, with some help. 1 = No, unable to do so.	0 = 42 (100.0%) 0.5 = 0 (0.0%) 1 = 0 (0.0%)	0 = 42 (100.0%) 0.5 = 0 (0.0%) 1 = 0 (0.0%)	0 = 24 (96.0%) 0.5 = 1 (4.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 0.5 = 0 (0.0%) 1 = 0 (0.0%)
	Walk?	0 = Yes, without help. 0.5 = Yes, with some help. 1 = No, unable to do so.	0 = 41 (97.6%) 0.5 = 1 (2.4%) 1 = 0 (0.0%)	0 = 41 (97.6%) 0.5 = 1 (2.4%) 1 = 0 (0.0%)	0 = 25 (100.0%) 0.5 = 0 (0.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 0.5 = 0 (0.0%) 1 = 0 (0.0%)
	Get in and out of bed?	0 = Yes, without help. 0.5 = Yes, with some help. 1 = No, unable to do so.	0 = 42 (100.0%) 0.5 = 0 (0.0%) 1 = 0 (0.0%)	0 = 42 (100.0%) 0.5 = 0 (0.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 0.5 = 0 (0.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 0.5 = 0 (0.0%) 1 = 0 (0.0%)
	Take a bath or shower	0 = Yes, without help. 0.5 = Yes, with some help. 1 = No, unable to do so.	0 = 42 (100.0%) 0.5 = 0 (0.0%) 1 = 0 (0.0%)	0 = 41 (97.6%) 0.5 = 1 (2.4%) 1 = 0 (0.0%)	0 = 24 (96.0%) 0.5 = 1 (4.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 0.5 = 0 (0.0%) 1 = 0 (0.0%)
2) Can you..	Use the telephone?	0 = Yes, without help. 0.5 = Yes, with some help. 1 = No, unable to do so.	0 = 42 (100.0%) 0.5 = 0 (0.0%) 1 = 0 (0.0%)	0 = 42 (100.0%) 0.5 = 0 (0.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 0.5 = 0 (0.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 0.5 = 0 (0.0%) 1 = 0 (0.0%)
	Get places out of walking distance?	0 = Yes, without help. 0.5 = Yes, with some help. 1 = No, unable to do so.	0 = 41 (97.6%) 0.5 = 1 (2.4%) 1 = 0 (0.0%)	0 = 41 (97.6%) 0.5 = 1 (2.4%) 1 = 0 (0.0%)	0 = 24 (96.0%) 0.5 = 1 (4.0%) 1 = 0 (0.0%)	0 = 24 (96.0%) 0.5 = 1 (4.0%) 1 = 0 (0.0%)

Question	Deficit	Coding	Frequency N (sample %)			
			Center-based CR responses		Virtual CR responses	
			Admission	Follow-up	Admission	Follow-up
	Go shopping for groceries and clothes?	0 = Yes, without help. 0.5 = Yes, with some help. 1 = No, unable to do so.	0 = 39 (7.1%) 0.5 = 3 (92.9%) 1 = 0 (0.0%)	0 = 41 (97.6%) 0.5 = 1 (2.4%) 1 = 0 (0.0%)	0 = 23 (92.0%) 0.5 = 2 (8.0%) 1 = 0 (0.0%)	0 = 23 (92.0%) 0.5 = 2 (8.0%) 1 = 0 (0.0%)
	Prepare your own meals?	0 = Yes, without help. 0.5 = Yes, with some help. 1 = No, unable to do so.	0 = 42 (100.0%) 0.5 = 0 (0.0%) 1 = 0 (0.0%)	0 = 42 (100.0%) 0.5 = 0 (0.0%) 1 = 0 (0.0%)	0 = 24 (96.0%) 0.5 = 1 (4.0%) 1 = 0 (0.0%)	0 = 23 (92.0%) 0.5 = 2 (8.0%) 1 = 0 (0.0%)
	Do your housework?	0 = Yes, without help. 0.5 = Yes, with some help. 1 = No, unable to do so.	0 = 38 (90.5%) 0.5 = 4 (9.5%) 1 = 0 (0.0%)	0 = 39 (7.1%) 0.5 = 3 (92.9%) 1 = 0 (0.0%)	0 = 24 (96.0%) 0.5 = 1 (4.0%) 1 = 0 (0.0%)	0 = 23 (92.0%) 0.5 = 2 (8.0%) 1 = 0 (0.0%)
	Take your own medicine?	0 = Yes, without help. 0.5 = Yes, with some help. 1 = No, unable to do so.	0 = 40 (95.2%) 0.5 = 2 (4.8%) 1 = 0 (0.0%)	0 = 42 (100.0%) 0.5 = 0 (0.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 0.5 = 0 (0.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 0.5 = 0 (0.0%) 1 = 0 (0.0%)
	Handle your own money?	0 = Yes, without help. 0.5 = Yes, with some help. 1 = No, unable to do so.	0 = 40 (95.2%) 0.5 = 2 (4.8%) 1 = 0 (0.0%)	0 = 40 (95.2%) 0.5 = 2 (4.8%) 1 = 0 (0.0%)	0 = 24 (96.0%) 0.5 = 1 (4.0%) 1 = 0 (0.0%)	0 = 23 (92.0%) 0.5 = 2 (8.0%) 1 = 0 (0.0%)
3) Do you have difficulty with..	Reaching or extending your arms above your shoulders?	0 = No. 0.25 = Yes, a little difficult. 0.5 = Yes, somewhat difficult. 0.75 = Yes, very difficult. 1 = Unable to do so. 1 = Do not do on doctor's orders.	0 = 32 (76.2%) 0.25 = 5 (11.9%) 0.5 = 4 (9.5%) 0.75 = 0 (0.0%) 1 = 1 (2.4%)	0 = 34 (81%) 0.25 = 3 (7.1%) 0.5 = 3 (7.1%) 0.75 = 1 (2.4%) 1 = 1 (2.4%)	0 = 14 (56.0%) 0.25 = 9 (36.0%) 0.5 = 1 (4.0%) 0.75 = 0 (0.0%) 1 = 1 (4.0%)	0 = 16 (64.0%) 0.25 = 6 (24.0%) 0.5 = 2 (8.0%) 0.75 = 0 (0.0%) 1 = 1 (4.0%)

Question	Deficit	Coding	Frequency N (sample %)			
			Center-based CR responses		Virtual CR responses	
			Admission	Follow-up	Admission	Follow-up
	Stooping, crouching, or kneeling down?	0 = No. 0.25 = Yes, a little difficult. 0.5 = Yes, somewhat difficult. 0.75 = Yes, very difficult. 1 = Unable to do so. 1 = Do not do on doctor's orders.	0 = 28 (66.7%) 0.25 = 6 (14.3%) 0.5 = 4 (9.5%) 0.75 = 4 (9.5%) 1 = 0 (0.0%)	0 = 27 (64.3%) 0.25 = 7 (16.7%) 0.5 = 6 (14.3%) 0.75 = 2 (4.8%) 1 = 0 (0.0%)	0 = 11 (44.0%) 0.25 = 8 (32.0%) 0.5 = 3 (12.0%) 0.75 = 3 (12.0%) 1 = 1 (4.0%)	0 = 13 (52.0%) 0.25 = 5 (20.0%) 0.5 = 2 (8.0%) 0.75 = 4 (16.0%) 1 = 1 (4.0%)
	Pushing or pulling large objects like a living room chair?	0 = No. 0.25 = Yes, a little difficult. 0.5 = Yes, somewhat difficult. 0.75 = Yes, very difficult. 1 = Unable to do so. 1 = Do not do on doctor's orders.	0 = 29 (76.2%) 0.25 = 8 (19.0%) 0.5 = 2 (4.8%) 0.75 = 3 (7.1%) 1 = 0 (0.0%)	0 = 37 (88.1%) 0.25 = 0 (0.0%) 0.5 = 0 (0.0%) 0.75 = 0 (0.0%) 1 = 4 (9.5%) Missing = 1 (2.4%)	0 = 16 (64.0%) 0.25 = 7 (28.0%) 0.5 = 2 (8.0%) 0.75 = 0 (0.0%) 1 = 0 (0.0%)	0 = 18 (72.0%) 0.25 = 5 (20.0%) 0.5 = 2 (8.0%) 0.75 = 0 (0.0%) 1 = 0 (0.0%)
	Lifting 10 lbs. (or 4.5kg) from the floor, like a heavy bag of groceries?	0 = No. 0.25 = Yes, a little difficult. 0.5 = Yes, somewhat difficult. 0.75 = Yes, very difficult. 1 = Unable to do so. 1 = Do not do on doctor's orders.	0 = 33 (78.6%) 0.25 = 4 (9.5%) 0.5 = 2 (4.8%) 0.75 = 2 (4.8%) 1 = 1 (2.4%)	0 = 36 (85.7%) 0.25 = 4 (9.5%) 0.5 = 0 (0.0%) 0.75 = 2 (4.8%) 1 = 0 (0.0%)	0 = 23 (92.0%) 0.25 = 2 (8.0%) 0.5 = 0 (0.0%) 0.75 = 0 (0.0%) 1 = 0 (0.0%)	0 = 22 (88.0%) 0.25 = 3 (12.0%) 0.5 = 0 (0.0%) 0.75 = 0 (0.0%) 1 = 0 (0.0%)
	Handling small objects, like picking up a coin from a table?	0 = No. 0.25 = Yes, a little difficult. 0.5 = Yes, somewhat difficult. 0.75 = Yes, very difficult. 1 = Unable to do so. 1 = Do not do on doctor's orders.	0 = 41 (97.6%) 0.25 = 0 (0.0%) 0.5 = 0 (0.0%) 0.75 = 1 (2.4%) 1 = 0 (0.0%)	0 = 39 (92.9%) 0.25 = 2 (4.8%) 0.5 = 0 (0.0%) 0.75 = 1 (2.4%) 1 = 0 (0.0%)	0 = 24 (96.0%) 0.25 = 1 (4.0%) 0.5 = 0 (0.0%) 0.75 = 0 (0.0%) 1 = 0 (0.0%)	0 = 23 (92.0%) 0.25 = 2 (8.0%) 0.5 = 0 (0.0%) 0.75 = 0 (0.0%) 1 = 0 (0.0%)

Question	Deficit	Coding	Frequency N (sample %)			
			Center-based CR responses		Virtual CR responses	
			Admission	Follow-up	Admission	Follow-up
	Standing for a long period, around 15 minutes?	0 = No. 0.25 = Yes, a little difficult. 0.5 = Yes, somewhat difficult. 0.75 = Yes, very difficult. 1 = Unable to do so. 1 = Do not do on doctor's orders.	0 = 31 (73.8%) 0.25 = 7 (16.7%) 0.5 = 2 (4.8%) 0.75 = 2 (4.8%) 1 = 0 (0.0%)	0 = 32 (76.2%) 0.25 = 4 (9.5%) 0.5 = 6 (14.3%) 0.75 = 0 (0.0%) 1 = 0 (0.0%)	0 = 22 (88.0%) 0.25 = 0 (0.0%) 0.5 = 2 (8.0%) 0.75 = 1 (4.0%) 1 = 0 (0.0%)	0 = 19 (76.0%) 0.25 = 5 (20.0%) 0.5 = 0 (0.0%) 0.75 = 1 (4.0%) 1 = 0 (0.0%)
	Standing up after sitting in a chair?	0 = No. 0.25 = Yes, a little difficult. 0.5 = Yes, somewhat difficult. 0.75 = Yes, very difficult. 1 = Unable to do so. 1 = Do not do on doctor's orders.	0 = 26 (61.9%) 0.25 = 14 (33.3%) 0.5 = 0 (0.0%) 0.75 = 2 (4.8%) 1 = 0 (0.0%)	0 = 31 (73.8%) 0.25 = 9 (21.4%) 0.5 = 0 (0.0%) 0.75 = 2 (4.8%) 1 = 0 (0.0%)	0 = 16 (64.0%) 0.25 = 9 (36.0%) 0.5 = 0 (0.0%) 0.75 = 0 (0.0%) 1 = 0 (0.0%)	0 = 21 (84.0%) 0.25 = 3 (12.0%) 0.5 = 1 (4.0%) 0.75 = 0 (0.0%) 1 = 0 (0.0%)
	Walking alone up and down a flight of stairs?	0 = No. 0.25 = Yes, a little difficult. 0.5 = Yes, somewhat difficult. 0.75 = Yes, very difficult. 1 = Unable to do so. 1 = Do not do on doctor's orders.	0 = 34 (81.0%) 0.25 = 5 (11.9%) 0.5 = 0 (0.0%) 0.75 = 3 (7.1%) 1 = 0 (0.0%)	0 = 32 (76.2%) 0.25 = 7 (16.7%) 0.5 = 3 (7.1%) 0.75 = 0 (0.0%) 1 = 0 (0.0%)	0 = 20 (80.0%) 0.25 = 5 (20.0%) 0.5 = 0 (0.0%) 0.75 = 0 (0.0%) 1 = 0 (0.0%)	0 = 21 (84.0%) 0.25 = 3 (12.0%) 0.5 = 1 (4.0%) 0.75 = 0 (0.0%) 1 = 0 (0.0%)
	Walking 2-3 neighborhood blocks?	0 = No. 0.25 = Yes, a little difficult. 0.5 = Yes, somewhat difficult. 0.75 = Yes, very difficult. 1 = Unable to do so. 1 = Do not do on doctor's orders.	0 = 32 (76.2%) 0.25 = 3 (7.1%) 0.5 = 3 (7.1%) 0.75 = 3 (7.1%) 1 = 1 (2.4%)	0 = 35 (83.3%) 0.25 = 2 (4.8%) 0.5 = 3 (7.1%) 0.75 = 2 (4.8%) 1 = 0 (0.0%)	0 = 18 (72.0%) 0.25 = 6 (24.0%) 0.5 = 1 (4.0%) 0.75 = 0 (0.0%) 1 = 0 (0.0%)	0 = 19 (76.0%) 0.25 = 4 (16.0%) 0.5 = 1 (4.0%) 0.75 = 1 (4.0%) 1 = 0 (0.0%)

Question	Deficit	Coding	Frequency N (sample %)			
			Center-based CR responses		Virtual CR responses	
			Admission	Follow-up	Admission	Follow-up
	Making a bed?	0 = No. 0.25 = Yes, a little difficult. 0.5 = Yes, somewhat difficult. 0.75 = Yes, very difficult. 1 = Unable to do so. 1 = Do not do on doctor's orders.	0 = 37 (88.1%) 0.25 = 3 (7.1%) 0.5 = 1 (2.4%) 0.75 = 1 (2.4%) 1 = 0 (0.0%)	0 = 38 (90.5%) 0.25 = 1 (2.4%) 0.5 = 3 (7.1%) 0.75 = 0 (0.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 0.25 = 0 (0.0%) 0.5 = 0 (0.0%) 0.75 = 0 (0.0%) 1 = 0 (0.0%)	0 = 24 (96.0%) 0.25 = 1 (4.0%) 0.5 = 0 (0.0%) 0.75 = 0 (0.0%) 1 = 0 (0.0%)
	Washing your back?	0 = No. 0.25 = Yes, a little difficult. 0.5 = Yes, somewhat difficult. 0.75 = Yes, very difficult. 1 = Unable to do so. 1 = Do not do on doctor's orders.	0 = 33 (78.6%) 0.25 = 4 (9.5%) 0.5 = 3 (7.1%) 0.75 = 0 (0.0%) 1 = 2 (4.8%)	0 = 37 (88.1%) 0.25 = 2 (4.8%) 0.5 = 2 (4.8%) 0.75 = 0 (0.0%) 1 = 1 (2.4%)	0 = 17 (68.0%) 0.25 = 5 (20.0%) 0.5 = 1 (4.0%) 0.75 = 1 (4.0%) 1 = 1 (4.0%)	0 = 16 (64.0%) 0.25 = 5 (20.0%) 0.5 = 1 (4.0%) 0.75 = 0 (0.0%) 1 = 3 (12.0%)
	Using a knife to cut food?	0 = No. 0.25 = Yes, a little difficult. 0.5 = Yes, somewhat difficult. 0.75 = Yes, very difficult. 1 = Unable to do so. 1 = Do not do on doctor's orders.	0 = 39 (92.9%) 0.25 = 2 (4.8%) 0.5 = 1 (2.4%) 0.75 = 0 (0.0%) 1 = 0 (0.0%)	0 = 40 (95.2%) 0.25 = 1 (2.4%) 0.5 = 0 (0.0%) 0.75 = 1 (2.4%) 1 = 0 (0.0%)	0 = 25 (100.0%) 0.25 = 0 (0.0%) 0.5 = 0 (0.0%) 0.75 = 0 (0.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 0.25 = 0 (0.0%) 0.5 = 0 (0.0%) 0.75 = 0 (0.0%) 1 = 0 (0.0%)
	Recreational or work activities in which you take some force or impact through your arm, shoulder, or hand?	0 = No. 0.25 = Yes, a little difficult. 0.5 = Yes, somewhat difficult. 0.75 = Yes, very difficult. 1 = Unable to do so. 1 = Do not do on doctor's orders.	0 = 32 (76.2%) 0.25 = 6 (14.3%) 0.5 = 1 (2.4%) 0.75 = 2 (4.8%) 1 = 1 (2.4%)	0 = 33 (78.6%) 0.25 = 6 (14.3%) 0.5 = 0 (0.0%) 0.75 = 2 (4.8%) 1 = 1 (2.4%)	0 = 23 (92.0%) 0.25 = 0 (0.0%) 0.5 = 0 (0.0%) 0.75 = 0 (0.0%) 1 = 1 (4.0%) Missing = 1 (4.0%)	0 = 19 (76.0%) 0.25 = 4 (16.0%) 0.5 = 1 (4.0%) 0.75 = 0 (0.0%) 1 = 1 (4.0%)

Question	Deficit	Coding	Frequency N (sample %)			
			Center-based CR responses		Virtual CR responses	
			Admission	Follow-up	Admission	Follow-up
4) Please answer the following..	In General, would you say your health is...?	0 = Excellent. 0.25 = Very Good. 0.5 = Good. 0.75 = Fair. 1 = Poor.	0 = 2 (4.8%) 0.25 = 8 (19.0%) 0.5 = 23 (54.8%) 0.75 = 8 (19.0%) 1 = 1 (2.4%)	0 = 8 (19.0%) 0.25 = 10 (23.8%) 0.5 = 17 (40.5%) 0.75 = 6 (14.3%) 1 = 1 (2.4%)	0 = 0 (0.0%) 0.25 = 3 (12.0%) 0.5 = 13 (52.0%) 0.75 = 8 (32.0%) 1 = 1 (4.0%)	0 = 3 (12.0%) 0.25 = 3 (12.0%) 0.5 = 12 (48.0%) 0.75 = 7 (28.0%) 1 = 0 (0.0%)
	Is your eyesight, using glasses or corrective lens if you use them...?	0 = Excellent. 0.25 = Very Good. 0.5 = Good. 0.75 = Fair. 1 = Poor.	0 = 5 (11.9%) 0.25 = 15 (35.7%) 0.5 = 21 (50.0%) 0.75 = 1 (2.4%) 1 = 0 (0.0%)	0 = 10 (23.8%) 0.25 = 16 (38.1%) 0.5 = 16 (38.1%) 0.75 = 0 (0.0%) 1 = 0 (0.0%)	0 = 3 (12.0%) 0.25 = 9 (36.0%) 0.5 = 9 (36.0%) 0.75 = 2 (8.0%) 1 = 1 (4.0%) Missing = 1 (4.0%)	0 = 5 (20.0%) 0.25 = 6 (24.0%) 0.5 = 10 (40.0%) 0.75 = 2 (8.0%) 1 = 2 (8.0%)
	Is your hearing, using a hearing aid if you use one...?	0 = Excellent. 0.25 = Very Good. 0.5 = Good. 0.75 = Fair. 1 = Poor.	0 = 6 (14.3%) 0.25 = 15 (35.7%) 0.5 = 15 (35.7%) 0.75 = 6 (14.3%) 1 = 0 (0.0%)	0 = 13 (31.0%) 0.25 = 14 (33.3%) 0.5 = 10 (23.8%) 0.75 = 4 (9.5%) 1 = 1 (2.4%)	0 = 11 (44.0%) 0.25 = 0 (0.0%) 0.5 = 0 (0.0%) 0.75 = 0 (0.0%) 1 = 13 (52.0%) Missing = 1 (4.0%)	0 = 7 (28.0%) 0.25 = 3 (12.0%) 0.5 = 11 (44.0%) 0.75 = 4 (16.0%) 1 = 0 (0.0%)
5) Do you consider yourself..	Just about right. Overweight? Underweight?	0 = Just about right. 1 = Overweight 1 = Underweight	0 = 9 (21.4%) 1 = 33 (78.6%)	0 = 13 (31.0%) 1 = 29 (69.0%)	0 = 9 (36.0%) 1 = 16 (64.0%)	0 = 10 (40.0%) 1 = 15 (60.0%)

Question	Deficit	Coding	Frequency N (sample %)			
			Center-based CR responses		Virtual CR responses	
			Admission	Follow-up	Admission	Follow-up
6) How many times have you..	Had a fall in the past 12 months that was serious enough to limit some of your normal activities? For example, the fall resulted in a broken bone, bad cut, or sprain?	0 = None. 1 = Once 2 = Twice or more	0 = 37 (88.1%) 1 = 4 (9.5%) 2 = 1 (2.4%)	0 = 40 (95.2%) 1 = 1 (2.4%) 2 = 1 (2.4%)	0 = 23 (92.0%) 1 = 1 (4.0%) 2 = 1 (4.0%)	0 = 23 (92.0%) 1 = 1 (4.0%) 2 = 1 (4.0%)
7) In the past week how often did you feel..	That everything you did was an effort?	0 = Rarely or never (<1 day). 0.33 = Some of the time (1-2). 0.66 = Occasionally (3-4). 1 = All of the time (5-7 days).	0 = 29 (69.0%) 0.33 = 7 (16.7%) 0.66 = 2 (4.8%) 1 = 4 (9.5%)	0 = 28 (66.7%) 0.33 = 10 (23.8%) 0.66 = 2 (4.8%) 1 = 2 (4.8%)	0 = 15 (60.0%) 0.33 = 7 (28.0%) 0.66 = 3 (12.0%) 1 = 0 (0.0%)	0 = 16 (64.0%) 0.33 = 6 (24.0%) 0.66 = 3 (12.0%) 1 = 0 (0.0%)
	Lonely?	0 = Rarely or never (<1 day). 0.33 = Some of the time (1-2). 0.66 = Occasionally (3-4). 1 = All of the time (5-7 days).	0 = 35 (83.3%) 0.33 = 2 (4.8%) 0.66 = 3 (7.1%) 1 = 2 (4.8%)	0 = 33 (78.6%) 0.33 = 5 (11.9%) 0.66 = 2 (4.8%) 1 = 2 (4.8%)	0 = 18 (72.0%) 0.33 = 5 (20.0%) 0.66 = 2 (8.0%) 1 = 0 (0.0%)	0 = 16 (64.0%) 0.33 = 3 (12.0%) 0.66 = 2 (8.0%) 1 = 2 (8.0%)
	That you could not “get going”?	0 = Rarely or never (<1 day). 0.33 = Some of the time (1-2). 0.66 = Occasionally (3-4). 1 = All of the time (5-7 days).	0 = 29 (69.0%) 0.33 = 9 (21.4%) 0.66 = 3 (7.1%) 1 = 1 (2.4%)	0 = 29 (69.0%) 0.33 = 9 (21.4%) 0.66 = 2 (4.8%) 1 = 2 (4.8%)	0 = 15 (60.0%) 0.33 = 8 (32.0%) 0.66 = 2 (8.0%) 1 = 0 (0.0%)	0 = 16 (64.0%) 0.33 = 7 (28.0%) 0.66 = 1 (4.0%) 1 = 1 (4.0%)

Question	Deficit	Coding	Frequency N (sample %)			
			Center-based CR responses		Virtual CR responses	
			Admission	Follow-up	Admission	Follow-up
8) In the past 12 months, have you seen a doctor for..	Pneumonia?	0 = No 1 = Yes	0 = 40 (95.2%) 1 = 2 (4.8%)	0 = 40 (95.2%) 1 = 2 (4.8%)	0 = 25 (100.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 1 = 0 (0.0%)
	Urinary tract infection	0 = No 1 = Yes	0 = 39 (92.9%) 1 = 3 (7.1%)	0 = 39 (92.9%) 1 = 1 (2.4%) Missing = 1 (2.4%)	0 = 23 (92.0%) 1 = 2 (8.0%)	0 = 24 (96.0%) 1 = 1 (4.0%)
9) Has a doctor ever told you that you..	have osteoarthritis in the knee?	0 = No 1 = Yes	0 = 36 (85.7%) 1 = 6 (14.3%)	0 = 36 (85.7%) 1 = 6 (14.3%)	0 = 21 (84.0%) 1 = 4 (16.0%)	0 = 21 (84.0%) 1 = 4 (16.0%)
	have osteoarthritis in the hip?	0 = No 1 = Yes	0 = 36 (85.7%) 1 = 6 (14.3%)	0 = 36 (85.7%) 1 = 6 (14.3%)	0 = 22 (88.0%) 1 = 3 (12.0%)	0 = 22 (88.0%) 1 = 3 (12.0%)
	have osteoarthritis in one or both hands?	0 = No 1 = Yes	0 = 39 (92.9%) 1 = 3 (7.1%)	0 = 39 (92.9%) 1 = 3 (7.1%)	0 = 22 (88.0%) 1 = 3 (12.0%)	0 = 22 (88.0%) 1 = 3 (12.0%)
	have rheumatoid arthritis?	0 = No 1 = Yes	0 = 40 (95.2%) 1 = 2 (4.8%)	0 = 40 (95.2%) 1 = 2 (4.8%)	0 = 25 (100.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 1 = 0 (0.0%)
	have any other type of arthritis?	0 = No 1 = Yes	0 = 35 (83.3%) 1 = 7 (16.7%)	0 = 35 (83.3%) 1 = 7 (16.7%)	0 = 20 (80.0%) 1 = 5 (20.0%)	0 = 20 (80.0%) 1 = 5 (20.0%)

Question	Deficit	Coding	Frequency N (sample %)			
			Center-based CR responses		Virtual CR responses	
			Admission	Follow-up	Admission	Follow-up
	have/had any of the following- emphysema, chronic bronchitis, chronic obstructive pulmonary disease (COPD), or chronic changes in lungs due to smoking?	0 = No 1 = Yes	0 = 37 (88.1%) 1 = 5 (11.9%)	0 = 37 (88.1%) 1 = 5 (11.9%)	0 = 24 (96.0%) 1 = 1 (4.0%)	0 = 24 (96.0%) 1 = 1 (4.0%)
	have high blood pressure or hypertension?	0 = No 1 = Yes	0 = 15 (35.7%) 1 = 27 (64.3%)	0 = 15 (35.7%) 1 = 27 (64.3%)	0 = 11 (44.0%) 1 = 14 (56.0%)	0 = 11 (44.0%) 1 = 14 (56.0%)
	have diabetes, borderline diabetes or that your blood sugar is high?	0 = No 1 = Yes	0 = 34 (81.0%) 1 = 8 (19.0%)	0 = 34 (81.0%) 1 = 8 (19.0%)	0 = 19 (76.0%) 1 = 6 (24.0%)	0 = 19 (76.0%) 1 = 6 (24.0%)
	have heart disease (including congestive heart failure or CHF)?	0 = No 1 = Yes	0 = 12 (28.6%) 1 = 30 (71.4%)	0 = 12 (28.6%) 1 = 30 (71.4%)	0 = 8 (32.0%) 1 = 17 (68.0%)	0 = 8 (32.0%) 1 = 17 (68.0%)
	have angina (or chest pain due to heart disease)?	0 = No 1 = Yes	0 = 29 (69.0%) 1 = 13 (31.0%)	0 = 29 (69.0%) 1 = 13 (31.0%)	0 = 19 (76.0%) 1 = 6 (24.0%)	0 = 19 (76.0%) 1 = 6 (24.0%)

Question	Deficit	Coding	Frequency N (sample %)			
			Center-based CR responses		Virtual CR responses	
			Admission	Follow-up	Admission	Follow-up
	have had a heart attack, or myocardial infarction?	0 = No 1 = Yes	0 = 21 (50.0%) 1 = 21 (50.0%)	0 = 21 (50.0%) 1 = 21 (50.0%)	0 = 10 (40.0%) 1 = 15 (60.0%)	0 = 10 (40.0%) 1 = 15 (60.0%)
	have peripheral vascular disease or poor circulation in your limbs?	0 = No 1 = Yes	0 = 41 (97.6%) 1 = 1 (2.4%)	0 = 41 (97.6%) 1 = 1 (2.4%)	0 = 25 (100.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 1 = 0 (0.0%)
	have experienced a stroke or CVA (cerebrovascular accident)?	0 = No 1 = Yes	0 = 2 (4.8%) 1 = 40 (95.2%)	0 = 2 (4.8%) 1 = 40 (95.2%)	0 = 25 (100.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 1 = 0 (0.0%)
	have experienced a mini-stroke or TIA (transient ischemic attack)?	0 = No 1 = Yes	0 = 40 (95.2%) 1 = 2 (4.8%)	0 = 40 (95.2%) 1 = 2 (4.8%)	0 = 25 (100.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 1 = 0 (0.0%)
	have a memory problem?	0 = No 1 = Yes	0 = 42 (100.0%) 1 = 0 (0.0%)	0 = 42 (100.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 1 = 0 (0.0%)
	have dementia or Alzheimer's disease?	0 = No 1 = Yes	0 = 42 (100.0%) 1 = 0 (0.0%)	0 = 42 (100.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 1 = 0 (0.0%)
	had parkinsonism or Parkinson's disease?	0 = No 1 = Yes	0 = 42 (100.0%) 1 = 0 (0.0%)	0 = 42 (100.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 1 = 0 (0.0%)

Question	Deficit	Coding	Frequency N (sample %)			
			Center-based CR responses		Virtual CR responses	
			Admission	Follow-up	Admission	Follow-up
	have intestinal or stomach ulcers?	0 = No 1 = Yes	0 = 42 (100.0%) 1 = 0 (0.0%)	0 = 42 (100.0%) 1 = 0 (0.0%)	0 = 23 (92.0%) 1 = 2 (8.0%)	0 = 23 (92.0%) 1 = 2 (8.0%)
	have a bowel disorder such as Crohn's disease, ulcerative colitis, or irritable bowel syndrome?	0 = No 1 = Yes	0 = 37 (88.1%) 1 = 5 (11.9%)	0 = 37 (88.1%) 1 = 5 (11.9%)	0 = 25 (100.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 1 = 0 (0.0%)
	experience bowel incontinence?	0 = No 1 = Yes	0 = 42 (100.0%) 1 = 0 (0.0%)	0 = 42 (100.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 1 = 0 (0.0%)
	experience urinary incontinence?	0 = No 1 = Yes	0 = 42 (100.0%) 1 = 0 (0.0%)	0 = 42 (100.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 1 = 0 (0.0%)
	have cataracts?	0 = No 1 = Yes	0 = 41 (97.6%) 1 = 1 (2.4%)	0 = 41 (97.6%) 1 = 1 (2.4%)	0 = 25 (100.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 1 = 0 (0.0%)
	have glaucoma?	0 = No 1 = Yes	0 = 42 (100.0%) 1 = 0 (0.0%)	0 = 42 (100.0%) 1 = 0 (0.0%)	0 = 24 (96.0%) 1 = 1 (4.0%)	0 = 24 (96.0%) 1 = 1 (4.0%)
	have macular degeneration?	0 = No 1 = Yes	0 = 42 (100.0%) 1 = 0 (0.0%)	0 = 42 (100.0%) 1 = 0 (0.0%)	0 = 24 (96.0%) 1 = 1 (4.0%)	0 = 24 (96.0%) 1 = 1 (4.0%)

Question	Deficit	Coding	Frequency N (sample %)			
			Center-based CR responses		Virtual CR responses	
			Admission	Follow-up	Admission	Follow-up
	had cancer?	0 = No 1 = Yes	0 = 40 (95.2%) 1 = 2 (4.8%)	0 = 40 (95.2%) 1 = 2 (4.8%)	0 = 23 (92.0%) 1 = 2 (8.0%)	0 = 23 (92.0%) 1 = 2 (8.0%)
	have osteoporosis, sometimes called low bone mineral density, or thin, brittle, or weak bones?	0 = No 1 = Yes	0 = 41 (97.6%) 1 = (2.4%)	0 = 41 (97.6%) 1 = (2.4%)	0 = 25 (100.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 1 = 0 (0.0%)
	have back problems, excluding fibromyalgia and arthritis?	0 = No 1 = Yes	0 = 6 (14.3%) 1 = 36 (85.7%)	0 = 6 (14.3%) 1 = 36 (85.7%)	0 = 24 (96.0%) 1 = 1 (4.0%)	0 = 24 (96.0%) 1 = 1 (4.0%)
	have an UNDER-active thyroid gland?	0 = No 1 = Yes	0 = 3 (7.1%) 1 = 39 (92.9%)	0 = 3 (7.1%) 1 = 39 (92.9%)	0 = 21 (84.0%) 1 = 4 (16.0%)	0 = 21 (84.0%) 1 = 4 (16.0%)
	have an OVER-active thyroid gland?	0 = No 1 = Yes	0 = 42 (100.0%) 1 = 0 (0.0%)	0 = 42 (100.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 1 = 0 (0.0%)	0 = 25 (100.0%) 1 = 0 (0.0%)
	have kidney disease or kidney failure?	0 = No 1 = Yes	0 = 5 (11.9%) 1 = 37 (88.1%)	0 = 5 (11.9%) 1 = 37 (88.1%)	0 = 24 (96.0%) 1 = 1 (4.0%)	0 = 24 (96.0%) 1 = 1 (4.0%)

Data are presented as n (%).

Supplemental Table A.3 – Cardiovascular biomarker variables added to the CLSA-FI

Variable	**Cut-off value for deficit**
Systolic blood pressure	0: 90-140 mmHg[a] 1: <90 or >140 mmHg
Diastolic blood pressure	0: 60-90 mmHg 1: <60 or >90 mmHg
Resting heart rate	0: 60-99 bpm[a] 1: <60 or >99 bpm
Total cholesterol	0: <=6.2 mmol/L[a] 1: >6.2 mmol/L
High-density lipoprotein cholesterol	0: >= 1.03 mmol/L 1: <1.03 mmol/L
Low-density lipoprotein cholesterol	0: 0.98 -3.36 mmol/L 1: <0.98 or >3.36 mmol/L
Triglycerides	0: <1.67 mmol/L 1: >=1.67 mmol/L
Creatinine - Women	0: 45-90 umol/L[a] 1: <45 or >90 umol/L
- Men	0: 60-110 umol/L 1:<60 or >110 umol/L

[a]Abbreviations**:** mmHg, millimoles of mercury; BPM, beats per minute; mmol/L, millimoles per litre; umol/L, micromoles per litre.

Supplemental Table A.4. Frailty changes by estimated marginal means with 95% CI for main and sensitivity analyses

Outcome	Cardiac Rehabilitation Model		P Value
	Center-based	Virtual	
Main Analysis: Adjusted CLSA-FI[a] scores - Admission - Follow-up - Change between models (F(116,1) = 0.477)	 0.146 (0.140-0.151) 0.140 (0.120-0.162)	 0.077 (0.071-0.084) 0.083 (0.059-0.107)	 *.001** *.001** .491
Sensitivity Analysis: Marginal estimates of FICVD[a] - Admission - Follow-up - Change between models (F(116,1) = 0.746)	 0.159 (0.154-0.164) 0.157 (0.138-0.177)	 0.084 (0.078-0.091) 0.100 (0.077-0.123)	 *.001** *.001** .491
Marginal estimates of listwise deletion - Admission - Follow-up - Change between models (F(51,1) = 11.873)	 0.148 (0.140-0.155) 0.132 (0.122-0.142)	 0.064 (0.053-0.075) 0.070 (0.056-0.084)	 *.001** *.001** *.001**

[a]Abbreviations: CLSA-FI, Canadian Longitudinal Study on Ageing Frailty Index; FICVD, frailty index including cardiovascular biomarkers. Data are presented as mean (95% CI). Computed using alpha = 0.05.

Supplemental Table A.5. Simple slope analyses of frailty change by admission frailty[b] * CR[a] program model interaction on frailty change

Simple Slope Analyses	**R-square**	**Beta 95% CI[a]**		**F-Statistic**	**P**
	Beta	Lower	Upper		**Value**
(Ref. is center-based CR[a])					
Main Analysis	0.389	-0.813	-0.176	*4.709* (118, 16)	*.002**
- FI = 0.05	3.615	0.587	6.644		*.018**
- FI = 0.10	1.140	-1.154	3.435		.322
- FI = 0.15	-1.334	-3.870	1.200		.294
- FI = 0.20	-3.810	-7.369	-0.251		*.034**
- FI = 0.25	-6.285	-11.181	-1.390		*.011**
FICVD[a] Sensitivity Analysis	0.226	-0.906	-0.099	*2.105* (115, 16)	*.014**
- FI = 0.05	2.662	-1.451	6.775		.198
- FI = 0.10	0.149	-2.681	2.980		.915
- FI = 0.15	-2.362	-5.055	0.329		.081
- FI = 0.20	-4.875	-8.699	-1.051		*.012**
- FI = 0.25	-7.388	-12.878	-1.898		*.008**
Listwise Deletion Sensitivity Analysis	0.339	-0.253	0.131	*1.603* (50, 15)	.528
- FI = 0.05	1.648	0.059	3.237		*.043**
- FI = 0.10	1.342	0.217	2.467		*.020**
- FI = 0.15	1.036	-0.328	2.401		.135
- FI = 0.20	0.730	-1.347	2.808		.485
- FI = 0.25	0.424	-2.513	3.361		.773

[a]Abbreviations: CR, cardiac rehabilitation; CI, confidence interval; FICVD, frailty index including cardiovascular biomarkers. [b]Frailty values were multiplied by 100 to increase interpretability of findings, corresponding beta-coefficients relate to 1-unit increases in frailty. Computed using alpha = 0.05. Model used center-based CR as the reference.

Supplemental Table A.6. Admission and follow-up mean differences in cardiovascular biomarkers by CR model

Cardiovascular Biomarker	**Time**	**Cardiac Rehabilitation Model**		**P Value**
		Center-Based	Virtual	
Triglycerides	Admission	1.76 ± 1.01	1.54 ± 0.76	.168
	Follow-up	1.30 ± 0.09	1.04 ± 0.09	.059
Total cholesterol	Admission	3.74 ± 1.07	3.43 ± 0.76	.062
	Follow-up	3.19 ± 0.11	2.89 ± 0.09	.051
HDL-cholesterol[a]	Admission	1.10 ± 0.28	1.13 ± 0.24	.579
	Follow-up	1.26 ± 0.04	1.43 ± 0.05	*.010**
LDL-cholesterol[a]	Admission	1.85 ± 0.84	1.59 ± 0.65	.053
	Follow-up	2.33 ± 0.12	2.69 ± 0.15	.073
Creatine kinase	Admission	110.15 ± 64.48	115.10 ± 75.66	.685
	Follow-up	217.82 ± 15.92	268.72 ± 22.53	.091
Creatinine	Admission	86.65 ± 35.41	77.28 ± 15.32	.062
	Follow-up	124.20 ± 15.95	176.33 ± 30.61	.111
C-Reactive protein	Admission	6.70 ± 16.57	4.03 ± 5.25	.240
	Follow-up	5.43 ± 2.34	7.64 ± 4.16	.628
Systolic blood pressure	Admission	122.72 ± 19.84	125.53 ± 15.02	.371
	Follow-up	122.15 ± 2.05	121.17 ± 2.56	.764
Diastolic blood pressure	Admission	72.19 ± 10.11	71.64 ± 9.05	.746
	Follow-up	69.55 ± 1.28	71.02 ± 1.50	.460
Resting pulse	Admission	66.89 ± 10.82	65.45 ± 10.73	.447
	Follow-up	65.42 ± 1.63	69.05 ± 2.24	.182

[a]Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein. Data are presented as mean ± SD. Computed at alpha = 0.05.

Supplemental Table A.7. Multivariable linear regression analysis of admission CLSA-FI[a,b] on change in cardiovascular biomarkers

Cardiovascular Biomarker	Beta	Beta 95% CI[a]		P Value
		Lower	Upper	
- Triglycerides	-0.009	-0.034	0.016	.476
- Total cholesterol	0.004	-0.023	0.032	.725
- High-density lipoprotein cholesterol	0.001	-0.008	0.011	.753
- Low-density lipoprotein cholesterol	-0.003	-0.035	0.028	.828
- Creatine kinase	1.806	-3.435	7.047	.492
- Creatinine	-2.572	-7.711	2.567	.318
- C-reactive protein	0.085	-0.636	0.807	.813
- Systolic blood pressure	-0.045	-0.558	0.468	.861
- Diastolic blood pressure	0.293	-0.003	0.591	.051
- Resting pulse	0.191	-0.336	0.719	.469

[a]Abbreviations: CLSA-FI, Canadian Longitudinal Study on Ageing Frailty Index; CI, confidence interval. [b]CLSA-FI values were multiplied by 100 to increase interpretability of findings, corresponding beta-coefficients relate to 1-unit increases in CLSA-FI. Computed using alpha = 0.05.

Supplemental Table A.8. Sensitivity analysis – linear regression of admission FICVD[a,b] on change in cardiovascular biomarkers

Cardiovascular Biomarker	Beta	Beta 95% CI[a]		P Value
		Lower	Upper	
- Triglycerides	-0.008	-0.036	0.019	.563
- Total cholesterol	0.005	-0.025	0.036	.739
- High-density lipoprotein cholesterol	0.003	-0.007	0.014	.506
- Low-density lipoprotein cholesterol	-0.004	-0.039	0.031	.814
- Creatine kinase	0.923	-4.983	6.829	.755
- Creatinine	-3.162	-8.926	2.600	.274
- C-reactive protein	0.332	-0.478	1.144	.414
- Systolic blood pressure	-0.069	-0.636	0.497	.805
- Diastolic blood pressure	0.336	0.008	0.664	*.042**
- Resting pulse	0.177	-0.412	0.766	.549

[a]Abbreviation: FICVD, frailty index including cardiovascular biomarkers; CI, confidence interval.
[b]FICVD values were multiplied by 100 to increase interpretability of findings, corresponding beta-coefficients relate to 1-unit increases in FICVD. Computed using alpha = 0.05

Supplemental Table A.9. Simple slope sensitivity analyses of cardiovascular biomarker change by admission FICVD[a,b] * CR[a] program model interaction

Cardiovascular Biomarker	**R Square** - Beta	**Beta 95% CI[a]**		**F-Statistic**	**P Value**
		Lower	Upper		
Simple Slope Analysis (Ref. is center-based CR[a])					
Triglycerides	0.134	-0.111	-0.003	*1.198* (115, 16)	*.035**
- FI = 0.05	0.312	-0.226	0.851		.248
- FI = 0.10	0.024	-0.348	0.397		.895
- FI = 0.15	-0.263	-0.630	0.103		.153
- FI = 0.20	-0.551	-1.077	-0.024		*.038**
- FI = 0.25	-0.839	-1.592	-0.086		*.027**
Total cholesterol	0.233	-0.116	-0.000	*2.349* (115, 16)	*.048**
- FI = 0.05	0.384	-0.218	0.988		.204
- FI = 0.10	0.094	-0.320	0.509		.648
- FI = 0.15	-0.195	-0.582	0.191		.314
- FI = 0.20	-0.485	-1.030	0.059		.077
- FI = 0.25	-0.775	-1.559	0.007		.050
HDL-cholesterol[a]	0.393	-0.013	0.029	*5.024* (115, 16)	.462
- FI = 0.05	-0.158	-0.372	0.054		.140
- FI = 0.10	-0.118	-0.267	0.029		.112
- FI = 0.15	-0.078	-0.227	0.069		.290
- FI = 0.20	-0.038	-0.251	0.174		.716
- FI = 0.25	0.001	-0.302	0.304		.994
LDL-cholesterol[a]	0.178	-0.059	0.073	*1.678* (115, 16)	.827
- FI = 0.05	-0.390	-1.072	0.291		.253
- FI = 0.10	-0.354	-0.829	0.120		.138
- FI = 0.15	-0.317	-0.774	0.138		.166
- FI = 0.20	-0.281	-0.924	0.361		.383
- FI = 0.25	-0.244	-1.162	0.672		.594
Creatine kinase	0.127	-18.865	3.319	*1.128* (115, 16)	.164
- FI = 0.05	30.044	-82.273	142.361		.593
- FI = 0.10	-8.821	-86.228	68.585		.820
- FI = 0.15	-47.687	-121.988	26.614		.201
- FI = 0.20	-86.552	-192.390	19.284		.104
- FI = 0.25	-125.418	-277.189	26.352		.101

Cardiovascular Biomarker	**R Square** - Beta	**Beta 95% CI[a]**		**F-Statistic**	**P Value**
		Lower	Upper		
Creatinine	0.058	-13.907	7.788	*0.483* (115, 16)	.574
- FI = 0.05	35.914	-74.097	145.926		.515
- FI = 0.10	20.617	-55.741	96.975		.590
- FI = 0.15	5.319	-68.450	79.089		.885
- FI = 0.20	-9.978	-114.558	94.601		.848
- FI = 0.25	-25.276	-174.659	124.106		.735
C-reactive protein	0.260	-1.135	1.948	*2.717* (115, 16)	.599
- FI = 0.05	-6.269	-21.973	9.433		.426
- FI = 0.10	-4.237	-15.067	6.593		.435
- FI = 0.15	-2.205	-12.543	8.133		.670
- FI = 0.20	-0.172	-14.847	14.502		.981
- FI = 0.25	1.859	-19.180	22.900		.859
Systolic blood pressure	0.186	-0.769	1.390	*1.767* (115, 16)	.566
- FI = 0.05	-7.037	-17.840	3.765		.195
- FI = 0.10	-5.485	-12.984	2.012		.146
- FI = 0.15	-3.933	-11.287	3.419		.286
- FI = 0.20	-2.381	-12.881	8.118		.650
- FI = 0.25	-0.829	-15.821	14.161		.912
Diastolic blood pressure	0.222	-0.924	0.339	*2.214* (115, 16)	.357
- FI = 0.05	3.070	-3.455	9.596		.348
- FI = 0.10	1.609	-2.888	6.106		.475
- FI = 0.15	0.147	-4.078	4.373		.944
- FI = 0.20	-1.314	-7.271	4.642		.659
- FI = 0.25	-2.775	-11.325	5.774		.517
Resting pulse	0.150	-1.826	0.431	*1.367* (115, 16)	.219
- FI = 0.05	0.892	-10.608	12.393		.876
- FI = 0.10	-2.594	-10.581	5.392		.517
- FI = 0.15	-6.082	-13.766	1.601		.116
- FI = 0.20	-9.569	-20.434	1.294		.080
- FI = 0.25	-13.057	-28.573	2.459		.095

[a]Abbreviations: CR, cardiac rehabilitation; FICVD, frailty index including cardiovascular biomarkers; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein. [b]FICVD values were multiplied by 100 to increase interpretability of findings, corresponding beta-coefficients relate to 1-unit increases in FICVD. Computed using alpha = 0.05

Supplemental Table A.10. Listwise deletion sensitivity analysis - linear regression of admission CLSA-FI[a,b] on change in cardiovascular biomarkers

Cardiovascular Biomarker	**Beta**	**Beta 95% CI[a]**		**P Value**
		Lower	Upper	
- Triglycerides	-0.012	-0.042	0.018	.429
- Total cholesterol	0.008	-0.025	0.042	.614
- High-density lipoprotein cholesterol	0.008	-0.007	0.024	.306
- Low-density lipoprotein cholesterol	0.051	0.004	0.098	*.033**
- Creatine kinase	3.678	-2.807	10.164	.266
- Creatinine	3.027	-3.811	9.867	.261
- C-reactive protein	-0.306	-1.281	0.668	.532
- Systolic blood pressure	-0.053	-0.763	0.655	.879
- Diastolic blood pressure	0.018	-0.462	0.499	.939
- Resting pulse	0.048	-0.580	0.677	.878

[a]Abbreviations: CLSA-FI, Canadian Longitudinal Study on Ageing Frailty Index; CI, confidence interval. [b]CLSA-FI values were multiplied by 100 to increase interpretability of findings, corresponding beta-coefficients relate to 1-unit increases in CLSA-FI. Computed using alpha = 0.05.

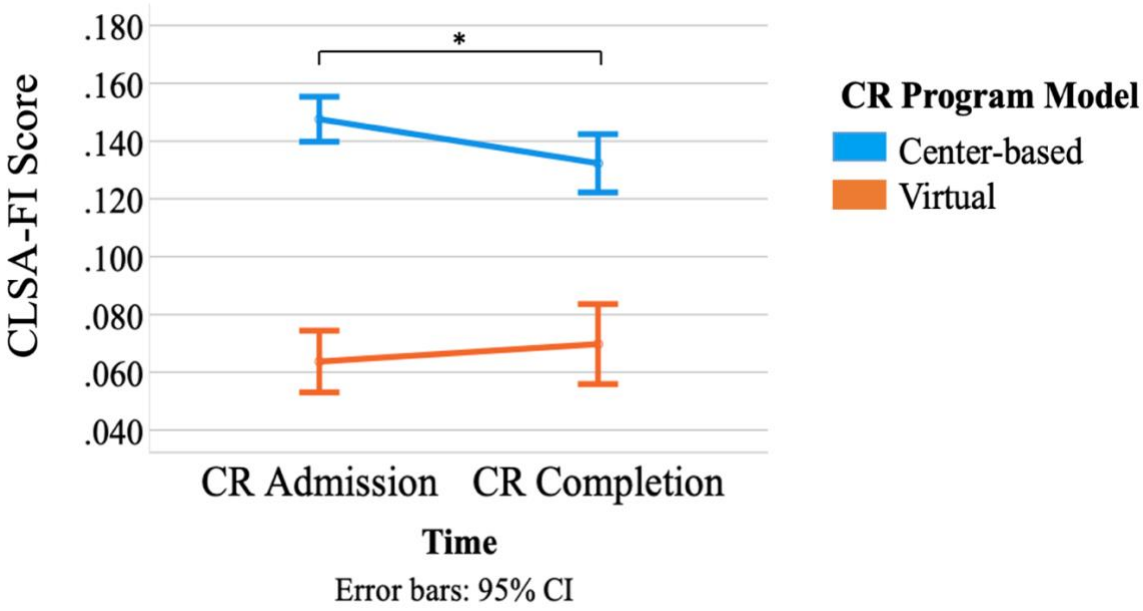
Supplemental Table A.11. Listwise deletion simple slope sensitivity analyses of frailty change by admission CLSA-FI[a,b] * CR[a] program model interaction

Cardiovascular Biomarker	R Square - Beta	Beta 95% CI[a]		F-Statistic	P Value
		Lower	Upper		
Simple Slope Analysis (Ref. is center-based CR)					
Triglycerides	0.608	-0.090	0.046	*5.280* (51, 15)	.531
- FI = 0.05	-0.075	-0.643	0.493		.792
- FI = 0.10	-0.183	-0.585	0.219		.367
- FI = 0.15	-0.291	-0.776	0.194		.236
- FI = 0.20	-0.398	-1.137	0.339		.284
- FI = 0.25	-0.506	-1.550	0.536		.335
Total cholesterol	0.569	-0.120	0.029	*4.495* (51, 15)	.229
- FI = 0.05	0.063	-0.562	0.690		.838
- FI = 0.10	-0.163	-0.608	0.282		.466
- FI = 0.15	-0.390	-0.923	0.142		.148
- FI = 0.20	-0.617	-1.422	0.187		.130
- FI = 0.25	-0.845	-1.981	0.291		.143
HDL-cholesterol[a]	0.338	0.001	0.069	*1.742* (51, 15)	*.040**
- FI = 0.05	0.008	-0.276	0.292		.954
- FI = 0.10	0.187	-0.014	0.388		.069
- FI = 0.15	0.366	0.124	0.607		*.003**
- FI = 0.20	0.545	0.179	0.910		*.004**
- FI = 0.25	0.724	0.208	1.240		*.007**
LDL-cholesterol[a]	0.475	0.031	0.226	*3.077* (51, 15)	*.011**
- FI = 0.05	-0.087	-0.907	0.733		.832
- FI = 0.10	0.557	-0.022	1.136		.060
- FI = 0.15	1.201	0.512	1.890		*.001**
- FI = 0.20	1.845	0.801	2.889		*<.001**
- FI = 0.25	2.489	1.012	3.967		*.001**
Creatine kinase	0.428	2.633	30.136	*2.545* (51, 15)	*.020**
- FI = 0.05	-20.311	-133.550	92.927		.721
- FI = 0.10	61.612	-17.591	140.816		.125
- FI = 0.15	143.536	47.732	239.340		*.004**
- FI = 0.20	225.460	78.700	372.220		*.003**
- FI = 0.25	307.384	99.169	515.598		*.004**

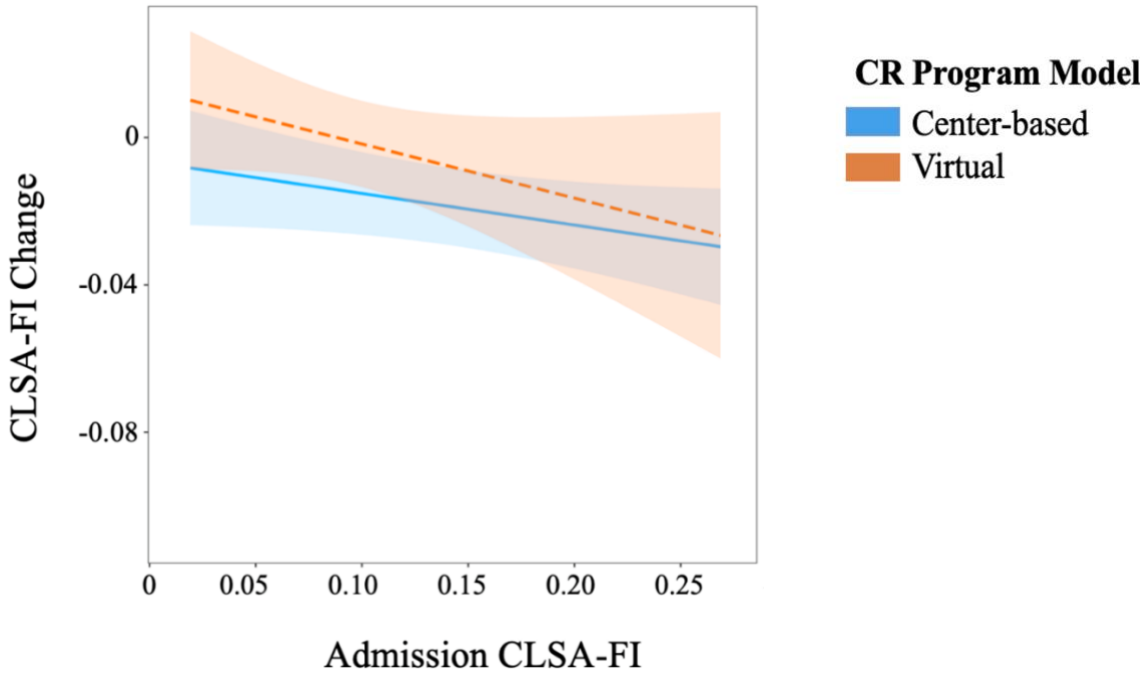
Cardiovascular Biomarker	R Square - Beta	Beta 95% CI[a]		F-Statistic	P Value
		Lower	Upper		
Creatinine	0.138	-6.794	23.793	*0.445* (51, 15)	.272
- FI = 0.05	-19.892	-145.771	105.986		.753
- FI = 0.10	22.606	-66.331	111.543		.613
- FI = 0.15	65.104	-42.923	173.132		.233
- FI = 0.20	107.602	-57.096	272.301		.197
- FI = 0.25	150.100	-82.873	383.075		.203
C-reactive protein	0.165	-3.181	1.181	*0.676* (51, 15)	.364
- FI = 0.05	12.470	-5.593	30.534		.173
- FI = 0.10	7.469	-5.365	20.304		.249
- FI = 0.15	2.468	-13.061	17.998		.751
- FI = 0.20	-2.532	-26.104	21.039		.830
- FI = 0.25	-7.533	-40.821	25.754		.652
Systolic blood pressure	0.412	-1.962	1.269	*2.384* (51, 15)	.669
- FI = 0.05	-9.590	-23.091	3.909		.161
- FI = 0.10	-11.323	-20.856	-1.789		*.021**
- FI = 0.15	-13.055	-24.462	-1.648		*.026**
- FI = 0.20	-14.787	-32.106	2.530		.093
- FI = 0.25	-16.520	-41.022	7.530		.183
Diastolic blood pressure	0.473	0.358	2.339	*3.063* (51, 15)	*.008**
- FI = 0.05	-4.706	-13.095	3.682		.267
- FI = 0.10	2.039	-3.927	8.006		.497
- FI = 0.15	8.785	1.720	15.850		*.016**
- FI = 0.20	15.531	4.886	26.176		*.005**
- FI = 0.25	22.277	7.250	37.303		*.004**
Resting pulse	0.201	-2.421	0.562	*0.867* (51, 15)	.218
- FI = 0.05	7.300	-5.066	19.668		.243
- FI = 0.10	2.654	-6.076	11.384		.545
- FI = 0.15	-1.992	-12.516	8.531		.706
- FI = 0.20	-6.638	-22.655	9.378		.411
- FI = 0.25	-11.284	-33.947	11.377		.323

[a]Abbreviations: CLSA-FI, Canadian Longitudinal Study on Ageing Frailty Index; CR, cardiac rehabilitation; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[b]CLSA-FI values were multiplied by 100 to increase interpretability of findings, corresponding beta-coefficients relate to 1-unit increases in CLSA-FI. Computed using alpha = 0.05.

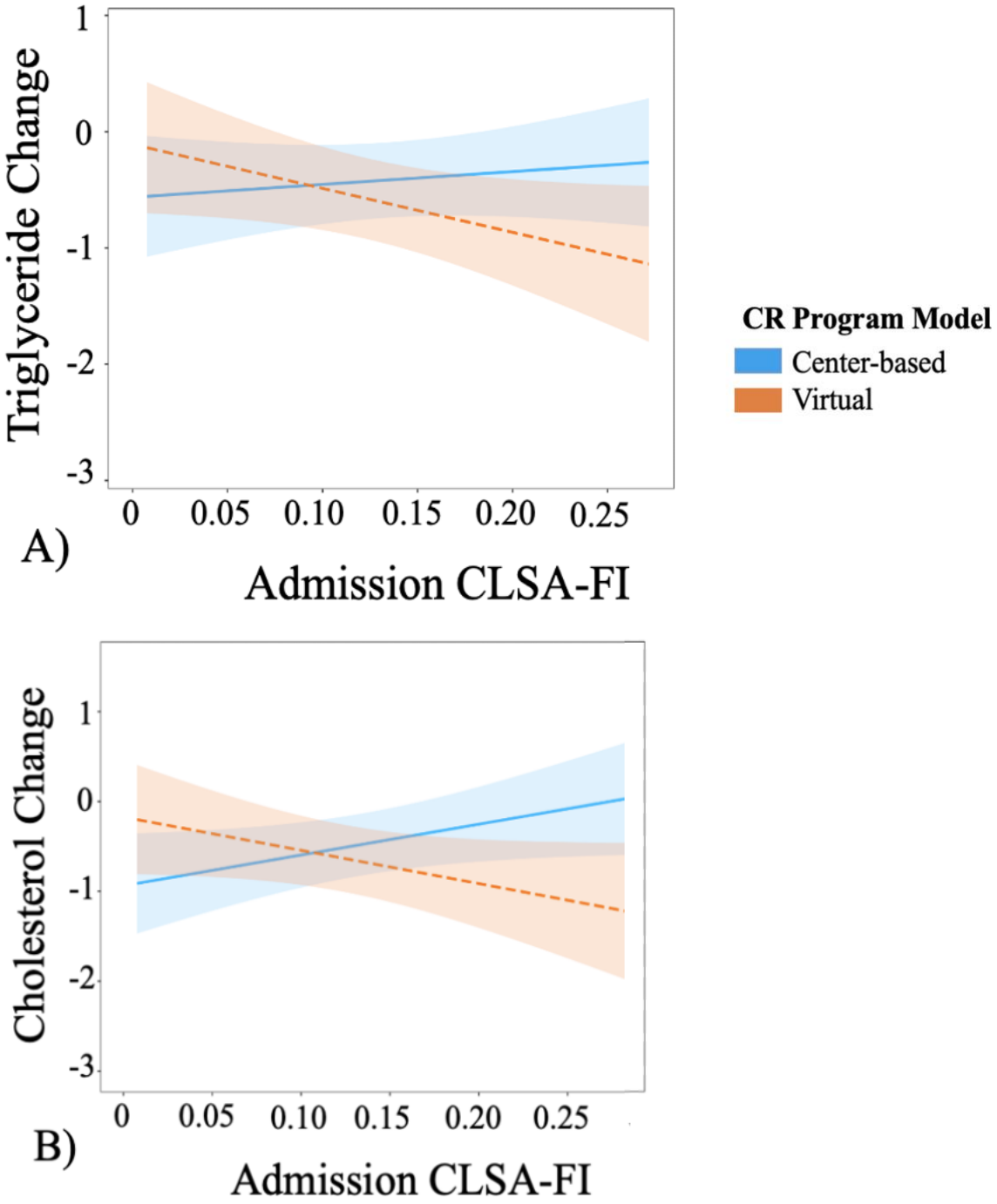
4.7. Supplemental Figures Package



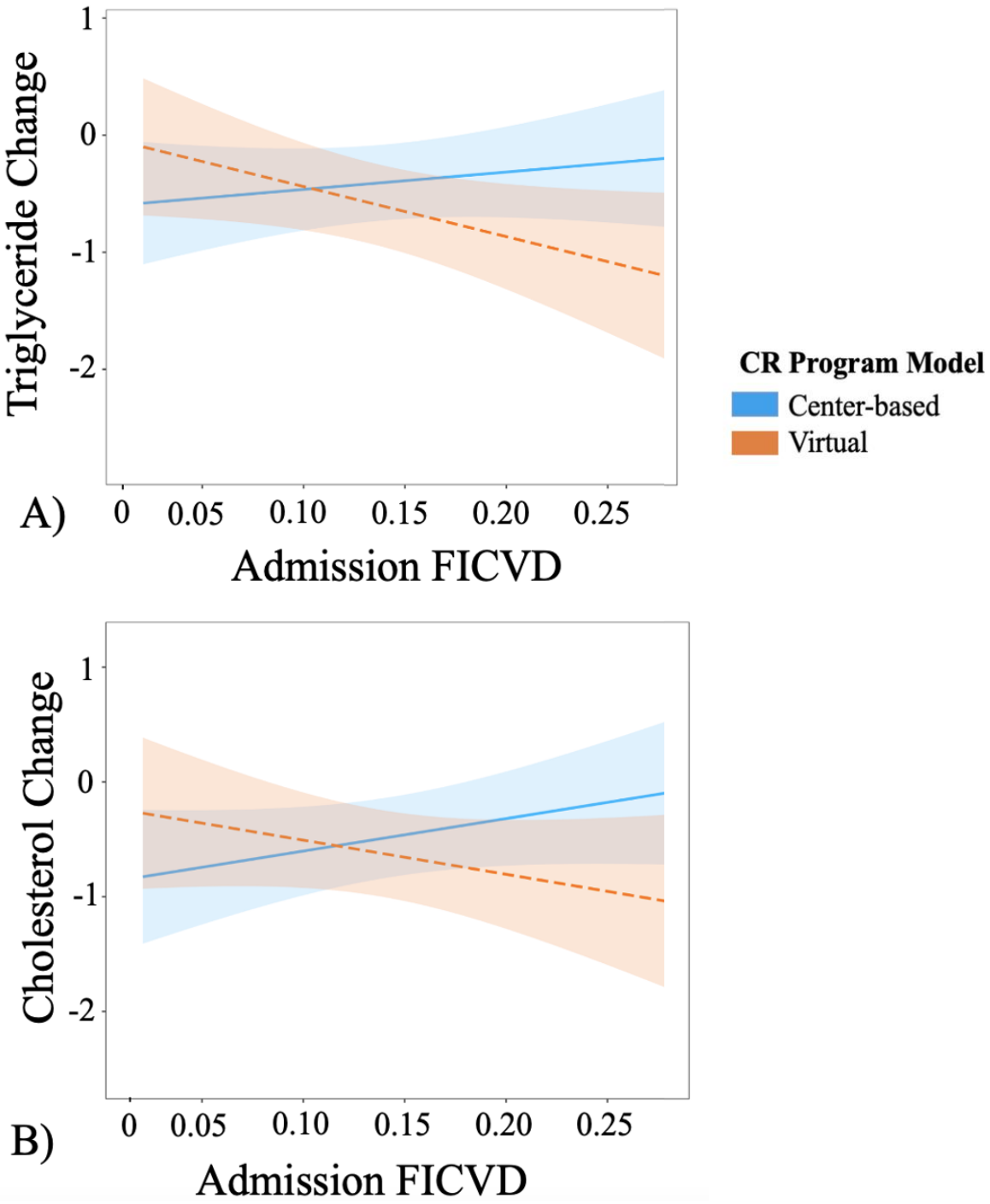
Supplemental Figure 1. Estimated marginal means of our listwise deletion sensitivity analysis on CLSA-FI scores at admission and follow-up (*p <.05).



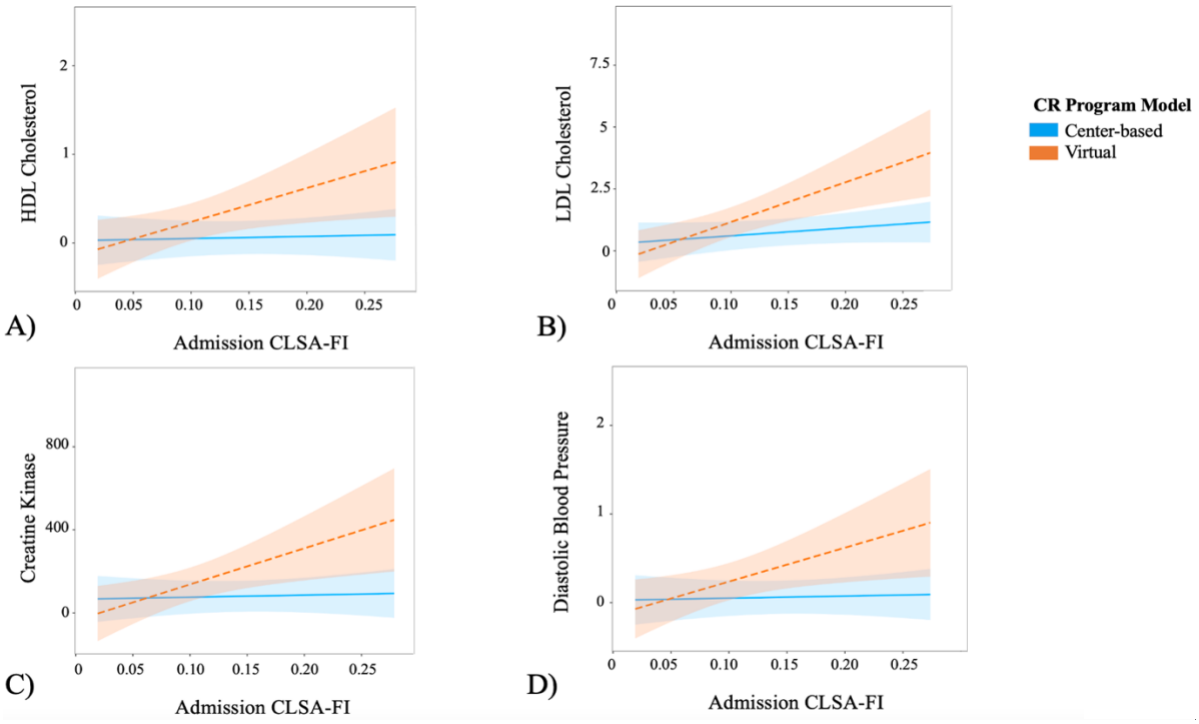
Supplemental Figure 2. Simple slope of listwise deletion sensitivity analysis predicting frailty change by admission frailty, stratified by CR model.



Supplemental Figure 3. Simple slopes of main analysis predicting: **A)** Triglyceride change by admission frailty, stratified by CR model**, B)** Cholesterol change by admission frailty, stratified by CR model.



Supplemental Figure 4. Simple slopes of sensitivity analysis predicting: **A)** Triglyceride change by admission FICVD score, stratified by CR model, **B)** Cholesterol change by admission FICVD score, stratified by CR model.



Supplemental Figure 5. Simple slopes of listwise deletion sensitivity analysis predicting **A)** HDL cholesterol change by admission frailty, stratified by CR model, **B)** LDL cholesterol change by admission frailty, stratified by CR model, **C)** Creatine kinase change by admission frailty, stratified by CR model, **D)** Diastolic blood pressure change by admission frailty, stratified by CR model.

CHAPTER 5. Discussion

Frailty [119] and CVD [3, 10] are two health concerns which disproportionately impact the lives of older adults. Paired with an aging Canadian population [28], implications concerning the burden of frailty and incidence of CVD can be expected to escalate in the forthcoming years. Importantly, the associated physiological processes [120, 128] of frailty and CVD elevate the risk for rapid health deficit accumulation, resulting in greater vulnerability to failing health [12], morbidity [13, 14], and mortality [15]. Accordingly, there appears to be a bi-directional association between the two, such that the prevalence of CVD may increase the expression of frailty, and vice-versa [10, 11]. Hence, there is growing interest among researchers who seek to better understand the coexistence of these two health concerns [4, 6, 17, 34, 62, 63, 65, 128]. Here, we contribute to the existing literature on CVD and frailty a thorough evaluation comparing virtual and center-based CR on changes in frailty and cardiovascular biomarkers. Our study separates itself from the literature as a first of its kind study to (1) examine change in frailty levels among virtual CR participants; (2) compare virtual-based CR with center-based CR on changes in frailty; and (3) compare virtual-based CR with center-based CR on admission frailty in relation to cardiovascular biomarker changes. Our study was intended to understand CR practices as were routinely implemented during the COVID-19 pandemic, thus from this perspective, strengthens the generalizability of our findings to the public.

We identified four key findings from our study. First, CVD patients who attended the virtual CR model were significantly less frail than patients who attended center-based CR. Second, our main analysis found no significant mean differences between virtual and center-based CR programs on changes in frailty level from CR admission to completion.

Thirdly, however, the magnitude of frailty change was significantly influenced by frailty level at CR admission in CVD patients attending virtual CR versus center-based CR. Fourth, we found frailty levels at CR admission were associated with change in some, but not all cardiovascular biomarkers over the course of virtual CR only. Therefore, we demonstrate virtual CR as an alternative for instances when center-based CR is inaccessible, bridging the gap for eligible low-to-moderate risk patients to receive CR services and improve their health.

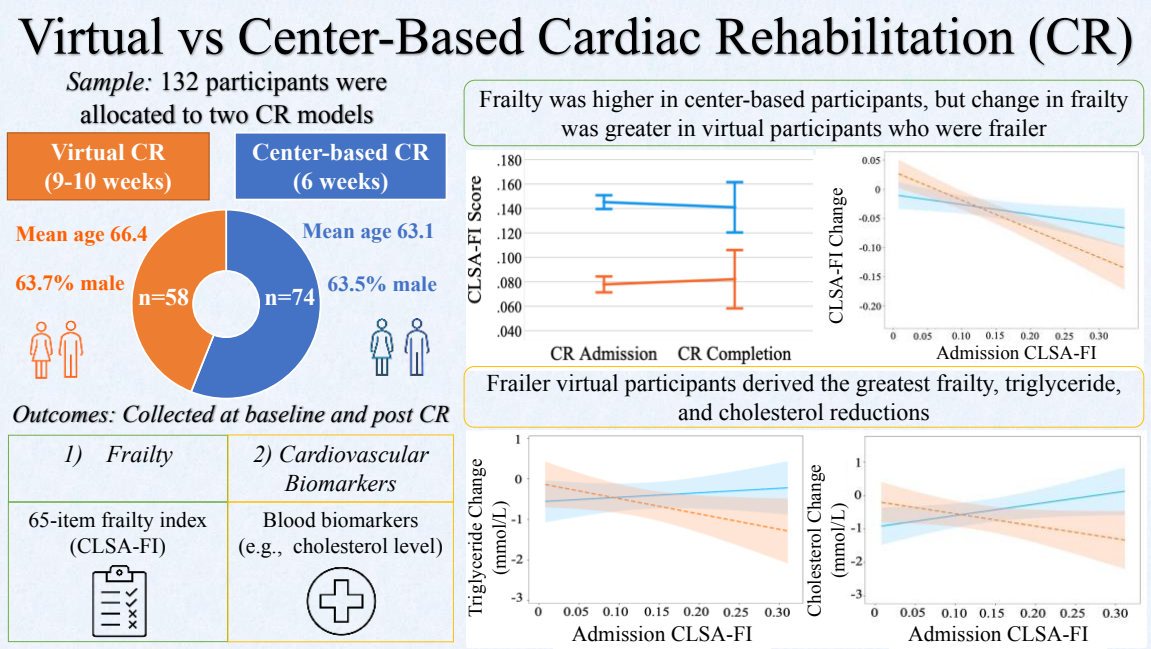


Figure 6. Central infographic of our study's sample, outcome measures, and results.

Our first key finding observed differences in frailty levels based on CR program allocation. Here, we observed participants who were allocated to center-based CR had significantly higher mean CLSA-FI and FICVD scores at CR admission, as compared to participants who were allocated to virtual CR (Figure 4, Supplementary Table A.4). However, these results were expected, as we anticipated virtual CR participants would have lower levels of admission frailty due to our study's risk-stratification process regarding CR

participants' program allocation. Our study's risk-stratification process was conducted exclusively by CR staff. To a lesser extent, CR participants' preference of CR model (i.e., request to enrol in either virtual or center-based CR) was considered by CR staff when deciding CR program allocation. Here, CR staff preferentially allocated participants who were deemed "low-to-moderate risk" (e.g., they experienced fewer orthopaedic limitations, were able to exercise unsupervised in a safe manner, and had fewer severe health concerns such low ejection fraction) to the virtual CR program. It was also conditional for virtual CR participants to have regular access to the internet. On the contrary, our study's center-based CR program accommodated all levels of patient "risk", meaning there were no criteria which made participants eligible to attend the center-based model. Here, we acknowledge that social determinants of health (e.g., income, education, occupation) may have introduced selection biases concerning our sample's CR allocation. The requirement for virtual CR participants to have regular internet access may have created different categories of socioeconomic status, education, or employment level between CR programs, therefore influencing our findings. These differences in program characteristics should be considered when interpreting our results; however, our observation that virtual CR participants were significantly less frail at CR admission aligns with previously published work recognising virtual-based health interventions as safe for lower risk participants [23, 24, 129].

Although participant safety remains a priority for unsupervised virtual CR programs [123, 129] and experiencing a subsequent cardiovascular event in CR is rare [130], the risk-stratification process may have been more challenging for virtual CR programs [23]. For example, during the COVID-19 pandemic there were virtual CR

participants from our study who did not complete a graded exercise stress test or laboratory blood work (i.e., cardiovascular biomarker data) at CR admission. Reasons contributing to the absence of routinely collected admission information were related to temporary suspension of all Nova Scotia Health laboratory testing not necessarily related to COVID-19 (i.e., laboratory blood work requestions were not completed) as well as patient hesitancy to attend "non-compulsory" hospital or outpatient clinic appointments (i.e., graded exercise stress test). We speculate the latter was in part due to the recommended social distancing guidelines put forth by Nova Scotian public health authorities (i.e., "stay the blazes home") and a general concern of contracting COVID-19 among a vulnerable demographic. As such, our study's Hearts and Health in Motion CR staff required an adaptive risk-stratification process while the novel virtual program was introduced. For instance, the level of missing patient information at CR admission (i.e., admission blood work and exercise stress test results) required staff at the Hearts and Health in Motion program to depend on enrolling participants' current levels of orthopaedic limitation and mobility, medical history, and clinical judgement when deciding upon CR program allocation. Additionally, the unsupervised design of virtual CR contrasts with the supervised nature of traditional center-based care, whereby "higher-risk" participants would have received continuous monitoring and immediate access to CR staff during exercise sessions, and would alleviate the level of scrutiny required in risk-stratification for center-based participants. For these reasons, it is understandable why our sample's virtual participants were less frail than the center-based counterparts, as well as why the allocation of low-to-moderate risk participants to virtual care may be essential to ensure the safety of its participants, especially when confronted with the challenges associated with the COVID-

19 pandemic. Nevertheless, we observed virtual CR participants with moderate levels of frailty (FI>0.25) at CR admission, indicating further examination on virtual CR to accommodate "high-risk" participants is warranted [129].

Our second key observation was that, despite observing higher frailty levels among center-based participants, our main and sensitivity analyses found mean differences in frailty, as measured by CLSA-FI and FICVD, were not significantly changed from admission to completion of CR in both program models (Figure 4, Supplemental Table A.4). These findings generally align with our first hypothesis that virtual CR would be associated with similar changes in frailty compared to center-based CR, demonstrating non-inferiority. However, our first hypothesis was based on the expectation that both models of CR would result in a lower frailty level, or at least in center-based participants, based on previous literature [17, 22, 94, 102]. Conversely, results from our listwise deletion sensitivity analysis indicated a significant difference between CR models on change in frailty, such that center-based CR participants observed a small significant decrease in frailty scores (mean difference = 0.016), while virtual CR participants observed a small non-significant increase in frailty scores (mean difference = 0.006) from admission to completion of CR (Supplemental Figure 1, Supplemental Table A.4). Although, these changes were not clinically meaningful based on previous literature evaluating clinically meaningful changes in frailty [117, 118]. According to previously published work, the threshold for a small, clinically meaningful change in frailty using an FI is ≥0.03 [117, 118]. For instance, when using an FI with 65-items, such as the CLSA-FI used in our study, a minimum improvement of 2/65 items would be required to reach the threshold for a small, clinically meaningful change of ≥0.03.

Previous literature suggests relative percent improvements in frailty are smaller for CR participants who are less frail at admission, compared to more severely frail participants [17, 22]. In our study, participants' ability to modify frailty scores in CR would be more difficult, as most of our sample had FI scores of <0.20 at admission (Center-based CR: 90.4%; Virtual CR: 91.3%, Table 4.1). As well, recent literature demonstrates that center-based CR is associated with improvements in frailty, however, each of these CR programs operated for a minimum duration of 12-weeks (range 12-24 weeks) [17, 22, 94, 102]. During our study, COVID-19 restrictions enforced capacity limits for center-based CR, reducing the normal program size of 25 down to 9-12 participants per program. By extension, COVID-19 restrictions required CR program durations to be shortened (i.e., Center-based = 6-weeks; Virtual = 9-10-weeks) from their usual duration of 12-weeks to help address the high volume of eligible CR patients who remained on a wait list. Therefore, it is possible that the brevity and limited volume of CR received by our study participants was insufficient to obtain a similar resolution in frailty as observed in previous studies.

Third, although our main analysis did not identify differences in frailty change between center-based and virtual CR participants (Figure 4, Supplementary Table A.4), our simple slope analyses revealed an influence of admission frailty, as measured by CLSA-FI and FICVD, on frailty change in CR (Figure 5, Supplementary Table A.5). Here, we found patients with higher levels of frailty at CR admission observed a greater magnitude of change in frailty, which is supported by previous literature [17, 22]. Importantly, we found virtual CR participants who were at least mildly frail at CR admission (i.e., FI ≥0.20) improved to a greater extent than center-based counterparts.

From our main analysis, CLSA-FI improvements ranged from -3.810 (-7.369, -0.251) to -6.285 (-11.181, -1.390) for virtual CR participants with admission CLSA-FI scores of 0.20 and 0.25, respectively (Supplemental Table A.5). Sensitivity analysis evaluating FICVD change by simple slopes demonstrated results that were consistent with our main analysis. Here, FICVD improvements ranged from -4.875 (-8.699, -1.051) to -7.388 (-12.878, -1.898) for virtual CR participants with admission FICVD scores of 0.20 and 0.25, respectively (Figure 5, Supplemental Table A.5). These findings were not observed in our listwise deletion sensitivity analysis ($F(50,16)=1.603$, $p=0.528$; Supplemental Figure 2, Supplemental Table A.5).

Previously published work examining the association between frailty and CR signified an improved FI score of 0.09-0.15 was considered a moderate improvement, while an improvement >0.15 was considered large [17]. In our study, we observed that the virtual CR group were more likely to obtain moderate (-0.11 at a FI of 0.20-0.29) and large improvements (-0.19 at a FI of ≥0.30) in our main analysis. Although these differences in frailty change were not observed at lower levels of admission frailty, we can conclude that CVD patients who were frailer at CR admission can improve their level of frailty, which aligns with previously published work [17, 22]. Here, we contribute to the previous literature by demonstrating that participants with higher CLSA-FI and FICVD scores at CR admission improved their frailty to a greater extent in virtual versus center-based CR (Figure 5, Supplemental Table A.5). However, our results may need to be taken with caution, as our sample had a limited number of participants with high levels of frailty (FI >0.20, n = 12; FI >0.30, n = 3) at admission to CR (Table 4.1).

Finally, apart from a significant increase in HDL cholesterol (i.e., "good" cholesterol) detected in virtual CR participants, we identified cardiovascular biomarkers were unchanged irrespective of CR model (Supplemental Table A.6). Moreover, follow-up analyses revealed that admission CLSA-FI scores were not associated with changes in any cardiovascular health outcomes (Supplemental Table A.7), and admission FICVD was only associated with increases in diastolic blood pressure (Supplemental Table A.8). Our pre-planned simple slope analyses using the CLSA-FI and FICVD showed an interaction between admission frailty score and CR program type on changes in cardiovascular biomarkers. Our main analysis found virtual CR participants with higher CLSA-FI scores at CR admission saw a greater reduction in triglycerides and total cholesterol over the course of CR as compared to center-based CR (Table 4.2, Supplemental Figure 3). As well, our simple slope sensitivity analysis using the FICVD demonstrated consistent findings with our main analyses, such that frailer virtual CR participants reduced their triglycerides to a greater extent than center-based participants (Supplemental Table A.9, Supplemental Figure 4). However, these changes were not observed at lower levels of admission frailty in both the CLSA-FI and FICVD (Table 4.2, Supplemental Table A.9), which partially supports our second hypothesis that frailer CR participants would be associated with greater improvements in cardiovascular biomarkers.

Our results are supported by previously published work favoring virtual over center-based CR on changes in HDL cholesterol [124], triglycerides [124, 125], and total cholesterol [126]. However, we are cautious in our interpretation of the findings, as our virtual CR programs were longer in duration (i.e., Virtual CR: 9-10 weeks; Center-based CR: 6-weeks) which provided up to an additional 4 weeks for virtual participants' acute

CVD event to resolve. Furthermore, based on the clinical judgement of CR staff, virtual participants were deemed "lower risk" than the center-based participants, introducing potential biases in our observations – this risk assessment process was expected prior to initiating the study. While previous publications suggest frailty assessments can predict outcomes in CR, such as incident hospitalization and mortality [15, 22, 66] or CR completion [17, 20], we observed admission frailty, as measured by the CLSA-FI or FICVD, was not consistently associated with changes in all cardiovascular biomarkers (Supplemental Table A.7, Supplemental Table A.8, respectively), and may require a longer duration for changes to come to fruition. Therefore, we caution the use of the CLSA-FI or FICVD in routine clinical practice in CR until more research is done.

5.1. Limitations

There are several limitations to our study. First was the reduced and inconsistent duration of the center-based and virtual CR models. Traditionally at Hearts and Health in Motion, center-based CR programs are offered for a duration of 12-weeks. However, during the COVID-19 pandemic, challenges such as capacity limits, public health restrictions, and growing wait list numbers required center-based programs to reduce to a duration of 6-weeks, which does not align with the North American gold standard of CR programming (12-weeks) [16]. Furthermore, the novel virtual CR program was offered for durations of 9 and 10-weeks, depending on the enrollment period (i.e., fall of 2021, winter of 2022, respectively). Despite a lack of standardization regarding the duration of virtual CR programs [129], these programs still remained under the 12-week North American gold standard for CR programs [16]. Therefore, not only were program durations different between CR models, but for virtual CR, within program differences were also a limitation.

Although these concerns were forewarned, uncontrollable, and necessary due to evolving COVID-19 public health guidelines, the differences in CR model durations should be viewed as a limitation to the reliability of our findings.

Our second limitation considers the structure and reproducibility differences between the virtual and center-based CR models. Center-based CR followed a set duration, type, frequency, and intensity of exercise, which was supervised, monitored, and reproducible across different cohorts of center-based participants. This contrasts with the virtual model, which, due to individualized exercise prescription, lacked consistency among different program classes, enrollment periods, and individuals participating in virtual CR. Although individualized exercise prescription in virtual CR targeted 150-minutes of moderate-vigorous exercise per week, at a Borg scale intensity equal to 11-13, we cannot state that exercise prescriptions were upheld by all virtual CR participants. Furthermore, depending on virtual participants' date of enrollment, virtual participant programs would have differed based on CR closures, staff redeployment, and program interruptions due to COVID-19. These issues were not apparent in the center-based program, as center-based CR was only offered in the fall of 2021 (i.e., August 2021 and November 2021 enrollment periods), when none of these circumstances occurred. In 2020, Moulson and colleagues [23] anticipated CR program interruptions across the country, which did not exempt the Hearts and Health in Motion programs. Therefore, the lack of consistency, as a result of shaping the program to address the needs of patients while appreciating program interruptions among different virtual CR programs should be viewed as a limitation of design.

Third, although studying the extent to which CR was implemented in routine care may strengthen the generalizability of our findings, the amount of missing patient data needs to be considered. The observed level of missing information was certainly exacerbated by COVID-19, which presented unanticipated circumstances to data collection. Accordingly, our analysis used multiple imputation to generate 28.4% missing variable values. However, this level of missingness is appropriate within multiple imputation guidelines [127]. Furthermore, interpreting our listwise deletion sensitivity analysis as opposed to our main analysis is not recommended. Applying listwise deletion to missing information does not satisfy a pattern of randomization, introducing inevitable selection biases which may confound results [131]. Therefore, our main analysis used multiple imputation to account for missing information. King and colleagues argue that multiple imputation is normally better, and almost never worse than listwise deletion methods when conducting research on datasets with missing values [132]. We believe multiple imputation provides a more robust technique of dealing with missing information than does listwise deletion, as missing values are generated by predictive mean matching valid responses found within the sample. Furthermore, we strengthened our justification of the multiple imputation method by determining that our data were missing completely at random, which is a rule for using multiple imputation techniques.

Fourth, not every CLSA-FI item was sensitive to change over time, meaning certain items could not be reversed. Thirty-five out of 65-items were reversible; for example, having difficulty in activities of daily living. Contrarily, 30 out of 65 variables could only be accumulated over time, such as chronic diseases like osteoarthritis. Therefore, the proportion of CLSA-FI items which could not be improved upon (i.e., 47%) may have

contributed to the lack of frailty change observed from our study, as only 53% of the CLSA-FI variables were sensitive to being accumulated and being reversible over the brief CR duration. Furthermore, the CLSA-FI does not provide a robust assessment of functional mobility and how mobility performance changes over time. Previously validated methods for assessing frailty, such as the Frailty Phenotype, have demonstrated changes in mobility (e.g., gait speed) are associated with changes in frailty. Therefore, we suggest that frailty assessments used as part of CR interventions should include a performance-based measure of mobility to assist in detecting changes in frailty among CR participants. Performance-based measures of mobility can be incorporated into routine frailty assessments, such as an FI, by using pre-existing assessments in CR (e.g., graded exercise stress test) or by introducing previously validated tools, such as a 6-minute-walk-test, to assist with detecting change in frailty over time. Finally, our study did not involve an extensive follow up period and was implemented over a very short term (August-2021 to April 2022). These concerns manifested as challenges to our study's data collection and sample size.

5.2. Implications for Future Research

Traditionally, CR programs will use a combination of clinical 'gestalt' and participant preferences when deciding upon virtual or center-based CR program allocation. We believe implementing routine frailty assessment in CR can strengthen the detection of a response to CR programs from enrolling participants. As such, we recommend future studies to compare clinical decision making with admission FI results to predict which CR model is best suiting for enrolling participants, specifically for improving patient outcomes and frailty levels among CR participants. As well, there is a knowledge gap concerning the association of frailty and virtual CR specifically related to comparing changes in frailty

between virtual and traditional center-based CR. Therefore, to further the body of knowledge contrasting frailty in virtual and center-based CR, future research should continue to examine the interaction among frailty, virtual CR, and center-based CR in different settings using different methods to confirm our study's findings. We recommend future studies to use a larger sample of virtual and center-based CR participants, evaluate the sensitivity of frailty change with different assessment tools, use longer follow-up assessment periods, and use randomized controlled trial study designs across varying CVD burden.

5.3. Conclusion

We provide an extensive evaluation of center-based and virtual CR on changes in frailty from CR admission to completion. We demonstrate that virtual CR is non-inferior to center-based CR on changes in frailty. We found significant changes in frailty were influenced by interaction between frailty at admission and CR model type, such that virtual CR facilitates greater frailty improvements. Finally, admission CLSA-FI scores may be suitable for predicting change in some cardiovascular biomarkers, however, it is not a robust predictor of cardiovascular biomarker change in CR.

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Appendix A. Questions Included in the CSLA–FI.

1. Can you...

...dress and undress yourself (including picking out clothes and putting on socks and shoes)?
...take care of your own appearance, combing your hair, shaving?
...walk?
...get in and out of bed?
...take a bath or shower (including getting in and out of the tub)?

Possible responses:
Yes, without help.
Yes, with some help.
No, unable to do so.

2. Can you.....
...use the telephone, including looking up numbers and dialing?
...get to places out of walking distance (i.e., you drive your own car, or travel alone on buses, or taxis)?
...go shopping for groceries or clothes (taking care of all shopping needs yourself)?
...prepare your own meals(i.e., you plan and cook full meals yourself)?
...do your housework (i.e., you can clean floors, etc.)?
...take your own medicine (in the right doses at the right time)?
...handle your own money(i.e., you write cheques, pay bills, etc.)?

Possible responses:
Yes, without help.
Yes, with some help.
No, unable to do so.

3. Do you have difficulty with any of the following?
Reaching or extending your arms above your shoulders?
Stooping, crouching, or kneeling down?
Pushing or pulling large objects like a living room chair?
Lifting 10 lbs. (or 4.5kg) from the floor, like a heavy bag of groceries?
Handling small objects, like picking up a coin from a table?
Standing for a long period, around 15 minutes?
Standing up after sitting in a chair?
Walking alone up and down a flight of stairs?
Walking 2-3 neighborhood blocks?
Making a bed?
Washing your back?
Using a knife to cut food?
Recreational or work activities in which you take some force or impact through your arm, shoulder or hand (e.g., golf, hammering, tennis, typing, etc.)?

Possible responses:
No.
Yes, a little difficult.
Yes, somewhat difficult.
Yes, very difficult.
Unable to do so.
Do not do on doctor's orders.

4. Please answer the following questions by choosing one option
In General, would you say your health is...?
Is your eyesight, using glasses or corrective lens if you use them...?
Is your hearing, using a hearing aid if you use one...?

Possible responses:
Excellent.
Very Good.
Good.
Fair.
Poor.

5. Do you consider yourself...
Overweight.
Underweight.
Just about right.

6. How many times have you had a fall in the past 12 months that was serious enough to limit some of your normal activities? For example, the fall resulted in a broken bone, bad cut, or sprain.
None.
Once.
Twice or more.

7. In the past week how often did you feel....
...that everything you did was an effort?
...lonely?
...that you could not "get going"?

Possible responses:
Rarely or never (less than 1 day).
Some of the time (1-2 days).
Occasionally (3-4 days).
All of the time (5-7 days).

8. In the past 12 months, have you seen a doctor for any of the following reasons?
Pneumonia?

Urinary Tract Infection (UTI)?

(Yes or no questions)

9. Has a doctor ever told you that you...
...have osteoarthritis in the knee?
...have osteoarthritis in the hip?
...have osteoarthritis in one or both hands?
…have rheumatoid arthritis?
…have any other type of arthritis?
…have/had any of the following- emphysema, chronic bronchitis, chronic obstructive pulmonary disease (COPD), or chronic changes in lungs due to smoking?
...have high blood pressure or hypertension?
...have diabetes, borderline diabetes or that your blood sugar is high?
...have heart disease (including congestive heart failure or CHF)?
...have angina (or chest pain due to heart disease)?
...have had a heart attack, or myocardial infarction?
...have peripheral vascular disease or poor circulation in your limbs?
...have experienced a stroke or CVA (cerebrovascular accident)?
...have experienced a mini-stroke or TIA (transient ischemic attack)?
...have a memory problem?
...have dementia or Alzheimer's disease?
...had parkinsonism or Parkinson's disease?
...have intestinal or stomach ulcers?
...have a bowel disorder such as Crohn's disease, ulcerative colitis, or Irritable Bowel syndrome?
...experience bowel incontinence?
...experience urinary incontinence?
...have cataracts?
...have glaucoma?
...have macular degeneration?
...had cancer?
...have osteoporosis, sometimes called low bone mineral density, or thin, brittle or weak bones?
...have back problems, excluding fibromyalgia and arthritis?
...have an UNDER-active thyroid gland (sometimes called hypothyroidism or myxedema)?
...have an OVER-active thyroid gland (sometimes called hyperthyroidism or Graves' disease?
...have kidney disease or kidney failure?

(Yes or no questions)