CHANGES IN FITNESS WITH LONG-TERM CARDIAC REHABILITATION

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CHAPTER 1

1.1 Brief Introduction

Although cardiovascular disease (CVD)-related mortality rates have declined over the past five decades (Roth et al., 2017), it remains the leading cause of mortality worldwide (WHO, 2017). With over 420 million people living with CVD globally, CVD poses a large economic burden with elevated risk of co-morbidities, recurrent events, and mortality (Roth et al., 2017). Interventions that modify risk factors for CVD and reduce recurrent events and mortality are urgently needed.

Exercise-based cardiac rehabilitation (CR) programs are well-established secondary prevention opportunities for individuals living with CVD. These structured programs are effective in helping members become more active, maintain physical fitness and functioning, and reduce the risk of recurrent cardiac events and all-cause and CVD-related mortality (Anderson et al., 2016; Clark, Hartling, Vandermeer, & McAlister, 2005; Taylor et al., 2004). There is a robust body of literature supporting the effectiveness of CR for improving aerobic fitness and muscle strength (Sandercock, Hurtado, & Cardoso, 2013; Ades, 2001; Sumide et al., 2009), which are key components of physical fitness protective against the risk of mortality (Martin et al., 2013; Hulsmann et al., 2004). Notably, the majority of these studies have focused on CR programs that are 12 months or shorter despite the importance of providing long-term opportunities for exercise in this high-risk population.

CVD statistics have declined from 1990 to 2010, but remain high in both sexes and in particular, less favourable in men until the age of 70 years. Between 1990 and 2010, the global age-standardized incidence of myocardial infarction decreased from 222.7 to 195.3 per 100,000 in men and from 136.3 to 115.0 in women, and the prevalence of angina decreased from 22.9 to 20.3 per 100,000 in men and from 17.7 to 15.9 in women (Moran et al., 2014). In 2013, the unconditional probability of premature mortality attributable to CVD was 11% for men and 7% for women between 30-70 years of age globally, however the mortality in women surpassed men after the age of 70-80 years (Roth et al., 2015). Despite these high CVD mortality and prevalence statistics, women experience equal, if not greater, benefits than men from participating in CR programs (Feola et al., 2015, Wise & Patrick, 2012; O'Farrell et al., 2000), yet they remain under-represented in CR (Supervia et al., 2017).

The overall aim of this thesis is to identify changes in aerobic fitness and muscle strength with long-term CR program enrollment in men and women with CVD. The first study in this thesis investigated changes in cardiorespiratory fitness and muscle strength with long-term CR enrollment in men and compared these changes with previously published rates of change. The second study modeled the association between age and fitness trajectories in men. The third and final study explored changes in cardiorespiratory fitness and muscle strength with long-term CR enrollment in women and compared these changes to previously published rates of change.

1.2 Epidemiology of Cardiovascular Disease

1.2.1 Global Epidemiology in Men and Women

CVD is a class of conditions that affect the circulatory system, such as coronary artery disease, arteriosclerosis, stroke, hypertension, heart failure, myocardial infarction, and valve diseases (Mendis et al., 2014). CVD remains the leading cause of mortality in North America (AHA, 2015) and worldwide (WHO, 2017). While overall mortality rates have decreased by 39% between 1990 and 2013, CVD mortality increased by 41% due to population growth and aging (Roth et al., 2015), and is further expected to increase by 31% to 23.6 million by 2030 (AHA, 2015). Despite these declining CVD mortality rates, the burden of CVD remains a major global health issue. In 2015, there were over 420 million cases of CVD worldwide, and CVD accounted for 33% (17.9 million) of all global deaths (Roth et al., 2017). Over 75% of these deaths occurred in low- and middle- income countries (Roth et al., 2017). CVD cost the global economy $863 billion USD in 2010, and is expected to increase by 20% to $1.04 trillion USD by 2030 (Bloom et al., 2017). Further, in the past 20 years, the global burden of CVD increased from 22 to 29 million disability-adjusted life-years (Moran et al., 2014).

In general, CVD rates are higher in men than women up to age of 70 years (Moran et al., 2014; Roth et al., 2015) but with advances in medical care, rates of CVD mortality and non-fatal sequalae have declined globally since 1990 and similarly in both sexes (Moran et al., 2014; Roth et al., 2015). Indeed, between 1990 and 2010, the age-standardized incidence of myocardial infarction decreased from 222.7 to 195.3 per 100,000 in men and from 136.3 to 115.0 in women, and the prevalence of angina decreased from 22.9 to 20.3 per 100,000 in men and from 17.7 to 15.9 in women (Moran et al., 2014). Similarly, the age-standardized rates of CVD mortality decreased by 22% in the past two decades in both sexes (Roth et al., 2015), although more men have died from CVD in 2013 up to age of 70 years compared women, after which point this trend reverses (Roth et al., 2015). Additional sex differences exist, including risk factor differences (Maas & Appelman, 2010), higher CVD hospitalizations, prevalence, mortality, and recurrence in men (Roth et al., 2015), and poorer prognoses and recovery in women, especially from bypass surgery (Finks, 2010; Harvard Health Publishing, 2017).

1.2.2 Epidemiology of Cardiovascular Disease in Canada

In Canada, the prevalence of CVD in adults changes across the lifespan. From 45-54 years of age, prevalence is 3.2% but rises slightly to 7.9% from ages 55-64 years and accelerates to 21.8% from 75-84 years of age (Public Health Agency of Canada, 2017). CVD mortality has decreased in the past 11 years, but still remains the second highest cause of death at 47,627 deaths/year (Statistics Canada, 2016). In 2016, CVD was responsible for almost 400,000 hospitalizations (16% of all hospitalizations) in Canada, and cost the Canadian economy $22 billion CAD in healthcare costs and reduced work productivity (Statistics Canada, 2016).

1.3 CVD Etiology and Risk Factors

CVD are typically caused by atherosclerosis, an inflammatory disorder of the blood vessels characterized by an accumulation of plaque deposits on the inner vessel wall, thus impeding delivery of nutrients and oxygen to the heart (Ruis-Esparza et al., 2013; Ross, 1993). There are also non-atherosclerotic origins of CVD, including those caused by heart arrhythmias, congenital heart defects, cardiomyopathy, valvular heart diseases, and infections of the myocardium (Mayo Clinic, 2018). Although atherosclerotic vascular manifestations are commonly observed in middle and late adulthood, evidence suggests that atherosclerotic changes can start as early as childhood and may be a result of the presence of CV risk factors (Hong, 2010).

CV risk factors are variables causally associated with increased CVD occurrence and are independent predictors of an increased chance of presenting with the disease (O'Donnell & Elosua, 2008). According to the World Health Organization (2018), non-modifiable CV risk factors include chronological age, male sex, ethnicity (Indigenous cultures), positive family history of CVD, and genetic predispositions (hereditary conditions, such as familial hypercholesterolemia). Modifiable risk factors include: physical inactivity, tobacco use, harmful alcohol consumption (>4 drinks/day or 14/week in men, >3 drinks/day or >7/week in women), unhealthy diet (i.e. high calorie and saturated fats), hypertension, hypercholesterolemia (total cholesterol and low-density lipoprotein cholesterol), type 2 diabetes, and abdominal obesity (WHO, 2018; Agarwal, 2012). The major traditional risk factors (type 2 diabetes, smoking, hypertension, physical inactivity, and hypercholestermia) alone explain 75% of the variance in the incidence of CVD (Magnus & Beaglehole, 2001; O'Donnell & Elosua, 2008). A meta-analysis of 61 studies (n=900,000) in western Europe and North America found that high-density lipoprotein cholesterol and total/high-density lipoprotein cholesterol ratio were also CVD risk factors in addition to total cholesterol (Lewington et al., 2007). In a large meta-analysis of 36 cohort studies with a mean 12.3-year follow-up (n=3.4 million), engagement in physical activity behaviours (150 minutes/week) compared to being inactive was associated with lower risk of type 2 diabetes by 26%, incidence of CVD by 17%, and CVD mortality by 23% (Wahid et al., 2016). In a study that followed 40,000 men for 16.6 years, researchers found that the reduced risk of CVD mortality was associated with higher levels of CRF and lower ratios of triglycerides to high-density lipoprotein cholesterol (Farrell et al., 2017).

Interventions targeting modifiable risk factors such as hypercholesterolemia, hypertension, and smoking, can be effective in reducing risk of CVD and recurrent events. For example, cholesterol-lowering pharmacotherapies have been shown to reduce CVD morbidity and mortality (Gundy et al., 2004; National Cholesterol Education Program, 2002; Law, Wald, & Thompson, 1994). The use of rosuvastatin has been shown to reduce low-density lipoprotein cholesterol by 50% and risk of CV events and mortality by 30-50% in over 18,000 patients with high cholesterol (Ridker et al., 2009). Anti-hypertensive agents also have an integral role in controlling blood pressure and reducing the risk of CVD and mortality (Antonakoudis et al., 2007). A large meta-analysis of 123 studies (n=613,815) showed that for every 10 mmHg reduction in systolic blood pressure, risk of CVD was also reduced by 20%, stroke by 27%, and all-cause mortality by 13% (Ettehad et al., 2016). Further, smoking cessation reduces the risk of myocardial infarction and all-cause mortality (CDC, 2010) and within only 24 months after quitting, eliminates approximately 50% of the risk of CVD (Kawachi et al., 1994).

Physical activity and exercise are also key interventions which modify both CVD and its associated risk factors. Meta-analyses have shown the protective effect of moderate-intensity physical activity, where engagement of 150-300 minutes per week can reduce the risk of CVD by 14-20% (Sattlemair et al., 2011). A 30% reduction in the risk of incident CVD was reported in 927 men and women who participated in ≥150 minutes of moderate-intensity physical activity per week compared to participants who were inactive (Sofi et al., 2007). Another cohort study of over 27,000 individuals found a 40% lower risk of CVD in participants who expended >1500 kcal/week compared to those who spent <200 kcal/week during exercise and physical activity time (Mora, Cook, Buring, Ridker, & Lee, 2007). Regular physical activity and exercise has been shown to modify traditional risk factors such as reduced central obesity (Poirier & Despres, 2001), dyslipidemia (low- and very low- density lipoprotein cholesterol) (Yoshida et al., 2010), hypertension (Diaz & Shimbo, 2013), metabolic syndrome (Tjonna et al., 2008), and type II diabetes (Aune, Norat, Leitzmann, Tonstad, & Vatten, 2015).

The protective effect of physical activity on CVD can be partially explained by anti-inflammatory effects that can decelerate the atherosclerotic process, including reduced thrombosis, coagulation, endothelial dysfunction, and insulin resistance, hypertension, diabetes, physical inactivity, and obesity (Cheng et al., 2013; Squires, Montero-Gomez, Allison, & Thomas, 2008; Lavie et al., 2009; Marchionni et al., 2003; Shah et al., 2009). Importantly, Mora et al. (2007) found that over half of the risk of incident CVD that is reduced through physical activity engagement is explained by risk factor modification, and 14% of the reduction in all-cause mortality achieved by exercise-based CR can be explained by the improvements in modifiable risk factors (Taylor, Unal, Critchley, & Caprewell, 2006).

The resultant physiological changes that occur through exercise training can contribute to improved health and reduced risk of CVD, namely through improved coronary artery blood flow (Bruning & Sturek, 2015) via increased coronary artery compliance (Tanaka et al., 2000), endothelial-dependent vasodilation (LaMonte et al., 2002), and angiogenesis (Laughlin, Oltmn, & Bowles, 1998). In addition, other benefits include reduced myocardial oxygen demand (Leon, 2000; Thompson et al., 2003), and increased protein turnover, oxidative capacity of working skeletal muscles, and expression of myostatin (Hambrecht et al., 2000). Researchers have theorized that some of the protective effects of physical activity may also be explained by its positive impact on the autonomic nervous system (Joyner & Green, 2009), evidenced by reduced autonomic dysfunction and improved heart rate variability and baroreflex sensitivity (Gademan et al., 2007). Exercise training can also counterbalance the long-term adverse effects of neurohumoral activation, which leads to improved cardiac function, reduced vasoconstriction, and improved blood delivery (Braith, Welsch, Feigenbaum, Kluess, & Pepine, 1999).

1.4 Cardiac Rehabilitation

CR is a medically-supervised program that can help individuals with CVD recover after experiencing cardiac events (National Heart, Lungs, and Blood Institute, 2016). The primary goal of CR is to stabilize, decelerate, or reverse the progression of CVD, which can translate into reduced risk of future cardiac events (Balady et al., 2011). CR places a strong emphasis on exercise training, but also takes a holistic approach to risk factor management by providing education on heart-healthy living, stress management, risk factor intervention and follow-up, and counseling to help individuals recover and return to a healthy, active lifestyle (Mampuya, 2012).

1.4.1 Phases of Cardiac Rehabilitation

CR is generally offered across three to four phases of recovery (targeting acute treatment, outpatient rehabilitation, and maintenance), although there may be slight regional differences in the design, implementation, delivery, and timelines of these phases (Price, Gordon, Bird, & Benson, 2016; Mampuya, 2012). The initial or acute phase (Phase 1) takes place in the hospital and occurs very shortly after the cardiac event and typically lasts 2-5 days (Price et al., 2016). A multidisciplinary team of healthcare professionals (cardiologists, nurses, physiotherapists, occupational therapists, dieticians, and pharmacists) focus on helping the individual regain mobility, assess risk factors, and provide educational support for risk factors and heart-healthy living. Intensity of exercise in phase I is typically very low, as it is more focused on improving functional mobility and may not follow formal exercise prescription with frequency, intensity, time, and type parameters (Price et al., 2016).

The sub-acute phase (Phase 2) occurs following discharge from the hospital, and lasts 1-4 weeks. During Phase 2, goals set and educational support provided in Phase 1 are continued, and cardiac responses to physical activity and exercise continue to be closely monitored by the team of trained health professionals. Exercise in this phase starts at a low intensity and progresses according to cardiologist guidance in an outpatient setting. Sometimes CR professionals combine this phase with the next as patients are living at home.

Individuals in Phase 3 continue to progress their exercise programs during outpatient exercise programs or home-based interventions, typically exercising at a frequency of three days/week for 6-12 weeks before proceeding into Phase 4 maintenance programs within the community. Participants in Phase 3 are encouraged to develop skills in self-monitoring of exercise responses, such as heart rate, breathing, rate of perceived exertion and blood pressure. They also receive ongoing educational support on risk factor management and healthy living. Phase 3 typically commences two weeks after coronary angiography, three to four weeks after myocardial infarction, and six weeks after bypass and valve surgeries (Mampuya, 2012). Early initiation of outpatient CR is associated with greater improvements fitness (McPhee, Winegard, MacDonald, McKelvie, & Millar; 2015; Valkeinen, Aaltonen, & Kujala, 2010). McPhee et al. (2015) reported greater improvement in peak metabolic equivalents (METs) for individuals who enrolled in Phase 3 CR within 114 days post-event compared to those who enrolled beyond this time. In a meta-analysis of 18 randomized controlled trials (922 participants) of exercise-based CR programs, individuals who enrolled in CR <90 days experienced a larger increase in VO_2max (18%) compared to those who were ≥90 days post-event (6%) (Valkeinen, Aaltonen, & Kujala (2010). The Canadian Cardiovascular Society outlines reasonable wait times between 30-60 days, but, in reality, the average wait time to enroll in outpatient CR programs in Canada is at least 66 days (O'Neill & Simpson, 2010). Delays have been reported up to 101 days post-coronary artery bypass grafting (Marzolini et al., 2015), and can occasionally extend up 9 months (Grace et al., 2012).

Phase 4 maintenance phase CR programs aim to facilitate long-term healthy lifestyle changes through continued exercise training, smoking cessation, and improved diet. In this phase, individuals continue to exercise through independent home programs, or may join formalized long-term exercise-CR programs to maintain physical activity and fitness levels (Price et al., 2016). Importantly, previous work (Bently, Khan, Oh, Grace, & Thomas, 2013) has reported that maintaining physically active lifestyles among graduates of Phase 3 programs is influenced by linkages to community resources, such as employment status, location of primary residence, perceived health, and CR support.

1.4.2 Benefits in Cardiac Rehabilitation

The evidence supporting short-term CR (<12months) in Phases 1-3 is strong and well-established. Several meta-analyses have shown that CR can lower CVD risk factors and risk of mortality and hospital admissions. A meta-analysis of 63 randomized controlled trials of CR programs (n=14,486, program length 6-36 months, median 10 months) found a 26% and 18% reduced risk of cardiovascular mortality and hospital admissions, respectively (Anderson et al., 2016). In a meta-analysis of 48 trials of CR programs (n=8,940, program length 3-12 months), reductions in all-cause (20%) and cardiac mortality (26%), total cholesterol (0.37 mmol/dL) and triglyceride levels (0.23 mmol/dL), blood pressure (3.2 mmHg), and smoking (56%) were reported (Taylor et al., 2004). Another meta-analysis of 63 randomized controlled trials of CR programs (n=21,295) observed a 17% reduction in risk of recurrent myocardial infarction at 12 months and 47% in all-cause mortality at 24 months following completion of CR (Clark et al., 2005). CR has been shown to reduce inflammation (measured by high-sensitivity C-reactive protein) (Milani, Lavie, & Mehra, 2004), body fat, depression, and anxiety (Maines, Lavie, Milani, Cassidy, Gilliland, & Murgo, 1997). Reduced chest pain, dyspnea, and fatigue, and improved stress management, high-density lipoprotein cholesterol levels (Maines et al., 1997), maximal oxygen consumption (Sumide et al., 2009), and skeletal muscle strength (Nishitani et al., 2013) have been reported after CR.

Studies with long-term follow-up in CR are much more limited compared to those focused on short-term programs, but early evidence suggests that the benefits of CR can be extended to the long-term. Goel et al. (2006) reported a 45-47% reduction in risk of all-cause mortality 6.3 years after completion of a 12-week Phase 3 CR program (n=2,009). Bentley et al. (2013) reported that 75% of Phase 3 CR graduates maintained at least 150 minutes/week of moderate physical activity 3.5 years later. These studies sampled adults not actively enrolled in any Phase 4 CR programs. Moreover, Gayda et al. (2006) reported changes in fitness after 10 years of enrollment in Phase 4 CR in 42 older men with CVD. The authors found a 5.4% increase in peak METs at 12 months of enrollment, but an overall decline of 2.2% after a mean follow-up of 10 years, similar to expected declines with aging (Gayda et al., 2006).

1.4.3 Risks in Cardiac Rehabilitation

The risks involved with participating in CR are very low. There is a risk of one cardiac event in every 8,484 cardiopulmonary exercise tests conducted, one cardiac event for every 50,000 patient hours of exercise training, and 1.3 cardiac arrests for every one million patient-hours of exercise (Pavy, Iliou, Tabet, & Corone, 2006). The incidences of adverse and life-threatening events are 3.13 and 0.26 events, respectively, for every 100,000 patient-hours of exercise training in maintenance-phase CR (Saito et al., 2014).

The only contraindications to CR are related to safety during exercise training. The Canadian Association of Cardiac Rehabilitation (Stone et al., 2009) discusses several contraindications to exercise-based CR, such as unstable angina, pulmonary arterial hypertension ≥60 mmHg, ventricular arrhythmias, intracavitary thrombi, severe obstructive cardiomyopathies, decompensated heart failure, severe aortic stenosis, uncontrolled inflammatory and infectious diseases, and musculo-skeletal disorders prohibiting exercise (CACR, 2007).

1.4.4 Cost-Effectiveness of Cardiac Rehabilitation

Many studies have shown that CR is cost-effective. A recent systematic review of 19 studies reported incremental cost-effectiveness ratios of CR ranging from $1,065 to $71,755 per quality-adjusted life-year, which resulted in reduced costs associated with subsequent events, surgical interventions, and hospitalizations (Shields, Wells, Doherty, Heagerty, Buck, & Davies, 2018). A cost utility of $640 saved per quality-adjusted life-year gained was reported in a recent systematic review after an 8-week CR program, which was sustained after a two-year follow-up (Yu et al., 2004). Ades, Pashkow, & Nestor (1997) showed that short-term CR was more cost-effective than statin therapy, thrombolytics and coronary artery bypass surgery in terms of dollars/year of life saved and rehospitalisation costs. CR following myocardial infarction or coronary artery bypass surgery resulted in 45% lower hospitalization rates, 15% higher rates of return to work, and a total savings of $12,000 USD per patient (Levin, Perk, & Hedback, 1991). Further, medical costs have been reduced by $739 USD/patient after just 21 months after completion of a 12-week CR program (Oldridge et al., 1993).

1.4.5 Cardiac Rehabilitation Remains Underutilized in Canada

Despite the established benefits and cost effectiveness of CR programs, CR programs are underutilized (Grace et al., 2012; Brady, Purdham, Oh, & Grace, 2012; Mampuya, 2012). Low rates of physician referrals are an important factor, whereby referral rates in Canada are only made for 30-52% of cases (Aragam et al., 2011; Brady, Purdham, Oh, & Grace, 2012). Of concern, even among individuals who receive referrals to CR, less than 50% carry through to enroll in these programs (Grace et al., 2011). Indeed, one Ontario study cited a 22% enrollment rate in CR programs (Swabey, Suskin, Arthur, & Ross, 2004). Methods to improve referral rates have successfully increased patient enrollment. In a large prospective, controlled study (n=2,623) in Ontario, Grace et al. (2011) found that a novel approach that combined automatic and liaison referral (personal discussion with nurse or physiotherapist) increased referral to CR programs from 32% to 86% and enrollment from 29% to 74% compared to usual practice.

In addition to low referral and enrollment rates, the availability of early CR programs and service capacity of existing programs remains low (Candido et al., 2011). From 2006 Ontario health service data, there were 53,000 hospitalizations due to cardiac events but service capacity of CR programs for only 18,000 people (34% of total hospitalizations) (Candido et al., 2011). In Canada, there is only one CR spot is available per 4.55 patients with CVD (Tran et al., 2018). Other barriers to enrollment in outpatient CR facilities include high membership costs, transportation challenges, and limited available centres (Leon et al., 2005).

These low numbers in enrollment in early phases of CR can lead to even lower enrollment in long-term CR programs. Consequently, there is little research to date reporting on outcomes of these long-term programs. Since the earlier phases of CR typically last five months in North America (Ndegwa, 2010), the transition to maintenance-phase, long-term CR programs is critical for maintaining healthy, active lifestyles and thereby lowering the risk of future CVD events and mortality.

1.4.6 Exercise Programming in Cardiac Rehabilitation

The Canadian Association of Cardiac Rehabilitation describes guidelines for a comprehensive exercise program of aerobic, resistance, and flexibility training for individuals enrolled in outpatient CR programs in Phases 2-4 (Stone et al., 2009; Price et al., 2016). Aerobic endurance training is prescribed at 40-85% of heart rate reserve for 20-40 minutes per session, 3-5 sessions per week. Resistance training is prescribed at 30-40% and 50-60% of one-repetition maximum for upper and lower body, respectively; however, the initiation of upper body training may be delayed by eight weeks in individuals undergoing invasive cardiac surgery (Stone et al., 2009; Price et al., 2016). Individuals are recommended to complete 2-3 sessions per week of 1-3 sets of 12-15 repetitions for 6-10 different exercise (upper and lower body). Flexibility training is static and dynamic stretching consisting of at least four sets of upper and lower body of 15-60 seconds per stretch. Individuals are also encouraged to engage in other forms of free-living physical activity outside of formal exercise sessions in order to reach the recommended 30-60 minutes per day of moderate-intensity physical activity 5-7 days per week.

Exercise programs are highly individualized, and developed based on a combination of many clinical and functional considerations, such as the results from the first cardiopulmonary exercise test, the individual's physical abilities and limitations, motivations and barriers to exercise, goals, and current and past physical activity levels (Price et al., 2016). Physiotherapists, registered kinesiologists, and other exercise professionals oversee and monitor group exercise sessions during Phase 3 and 4 CR to facilitate effective, safe, and minimal risk exercise training, such as monitoring participant's responses to exercise, blood pressure, heart rate, rate of perceived exertion, and movement patterns during exercise to reduce injury risk (Price et al., 2016). The multi-disciplinary team is involved in all aspects of program delivery, including pre-enrollment medical, physical and fitness assessments (i.e. cardiopulmonary exercise test and muscle strength assessments). Physiotherapists, kinesiologists, and other trained staff have critical roles in developing the exercise prescriptions, supervision of group exercise sessions, and providing available educational resources with opportunities to consult with dieticians, nutritionists, and nurses who have expertise in smoking cessation and weight loss (Price et al., 2016).

Exercise training in CR programs is important for improved cardiorespiratory fitness and skeletal muscle strength outcomes.

1.5 Cardiorespiratory Fitness

CRF is the ability of circulatory and respiratory systems to deliver oxygen to skeletal muscles during prolonged physical activity or exercise. CRF is important since higher levels are consistently shown to be protective against the risk of CVD and all-cause mortality in the general (Kodama at al., 2009; Lee et al., 2011) and CVD populations (Martin et al., 2013; Franklin, Swain, & Shepherd, 2003; Beatty, Schiller, & Whooley, 2012). In persons with CVD, all-cause and CVD mortality is reduced by 25% for each MET increase in CRF (Martin et al., 2013). Importantly, CRF is a stronger predictor of these risks than other common clinical exercise tests in the medical community (Mora et al., 2003; Roger et al., 1998; Goraya et al., 2000). In individuals with coronary heart disease, participation in CR programs is effective in improving CRF, which is associated with reduced risk of CVD mortality, heart failure and myocardial infarction (Beatty, Schiller, & Whooley, 2012). CRF can be interpreted as a surrogate measure of physical activity (Hootman et al., 2001) that is indicative of CVD risk (Williams, 2010).

The health benefits of CRF extend beyond reduced risks of mortality and morbidity. Recognized as a vital sign (Ross et al., 2016; Loprinzi, 2018), CRF is an important indicator of frailty, physical limitations, and functional ability (i.e. activities of daily living) (Loprinzi, 2018; Kaminsky et al., 2013), and an important predictor of healthcare utilization in younger and older adults (Rockwood, Song, & Mitnitski, 2011). CRF is associated with improved physical function in both older adult and CVD populations (Guralnik et al., 2000; Onder et al., 2005; Boxer et al., 2010; Markides et al., 2001; Kaminsky et al., 2013).

A cardiopulmonary exercise test is the criterion standard for assessing CRF, where maximal oxygen consumption (VO_2max) is measured through indirect calorimetry (Fletcher, Froelicher, Hartley, Haskell, & Pollock, 1990). Indirect calorimetry allows for measurement of the volume of oxygen consumed per unit of time, which can be expressed in absolute units (l/min) or relative units (ml.kg-1.min-1). VO_2max, the primary outcome of a cardiopulmonary exercise test, is a product of cardiac output (heart rate and stroke volume, which are influenced by peripheral vasodilatory responses and cardiac, ventilator, and hematological factors) and oxygen extraction (influenced by mitochondrial oxidative capacity, and capillary surface area) (Betik & Hepple, 2008). A trained cardiovascular technician conducts this test using a progressive incremental or ramp protocol, typically performed on a bicycle or treadmill. VO_2peak, the highest recorded value of VO_2 from a symptom-limited test, is commonly reported particularly in special or clinical populations when physiological maximum oxygen consumption is not achieved.

1.5.1 Changes in Cardiorespiratory Fitness with Aging

CRF is known to decline with age, at a rate that is generally accepted to be approximately 10% per decade after the age of 25-30 years (Fleg et al., 2005; Jackson et al. 2009; Milanovic et al., 2013; Stathokostas, Jacob-Johnson, Petrella, & Paterson, 2013). However, the high inter-individual variability in this rate of decline suggests that this is an overly simplistic viewpoint. Longitudinal studies have shown that the rate of decline in CRF is different for different age groups (Fleg et al., 2009; Jackson et al., 2009), indeed accelerating with age: 0.5%/year in adults aged 30-39 years, 1%/year from 40-49 years, 1.6%/year from 50-59 years, 2%/year from 60-69 years, and 2.5%/year in adults 70 years and older (Fleg et al., 2005).

Studies have explored potential factors that may explain this variability. Historically, PA levels were believed to influence the rate of age-associated decline in CRF (Dehn & Bruce, 1972), but more recent emerging evidence suggests there are likely a multitude of factors at play.

A cohort study that followed 810 adults for 7.9 years found that although CRF was consistently higher in individuals who were physically active compared to those who were not, the rate of decline over time was the same across any level of physical activity (Hakola et al., 2011). A smaller cohort study (n=62) found that physical activity accounted for <5% of the variance of change in CRF over 10 years, suggesting that age-associated changes in fitness is not simply due to reduced physical activity levels (Stathokostas et al., 2004). Similarly, longitudinal analyses in healthy adults have also reported that age-associated rates of decline in CRF were similar across several subgroups of physical activity levels (Jackson et al., 2009; Fleg et al., 2005).

The differences observed across age groups may be explained by physiological processes with aging, such as reduced peripheral oxygen utilization, skeletal muscle oxidative capacity due to mitochondrial dysfunction with age, and diminished oxygen delivery resulting from age-related reductions in cardiac output and maximum heart rate (Betik & Hepple, 2008; Fleg, 2012). Additional physiological changes include reduced vascular conductance with aging resulting from altered myogenic responses and decreased endothelial-derived vasoreactivity (Betik & Hepple, 2008).

1.5.2 Cardiorespiratory Fitness in Cardiovascular Disease

Individuals with CVD are often physically de-conditioned before the occurrence of cardiovascular events likely due to genetic factors and an accumulation of CVD risk factors (Martin et al., 2013; Baliaga & Haas, 2015), and remain less fit than their non-CVD counterparts long after their events (Gayda et al., 2006). Living with modifiable CVD risk factors (i.e. smoking, hypertension, obesity, and physical inactivity) has adverse effects on the CV system, including reduced blood flow from atherosclerosis, stenosis, or endothelial dysfunction (Leon et al., 2005; Bruning & Sturek, 2015), chronic heart conditions such as heart failure and unstable angina (Ruis-Esparza et al., 2013), and damage or necrosis to the myocardium and surrounding vessels (De Waard et al., 2016). These effects can lead to reduced CRF as individuals become more sedentary and less capable of meeting the 150 minutes/week of moderate-intensity physical activity recommended (Leon et al., 2005). In cases of macroscopic atherosclerosis, individuals with CVD have attenuated myocardial oxygen delivery despite increased oxygen demand, which lowers CRF as cellular anaerobic pathways become activated and angina occurs (Bruning & Sturek, 2016).

1.5.3 Improved Cardiorespiratory Fitness with Cardiac Rehabilitation

There is a large body of evidence supporting the use of short-term CR programs (<12 months) to improve CRF. Three to six months of supervised exercise training has been shown to elicit an 11-36% increase in CRF in individuals with CVD (Ades, 2001; Sandercock, Hurtado, Cardoso, 2013; Sumide et al., 2009). Importantly, the largest gains in CRF were seen in the most de-conditioned participants (Laddu et al., 2018; Wenger et al., 1995). Data from a meta-analysis of 31 studies and 3,827 participants provided strong evidence of improved CRF by 1.55-METs after completion of CR programs 4-12 months in length (Sandercock, Hurtado, & Cardoso, 2013).

Improvements in fitness after exercise training can result from coronary artery blood flow (Bruning & Sturek, 2016) through increased coronary artery compliance (Tanaka, Dinenno, Monahan, Clevenger, DeSouza, & Seals, 2000), endothelial-dependent vasodilation (LaMonte et al., 2012) and angiogenesis in adults with CVD (Laughlin, Oltman, & Bowles, 1998). Additionally, myocardial ischemia is reduced with exercise training through decreased rate pressure product and myocardial oxygen demand (Leon, 2000; Thompson et al., 2003), and through ischemic preconditioning whereby the myocardium blood supply is protected (Murry, Jennings, & Reimer, 1986; Bolli, 2000). Adaptations in the heart and vessels resulting from short-term exercise training (<6 months) include increased coronary artery blood flow, which continuously reduces ischemia and increases the ability to exercise at higher volumes and intensities, thus improving CRF over time (Bruning & Sturek, 2016).

Much less is known about the changes in CRF with long-term enrollment in CR. The preliminary evidence, however, is promising with one study reporting that exercise capacity (workload, exercise time, and perceived exertion) was maintained two years after completion of a four-week CR program (n=73) (Boesch et al., 2005). Similarly, in a study that assessed 108 participants following a six-month home-based CR program, CRF levels were maintained over the six-year follow-up period (Smith, McKelvie, Thorpe, & Arthur, 2011). While these two studies showed preservations in fitness at their follow-up points, exercise after completion of CR program was not tracked. This limitation is absent in the two previous studies examining changes in fitness with active enrollment in long-term CR (Gayda et al., 2006; Belardinelli et al., 2012). Gayda et al. (2006) investigated the impact of an ongoing long-term CR in 43 adults with coronary heart disease (mean entry age 72 years) and reported an initial 5.4% increase in metabolic equivalents after the first 12 months of the program, but an overall decline of 2.2%/year over the 12-13-year follow-up. Despite the positive findings reported, the authors were unable to provide insight into potential non-linear trajectories of change in CRF over the follow-up periods, as assessments were measured only at two time points. More recently, Belardinelli et al. (2012) prospectively tracked changes in CRF over 10 years of active CR enrollment. They reported a 1.5%/year decline in a small homogenous sample of individuals with chronic heart failure. There is a need for further research of long-term CR sampling more participants with more diverse cardiovascular profiles representative of the general CR population, and for changes in CRF to be tracked more frequently to fully understand the trajectories of change over time.

1.6 Skeletal Muscle Strength

Muscle strength is the amount of force that skeletal muscle can produce with maximal movement (Scott, 2008). Higher levels of muscle strength are associated with reduced risk of all-cause and cancer mortality in the general population (Ruiz et al., 2008) and in individuals with CVD, independent of CRF (Hulsmann et al., 2004). A 42-year cohort study of over 38,000 men showed that low levels of muscle strength in young adulthood was associated with increased risk of CVD and CVD mortality by middle-age and older age (Timpka, Petersson, Zhou, & Englund, 2014). In a large prospective study (n=502,293 aged 40-69 years old), higher muscle strength was protective against all-cause, cardiovascular, and many cancer mortalities in the general population (Celis-Morales et al., 2018). Interestingly, Newman et al. (2006) found that low muscle mass did not explain the relationship between muscle strength and mortality risk, suggesting that muscle strength, rather than muscle mass, appears more important in mortality risk estimation.

From a functional standpoint, maintaining muscle strength can help preserve the ability to perform daily living activities (Brill, Macera, Davis, Blair, & Gordon, 2000) and reduce the risk of falls in older adults (Ishigaki, Ramos, Carvalho, & Lunardi, 2014). In CVD populations, the improvements in muscle strength after resistance training are associated with better physical function (Gary, Cress, Higgins, Smith, & Dunbar, 2012), improved quality of life (Jankowska et al., 2008), and reduced depression (Aidar et al., 2014).

The criterion standard measurement of skeletal muscle strength is the one repetition maximum test (1RM), which is the maximum weight an individual can lift in a single repetition maintaining appropriate form (Peterson, Phea, & Alvar, 2005). When a 1RM test is too difficult to perform (i.e. risk of injury or untrained in weight lifting), can be estimated using alternative tests, such as 3RM or 10RM, hand grip strength, and prediction equations (Nascimento et al., 2007).

1.6.1 Changes in Skeletal Muscle Strength with Aging

Similar to the non-linear changes in CRF seen over time, the small body of available evidence suggests that changes in skeletal muscle strength follow a similar trajectory (von Haehling, Morley, & Anker, 2010; Zatiorsky & Kreamer, 2008; Doherty, 2003). However, there is no clear consensus on the rates of decline in muscle strength (between 1.5-5%/year (von Haehling, Morley, & Anker, 2010; Goodpaster et al., 2006; Zatsiorsky & Kreamer, 2008; Marcell, Hawkins, & Wiswell, 2014; Frontera et al., 2000; Doherty, 2003)., and information on sex differences is limited. A consistent trend reported in the literature however is that muscle strength remains fairly stable up to the age of 50 years, commonly followed by a decline of 1.5%/year from 50-59 years, 2%/year from 60-69 years, and at least 3%/year after age 70 (von Haehling, Morley, & Anker, 2010; Zatsiorsky & Kreamer, 2008). A small study of 12 men reported similar declines in muscle strength at 1.98-2.48%/year from 65 to 77 years of age (Frontera et al., 2000). Of note, one study (n=654, age range 20-93 years) reported early decline in muscle strength (8-10%/decade) for men and women in their 40s (Lindle et al., 1997).

The literature is inconsistent whether changes in muscle strength are different in men versus women. Goodpaster et al. (2006) sampled 1,880 older adults aged 70-79 years, and observed a 3.6%/year decline in muscle strength in men and 2.8%/year in women. Faster declines in strength in men 50-90 years of age were also reported in Lindle et al. (1997) but no sex differences were found other studies who reported overall rates of decline 2-5% in individuals aged 50-80 years (Marcell, Hawkins, & Wiswell, 2014; Doherty, 2003).

Sacropenia-related changes explain the changes in skeletal muscle strength observed with aging. These include muscle atrophy, loss of muscle mass and muscle fibres, reduced fibre size (Surraka, 2005; Zatsiorsky & Kreamer, 2008), decreased testosterone, skeletal muscle protein synthesis, and muscle repair capacity, and an increased catabolic hormones and other substances that increase the rate of muscle loss (Sharkley & Gaskill, 2007; Doherty, 2003; Raggi & Berardi, 2012). Despite reductions in muscle mass, exercise interventions that may reverse or decelerate this do not necessarily translate into analogous increases in muscle strength (Goodpaster et al., 2006; Fronter et al., 2000). In fact, the two do not decline equally, where muscle strength declines at 3%/year while muscle mass only declines at 1%/year (Goodpaster et al., 2006; Fronter et al., 2000).

1.6.2 Skeletal Muscle Strength in Cardiovascular Disease

Compromised skeletal muscle strength in individuals living with CVD is concerning as it poses an increased risk of morbidity and mortality (Hulsmann et al., 2004) and is predictive of physical limitations and disability (Park et al., 2006). Individuals with CVD experience lower levels of muscle strength than the general population before and after the occurrence of cardiovascular events (Santos et al., 2014; Nishitani et al., 2013). Harrington et al. (1997) found reduced quadriceps and total leg muscle cross-sectional area in individuals with CVD compared to adults without CVD, which was positively correlated to their reduced muscle strength. Santos et al. (2014) demonstrated that lower-limb muscle strength was 50% lower in individuals with CVD compared to those without, which decreases further by an additional 25-29% 10 days after cardiac surgery. Other studies have reported a 22-28% reduction in quadriceps and hamstring maximum muscle torque in individuals with coronary artery disease compared to age-matched controls (Ghroubi et al, 2007; Baum et al., 2009; Okada, Toth, & Vanburen, 2008; Harrington et al., 1997). Similarly, muscle strength was lower in individuals with heart failure compared to those without, possibly due to reduced contractility of portions of muscle mass (Okada, Toth, & Vanburen, 2008).

Changes in skeletal muscle structure and metabolism may be responsible for the observed reductions in strength in CVD populations, including muscle atrophy, metabolic dysfunction, lower muscle fibre cross-sectional area, and demand-perfusion mismatch (Fang & Thomas, 2003; Pinsky et al., 1990). Increased expression of myostatin and inflammatory cytokines following hypoxia and reduced cardiac output have been postulated to explain the reduction in skeletal muscle strength seen in individuals with coronary artery disease (Heineke et al., 2010; von Haehling, Steinbeck, Doehner, Springer, & Ankler, 2013).

Secondary factors such as physical inactivity and medication use may offer additional explanation for the reduced muscle strength observed in CVD populations. Reductions in everyday physical activity commonly observed in individuals with CVD lead to losses in muscle strength because regular stimuli of muscle activation are required to maintain muscle mass (Baum et al., 2009). A key physiological pathway of reduced muscle strength with inactivity seen in CVD cases is through the increased production of inflammatory cytokines, such as interleukin-I β, interleukin-VI, and tumor necrosis factor-α (Doherty, 2003; Morley et al., 2001). It is theorized that a consequence of this chronic inflammation is sarcopenia, whereby cytokines activate or block signalling pathways ultimately leading to proteolysis, reduced protein synthesis (Wang, Leung, Chow, & Cheung, 2017), and increased muscle atrophy from increased regulation of MurF1 (Londhe & Guttridge, 2015). Moreover, the use of statins to manage dyslipidemia can have adverse effects on skeletal muscle due to mitochondrial dysfunction, membrane disruption, and calcium handling (Parker & Thompson, 2012) and the use of anti-hypertensive medications is known to reduce walking performance and reduce lower-limb muscle strength (Loprinzi & Loenneke, 2016).

In the CVD population, there is limited evidence related to age-associated reductions in muscle strength. An early cross-sectional study of 638 adults with CVD and 961 adults without cardiac disease (age 30-89 years) found that knee extension and arm flexion strength declined similarly and linearly at 1%/year in both groups (Baum et al., 2009). In contrast, more recent longitudinal research in the general population shows accelerated declines with age (von Haehling, Morley, & Anker, 2010; Goodpaster et al., 2006; Zatsiorsky & Kreamer, 2008; Marcell, Hawkins, & Wiswell, 2014; Frontera et al., 2000; Doherty, 2003). No other studies have examined longitudinal trajectories in muscle strength in an aging CVD population.

1.6.3 Improved Skeletal Muscle Strength with Cardiac Rehabilitation

Although CR programs have historically focused more on aerobic exercise, moderate-load resistance training in CR programs has been shown to be effective and safe (Pollock et al., 2000; Sumide et al., 2009; Nishitani et al., 2013) such that CR programs now routinely incorporate resistance training into their models of care. Meta-analytic data have reported larger improvements in fat-free mass and both upper and lower body muscle strength in individuals with CVD after combined aerobic and resistance training compared to aerobic training alone, without compromising safety and study completion (Marzolini, Oh, & Brooks, 2012). Recent meta-analyses by Yamamoto et al. (2016) and Yang et al. (2015) have demonstrated improvements in upper and lower body muscle strength in CR programs lasting 4-48 weeks. Improvements in knee extension strength by 11-39% (Fragonli-Munn, Savage, & Ades; 1998; Sumide et al., 2009; Nishitani et al., 2013), chest press by 14% (Fragonli-Munn, Savage, & Ades (1998), grip strength by 7-13% (Nishitani et al., 2013) and knee flexion by 14-30% (Sumide et al., 2009; Nishitani et al., 2013) have been reported in resistance training programs lasting 3-12 months in CVD populations. These improvements may be attributed to increases in skeletal muscle capillary density, succinate dehydrogenase, and individual muscle fibre area that have been reported after exercise-based CR (Ades et al., 1996). Increased muscle strength following CR also result from increased protein turnover, blood flow, oxidative capacity of the working skeletal muscles, and reduced expression of myostatin (Yamamoto et al., 2016).

To date, there have been no longitudinal of studies investigating changes in skeletal muscle strength with long-term CR.

1.7 Research Objectives and Hypotheses

CVD remains the leading cause of death and produces a large economic burden to society. The impact of CVD can be reduced by targeting modifiable risk factors, such as exercise behaviours. While the benefits of short-term CR (3-12 months) have been well established, it is also important to examine whether these benefits can be continued in the long-term. To date, only two previous studies reported changes in CRF with long-term CR (Gayda et al., 2006; Belardinelli et al., 2012), but were limited small sample sizes and sample characteristics less representative of CR participants.

The purpose of this thesis was to investigate changes in fitness with long-term, maintenance-phase CR program enrollment in a diverse, representative CR cohort over many points in time to obtain clearer pictures of the changes. Three studies were conducted to address this overarching purpose. The specific objectives and hypotheses of these three studies are described below:

Study 1: Long-term enrollment in cardiac rehabilitation benefits cardiorespiratory fitness and skeletal muscle strength in men with cardiovascular disease: a retrospective study

Objectives:

1) To examine changes in cardiorespiratory fitness (as measured by VO_2peak in ml.kg-1.min-1, primary outcome), in men after at least 12 months of enrollment in a maintenance cardiac rehabilitation program.
2) To examine changes in skeletal muscle strength (as measured by 1-repetition-maximum chest press, seated back row, and knee extension (kg), secondary outcomes) in men after at least 12 months of enrollment in a maintenance cardiac rehabilitation program.
3) To compare these changes to previously published, age-specific, annualized rates of decline.

Hypotheses:

1) It was hypothesized that there would be an initial increase in cardiorespiratory fitness from enrollment in CR, followed by a decline after some unknown point in time due to effects of aging on the cardiovascular system.
2) Based on the literature, it was hypothesized that all three skeletal muscle strength outcomes would increase after enrollment, but decline after some unknown point in time due to the effects of aging.
3) Based on the literature, it was hypothesized that all fitness outcomes would decline over time but at faster rates compared to published rates from the literature.

Study 2: The association of age and initial fitness on changes in fitness with long-term enrollment in cardiac rehabilitation in men: a retrospective study

Objectives:

1) To model the association between age and cardiorespiratory fitness at time of enrollment and changes in cardiorespiratory fitness (VO_2peak, in ml.kg-1.min-1)) in men after at least 12 months of enrollment in a maintenance cardiac rehabilitation program.
2) To model the association between age and skeletal muscle strength at time of enrollment and changes in muscle strength (1-repetition maximum chest press, seated back row, and knee extension (kg)) in men after at least 12 months of enrollment in a maintenance cardiac rehabilitation program.

Hypotheses:

1) It was hypothesized that there would be an association between age and initial cardiorespiratory fitness levels and changes in cardiorespiratory fitness with time, where cardiorespiratory fitness decline at faster rates in older individuals and those with higher initial fitness levels.
2) It was hypothesized that there would be an association between age initial muscle strength levels and changes in muscle strength with time where muscle strength would decline at faster rates in older individuals and those with higher initial strength levels.

<u>Study 3:</u> A retrospective study of early evidence of fitness benefits in women after long-term membership in maintenance-phase cardiac rehabilitation

<u>Objectives:</u>

1) To examine changes in cardiorespiratory fitness (VO_2peak, ml.kg-1.min-1), in women after at least 12 months of enrollment in a maintenance cardiac rehabilitation program.
2) To examine changes in skeletal muscle strength (as measured by 1-repetition-maximum chest press, seated back row, and knee extension (kg), secondary outcomes) in women after at least 12 months of enrollment in a maintenance cardiac rehabilitation program.

<u>Hypotheses:</u>

1) It was hypothesized that there would be an initial increase in cardiorespiratory fitness from enrollment in CR, followed by a decline after some unknown point in time due to effects of aging on the cardiovascular system.
2) It was hypothesized that all three skeletal muscle strength outcomes would increase after enrollment, but decline after some unknown point in time due to the effects of aging.

1.8 Implications

Long-term, maintenance-phase CR programs that extend beyond 12 months in duration are available in some communities, but unlike the strong body of literature supporting improvements in fitness after short-term CR programs, research related to the effectiveness of long-term programs is scarce. The findings from this thesis will contribute new knowledge with respect to long-term changes in CRF and skeletal muscle strength that may occur from enrollment in long-term CR, which may be protective against mortality and recurrent events in the high-risk CVD population.

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CHAPTER 2

LONG-TERM ENROLLMENT IN CARDIAC REHABILITATION BENEFITS CARDIORESPIRATORY FITNESS AND SKELETAL MUSCLE STRENGTH IN MEN WITH CARDIOVASCULAR DISEASE: A RETROSPECTIVE STUDY

2.1 Abstract

BACKGROUND: Despite known associations between fitness and recurrent cardiovascular events, changes in cardiorespiratory fitness (CRF) and muscle strength with long-term cardiac rehabilitation (CR) have not been extensively examined. The purpose of this study was to: 1) Examine changes in CRF and muscle strength associated with long-term CR program enrollment in men, and 2) Compare these changes to previously published rates of decline (2.0%/year for CRF and 2.36%/year for muscle strength in age-matched individuals without CVD).

METHODS: Data were extracted from the program charts of 160 men (mean ± sd: 64 years ± 9 years) who were enrolled ≥1 year in a maintenance-phase CR program and who completed ≥2 exercise tests. CRF was represented by peak oxygen consumption (VO_2peak, ml/min/kg). Skeletal muscle strength was assessed using one-repetition maximum tests for chest press, seated row, and knee extension. Mixed models analyses with polynomial functions were used to determine changes in CRF (up to 5.5 years) and muscle strength (up to 10 years).

RESULTS: CRF increased non-linearly up to year 3 (minimum-maximum: 0.3-3.2%/year) then declined non-linearly to the 5.5-year endpoint (minimum-maximum: 1.0-2.6%/year). Chest

press and seated row strength declined at <1%/year over 10 years, while knee extension increased non-linearly by 0.2-1.4%/year from baseline until year 4 and then declined non-linearly at 1.0-3.6%/year until the 10-year endpoint. All declines were similar to literature rates.

CONCLUSIONS: These results indicate significant health benefits are associated with maintenance-phase CR programs for men. Enrollment was associated with preserved CRF and lower body muscle strength for 3-4 years.

2.1 Introduction

Although cardiovascular disease (CVD)-related mortality rates have declined since 1950 (WHO, 2010), CVD remains the leading cause of global mortality (Roth et al., 2017) with a high economic burden that will continue to increase with the aging population (Moran et al., 2014). In 2012, 17.5 million (31%) deaths worldwide were attributed to CVD, of which over seven million were from coronary artery disease (Roth et al., 2017). The global cost of CVD was $863B USD in 2010, which is expected to rise to $1.04T USD by 2030 (Bloom et al., 2017).

Although the risk of recurrent events is high among individuals with CVD (Kasassenbrood et al., 2016) cardiac exercise-based rehabilitation (CR) programs are well established, medically-supervised programs for risk factor modification (Anderson et al., 2016). CR can be offered across four phases of recovery (Price et a., 2016; Sears, 2017), from acute and sub-acute phases (Phases 1-2) to outpatient (Phase 3) and maintenance-phase community programs (Phase 4). The risks associated with CR are low and mainly attributed to the acute elevation in adverse event risk associated with exercise, with incidence rates for all adverse events and life-threatening events at 3.13 and 0.23 per 100,000 patient-hours of exercise training, respectively (Saito et al., 2014). Several meta-analyses have established the effectiveness of CR for reducing cardiovascular (Anderson et al., 2016) and all-cause mortality (Taylor et al., 2004) and hospital admissions (Anderson et al., 2016). The exercise training component of CR is effective in improving measures of fitness, including cardiorespiratory fitness (CRF) (Sumide et al. 2009; Ades, 2001; Sandercock, Hurtado, & Cardoso, 2013) and skeletal muscle strength (Nishitani et al., 2013; Yang et al., 2015; Yamamoto et al., 2016). CRF, commonly measured by peak oxygen consumption (VO_2 peak), is considered an important vital sign (Ross et al., 2016; Loprinzi, 2018) and higher CRF is protective against the risk of CVD and all-cause mortality

(Kodama et al., 2009; Martin et al., 2013). CRF declines with age, at a generally accepted rate of 1%/year from age 30 to 80 years (Fleg, 2012). However, longitudinal studies have shown that this rate is different for different age groups (Fleg, 2012; Fleg et al., 2005) where CRF declines at 0.5%/year in adults aged 30-39 years, 1%/year from 40-49 years, 1.6%/year from 50-59 years, 2%/year from 60-69 years, and 2.5%/year in adults 70 years and older (Fleg et al., 2005). Skeletal muscle strength is also associated with the risk of mortality in individuals with CVD (Hulsmann et al., 2004), and is known to decline with age, with little to no change from 40-49 years of age, 1.5%/year decline from 50-59 years, 2%/year decline from 60-69 years, and at least 3%/year from 70 years and over (von Haehling, Morley, & Anker, 2010; Rantanen et al., 1998; Keller & Engelhardt, 2013).

The previous evidence supporting CR has primarily focused on programs <12 months in duration that shown improvements in VO_2peak by 11-35% (Sumide et al., 2009; Sandercock, Hurtado, & Cardoso, 2013; Nishitani et al., 2013; Ades et al., 2001). However, much less is known about the changes in CRF with long-term CR programs despite the importance of long-term fitness in this at-risk population. To date, only two studies have reported changes in CRF with long-term enrollment in CR (Gayda et al., 2006; Belardinelli et al., 2012). Gayda et al. (2006) investigated changes in CRF in 43 adults (38 men and 5 women) with coronary heart disease (mean entry age 72 years) with enrollment in a long-term CR program, which reported an initial increase in METS of 5.4%/year in the first 12 months, and an overall decline by 2.2%/year over a 12-13 year follow-up. Belardinelli et al. (2012) reported a linear 1.5%/year decline in CRF throughout 10 years of CR participation in a cohort of 63 adults (49 men and 14 women) with chronic heart failure only.

The exercise component of CR also provides an opportunity to impact muscular strength after a cardiac event, and studies have shown improvement with short-term exercise interventions (Yamamoto et al., 2016; Fragnoli-Munn, Savage, Ades, 1998; Yang et al., 2015). A recent meta-analysis (22 trials, n=1095) found that 4-28 weeks of resistance training resulted in improved lower and upper extremity muscle strength in individuals with coronary artery disease (Yamamoto et al., 2016). Short-term CR programs (less than 12 months) are effective in improving knee extension strength by 35-39% and bench press by 14% (Fragnoli-Mun, Savage, & Ades, 1998). Changes in muscle strength over time, with longer-term enrollment in CR programs (more than 12 months), have not been previously examined.

The objectives of this study were to 1) Estimate changes in the primary outcome of CRF measured as the change in relative VO_2peak (ml.kg-1.min-1) and the secondary outcomes of upper and lower body muscle strength after at least 12 months of enrollment in a maintenance phase CR program, and 2) Compare these changes to previously published age-specific annualized rates of decline (von Haehling, Morley, & Anker, 2010; Keller & Engelhardt, 2014).

2.3 Methods

This study was a retrospective chart review of data for members in a community-based, maintenance phase, exercise program focused CR program. The study was approved by the Hamilton Integrated Research Ethics Board (#2017-1248).

2.3.1 Study eligibility

Participants' data were included in this analysis if they had VO_2peak data from at least two cardiopulmonary exercise tests (CPET) conducted using matching modalities for each one. Since we were interested in the effects of long-term enrollment in CR, data were only included for individuals with at least 12 months of enrollment.

2.3.2 CR program

This Phase 4 maintenance-phase, exercise-based CR program was offered to community-dwelling individuals ≥18 years old with CVD. Participants were eligible to participate in the program with cardiologist or family physician referral and after completion of a formal CPET. See Appendix 1 for supplemental information regarding participant intake package, health questionnaire, physiotherapist assessment, and exercise log sheets. All participants were considered to be enrolled in this Phase 4 program despite circumstances overlapping with traditional timelines of Phase 2-3 CR (i.e. being less than 6 months post-cardiac event). Moreover, all participants were not receiving Phase 2-3 interventions at time of enrollment.

In this CR program, initial exercise prescriptions were based on the results of CPETs and physical assessments. All members were prescribed a comprehensive program of aerobic and resistance training upon program entry, but the initiation of upper body resistance training was typically delayed by 6-8 weeks in individuals post-surgery. In addition to exercise training, blood pressure was regularly monitored and heart-healthy living education was provided via brochures and knowledge translation seminars.

Members were recommended to attend the program twice weekly and encouraged to exercise three days/week outside the program. They were prescribed 30 minutes of aerobic training at 60-65% of heart rate reserve. For the resistance training component, members were encouraged to perform 1-3 sets of 12 repetitions in all major muscle groups two days/week while being supervised by staff. Resistance training loads were prescribed at 30-40% and 50-60% of 1-repetition maximum (1RM) for upper and lower extremity, respectively.

2.3.3 Outcomes

VO_2peak, the primary outcome, was evaluated from the results of the annual CPETs conducted using cycle ergometry or treadmill. Relative VO_2peak (ml.kg-1.min-1) was measured using indirect calorimetry conducted by a cardiovascular technologist with physician supervision (Ndegwa, 2010). The analysis using absolute VO_2peak (l/min) is included in Tables 1-2 and Figures 1-3 of Appendix 2. Resting and peak heart rate (beats/minute) and systolic and diastolic blood pressure (mmHg), and peak aerobic power (kpm/min) were also assessed. Limiting symptoms (shortness of breath, leg fatigue, and chest pain) were monitored throughout the test.

Skeletal muscle strength assessments were performed on the same day of the annual CPETs, but only by the one testing site that had the necessary assessment equipment (Hydrafitness Omnikinetics Machine, Belton, Texas) (see Appendix 3 for a visual of the equipment). Thus, muscle strength results were only available for a subset of the data (n=70/160, 44%). The Hydrafitness Omnikinetics machine was used throughout the study period and calibration was maintained. 1RM tests for chest press, seated back row, and knee extension were performed.

2.3.4 Data extraction

Data from member files from January 1985 to December 2016 were extracted during the period of January-April 2017 (see Appendix 4 for the data extraction document). Demographic information included age (years), height (cm), weight (kg), date of cardiovascular event or surgical procedure, time-post event (years), reason for enrollment, date of exercise test(s), and duration of enrollment (years). Enrollment was defined as attending at least one exercise session per year within 30 days of recruitment (physician referral, consent, cardiopulmonary exercise testing, and program screening). Exercise data were extracted for all available time points for VO_2peak (ml.kg-1.min-1), and 1RM (kg) for chest press, seated back row, and knee extension. Resting and peak heart rate (bpm) and blood pressure (mmHg), and test modality (treadmill or cycle) were also extracted. Two research assistants who completed training in retrospective chart review at McMaster University assisted with the data extraction. Weekly meetings with research assistants took place to ensure high quality data, and extracted data were reviewed and cross-referenced for errors.

2.3.5 Statistical analysis

All analyses were performed using Stata 14 (StataCorp. 2015. College Station, TX: StataCorp LP). Descriptive statistics (means ±SD) and frequencies (n, %) were used to describe demographic information and baseline characteristics.

After controlling for age, mixed model analyses for longitudinal data were applied to address the relationship between the dependent variables (relative VO_2peak and three muscle strength outcomes: 1RM chest press, seated back row, and knee extension)) and the independent variable (enrollment time (years)). Mixed model analyses are highly flexible and allow for analysis of data with missing data, unequal number of measurements per participant, and varying gaps in time between measurements from participant to participant (Snijders et al., 2012). To build the model according to standard methods of complex multi-level modelling, we first established the relationship between the dependent variable and enrollment time (i.e., linear or non-linear) via lowess curves and mixed model analyses, tested for an interaction between enrollment time and covariate of baseline age and finally, identified random effects and the most appropriate covariance structure. The Bayesian Information Criteria was used to identify the best fitting model.

Age-adjusted annualized rates of change in CRF and muscle strength were calculated and compared to previously published literature rates (-2%/year in VO_2peak (Fleg et al., 2005) and -2.36%/year in muscle strength 1RM chest press, seated back row, and knee extension (von Haehling, Morley, & Anker, 2010; Keller & Engelhardt, 2014)) using one-sample proportion tests. Due to differing fitness declines with each decade of life, the literature comparison rates were weighted to the specific decade-ages of members at CR program entry (i.e. 40's, 50's, 60's, and 70's) (see Appendix 5 for the calculation of this rate).

2.4 Results

A flowchart representing the data extraction and inclusion process is displayed in Figure 2.1. Data from 599 member charts were extracted, and 199 met eligibility criteria. Due to insufficient data for women for the mixed models (n=39, 19.6%), women were not included in the analysis. Thus, relative VO_2peak data from 160 men (160/199; 80.4%) were included for analysis to examine changes in the primary outcome of CRF over time.

Figure 2.1. Flow of data extracted and included in the analysis

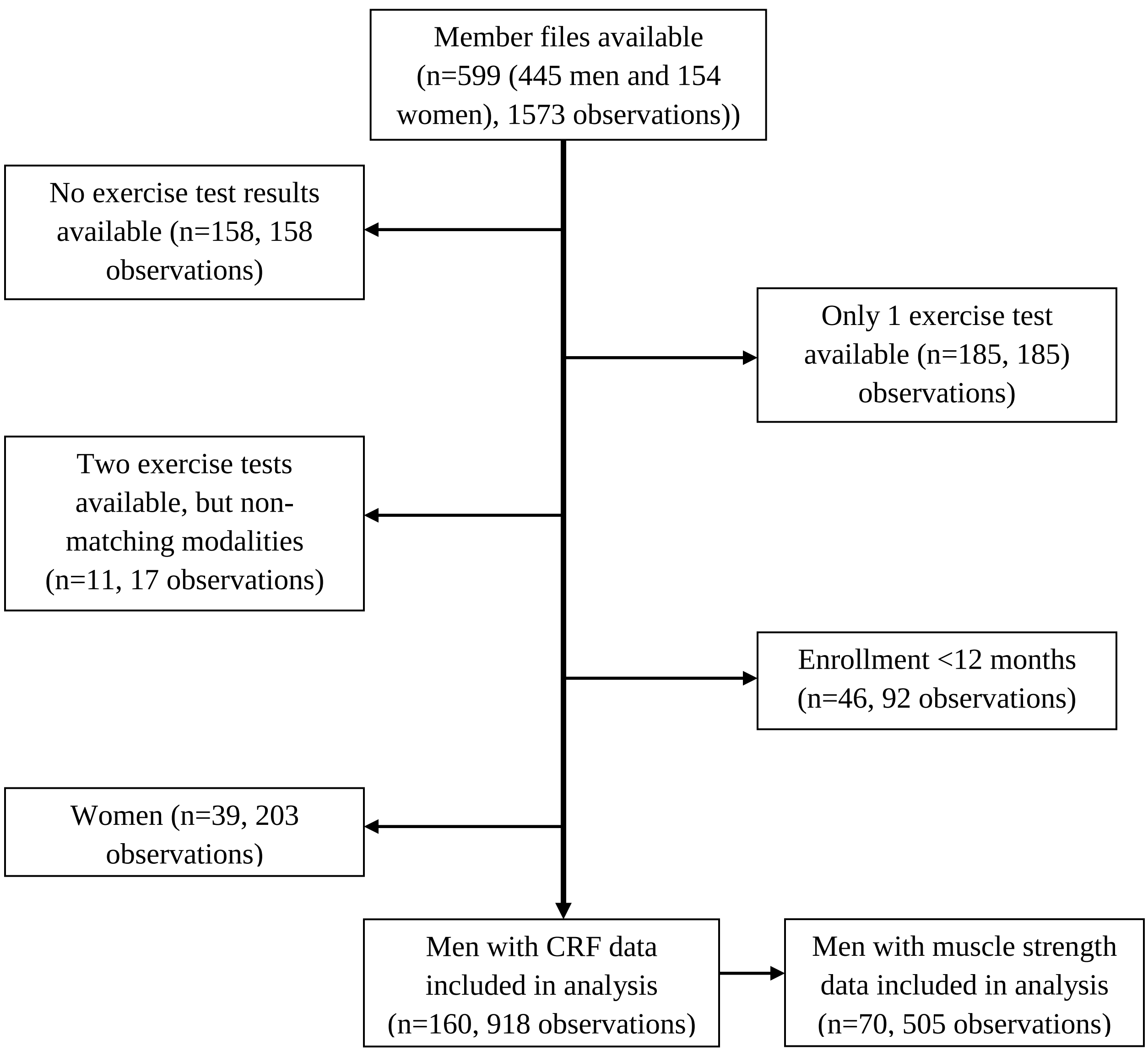


Table 2.1 summarizes the baseline characteristics of the 160 men included in the final analysis. Members started the CR program with an average VO_2peak of 22.7 ml.kg-1.min-1, which is lower than reference values for average men without CVD (varying from 32-34 ml.kg-1.min-1) (Heyward & Gibson, 2014). These reference values are similar to those reported in smaller Canadian studies (Stathokostas et al., 2004).

Table 2.1. Baseline characteristics of 160 men enrolled in the cardiac rehabilitation program

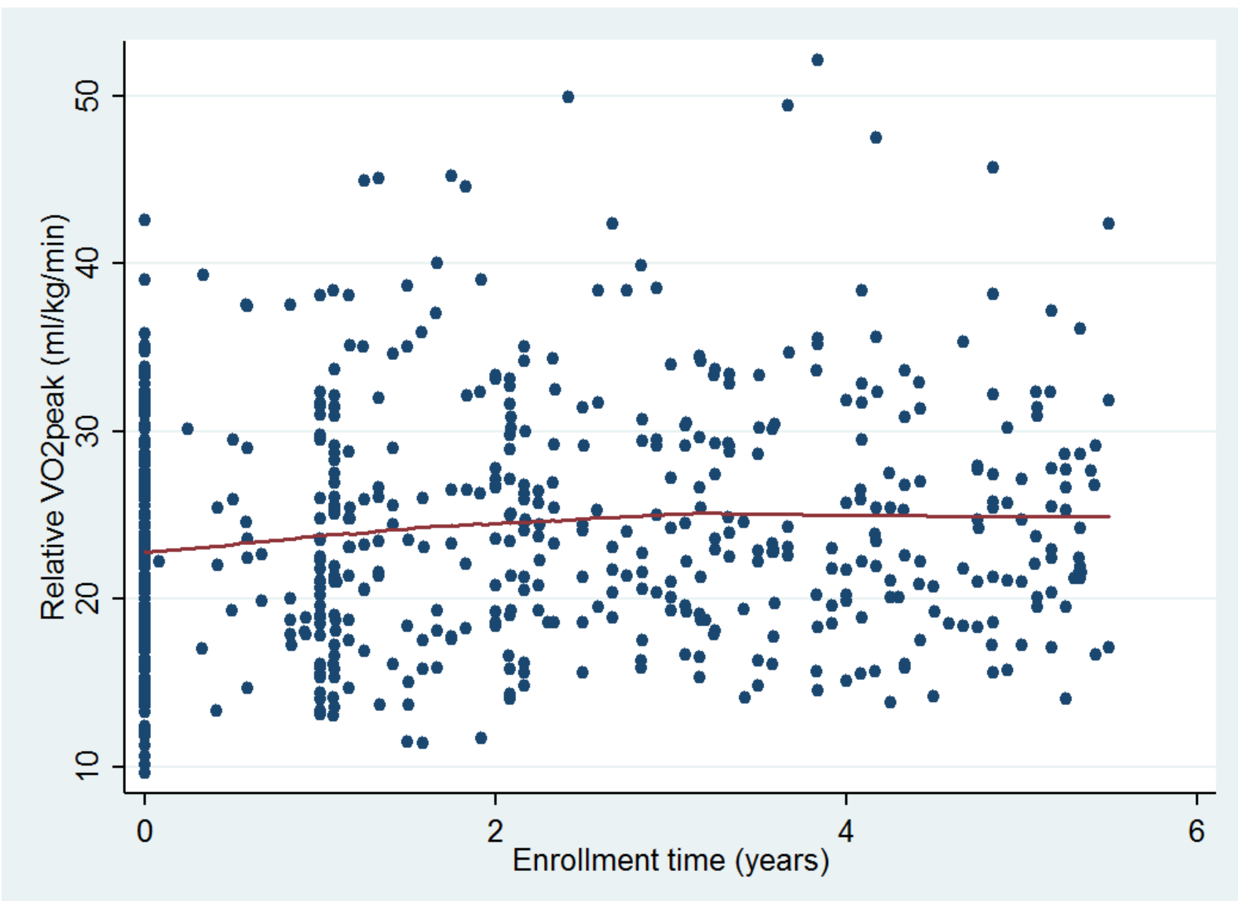
Variable	n	Value
Age (years)	160	64.3 ± 9.3
Weight (kg)	136	83.8 ± 13.1
Height (cm)	137	174.7 ± 7.2
Smoking history: n (%)	73	
Never smoked		23 (31.5)
Ever smoked		50 (68.5)
Reason for enrollment: n (%)	160	
CABG		63 (39.3)
Coronary angioplasty		36 (22.5)
Other heart surgery		9 (5.6)
Myocardial infarction		34 (21.3)
Cardiomyopathy		6 (3.8)
Other		12 (7.5)
Time post-event (years)	152	1.7 (3.0)
Enrollment duration (years)	160	6.6 ± 5.2
Resting heart rate (beats/min)	127	69 ± 12
Resting systolic BP (mmHg)	154	127 ± 18
Resting diastolic BP (mmHg)	154	77 ± 11
Peak heart rate (beats/min)	160	132 ± 23
Peak systolic BP (mmHg)	109	177 ± 32
Peak diastolic BP (mmHg)	108	80 ± 11
Relative VO_2peak (ml.kg-1.min-1)	160	22.7 ± 7.1
% of peak heart rate achieved	160	81 ± 12
Peak aerobic power (kpm/min)	152	915 ± 292
1RM chest press (kg)	70	68 ± 20
1RM seated backrow (kg)	70	54 ± 17
1RM leg extension (kg)	70	57 ± 17

Notes: Continuous variables are presented as means ± standard deviations. Categorical variables are presented as frequencies (percentage). Abbreviations: CABG coronary bypass grafting; BP blood pressure; 1RM one-repetition maximum.

Mean program duration was 6.6 years but upon closer inspection, there were only 37 men (23%) with durations exceeding 10 years for VO_2peak (See Appendix 6 for non-truncated CRF data). As such, there were fewer observations towards the upper limits of enrollment time. Thus, data were truncated at 5.5 years for VO_2peak and 10 years for muscle strength to preserve 75% available data, and improve the generalizability of the mixed models.

Figure 2.2 shows the lowess smoother curve depicting the trajectory of VO_2peak over the truncated 5.5 years of enrollment time. The data show a non-linear increase in VO_2peak from years 0-3 of program enrollment, followed by a non-linear decline beyond 3 years.

Figure 2.2. Trajectory of VO_2peak (n=160 men, 595 observations), truncated at 5.5 years



To capture the polynomial shape of this data, we added a quadratic term in enrollment time ($years^2$) to the mixed model effects. Based on the Bayesian Information Criteria, the polynomial model of years-$years^2$ with random intercepts and slopes best captured the change in VO_2peak over time observed in the lowess curve. Table 2.2 shows age-adjusted, non-linear changes in VO_2peak for the truncated enrollment time (Years 0-5.5) with no observed enrollment time by age interaction. The random effects variance components in this model included a random intercept and slope. Initial CRF levels varied between participants, thus a random intercept was included (variance estimate (SE) 35.1 (4.3), 95% CI 27.6, 44.6). The rate of change in CRF after baseline also varied between participants, and as such, a random slope was included (variance estimate (SE) 0.63 (0.18), 95% CI 0.42, 1.01). Further, a random effect on the $years^2$ term was tested, but found to be non-significant indicating that the growth rate in CRF accelerated and decelerated at a similar rate in all participants (variance estimate (SE) 3.4×10^{-21} (1.4×10^{-20}), 95% CI 1.5×10^{-24}, 8.0×10^{-18}). An independent covariance structure was identified as there was no correlation between the random intercept and random slope in this model.

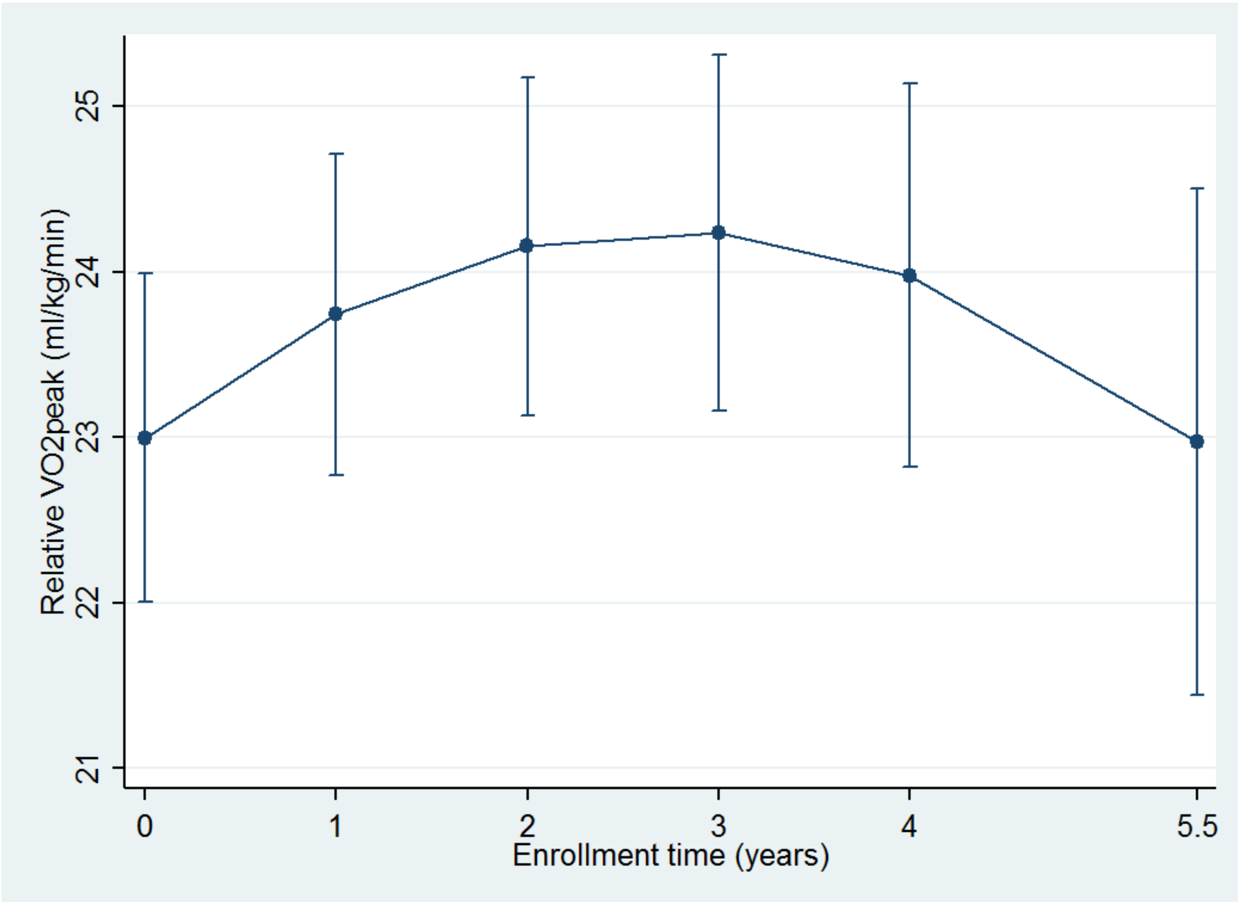
Table 2.2. Mixed model analysis on changes in VO_2peak levels over 5.5 years after controlling for age (n=160, 595 observations)

Fixed and random effects components from 0-5.5 years of enrollment			
Fixed Effects Variables	*β (SE)*	*95% CI*	*p-value*
IV1: Enrollment time	0.912 (0.23)	(0.46, 1.36)	<0.001*
IV2: Enrollment time^2	-0.167 (0.04)	(-0.26, -0.08)	<0.001*
Covariate: Baseline Age	-0.295 (0.05)	(-0.40, -0.19)	<0.001*
Constant	41.9 (3.4)	(35.2, 48.7)	<0.001*
Random Effects Variance Components	*Estimate (SE)*	*95% CI*	
Slope (enrollment time)	0.63 (0.18)	(0.42, 1.01)	
Intercept	35.1 (4.3)	(27.6, 44.6)	
Residual	6.96 (0.56)	(5.9, 8.2)	
Model Fit Statistics	*Statistic*		
Log log likelihood	-1702.5		
Bayesian Information Criteria	3449.7		

Abbreviations: IV independent variable; SE standard error; CI confidence interval;

Figure 2.3 depicts the non-linear changes in VO_2peak over enrollment time, and Table 2.3 compares time interval-specific changes to the literature value of -2%/year (Fleg et al., 2005). CRF increased for the first three years of enrollment, then in Year 3-5.5, CRF declined at rates similar to the literature value.

Figure 2.3. Mixed model graph of predicted VO_2peak trajectory in men



Note: Error bars represent 95% CI

Table 2.3. Computed %/year changes in VO_2peak by enrollment time interval compared to calculated age-specific literature values (-2%/year)

Time	Observed change	Literature value	p-value
0-1 years	+3.2%/year		<0.001*
>1-2 years	+1.7%/year		<0.001*
>2-3 years	+0.3%/year	-2%/year	0.018*
>3-4 years	-1.0%/year		0.212
>4-5.5 years	-2.6%/year		0.298

Comparison value from Fleg et al. (2005)

Figures 2.4-2.6 depict the lowess smoother curves that were used to determine the trajectory of the change in 1RM chest press, seated back row, and knee extension (see Figures 1-

3 of Appendix 7 for the non-truncated muscle strength data). Both chest press and seated back row showed a relatively linear decline over enrollment time, whereas knee extension showed a more pronounced quadratic relationship.

Figure 2.4. Trajectory of 1-repetition maximum chest press in 70 men (n=411 observations), truncated at 10 years

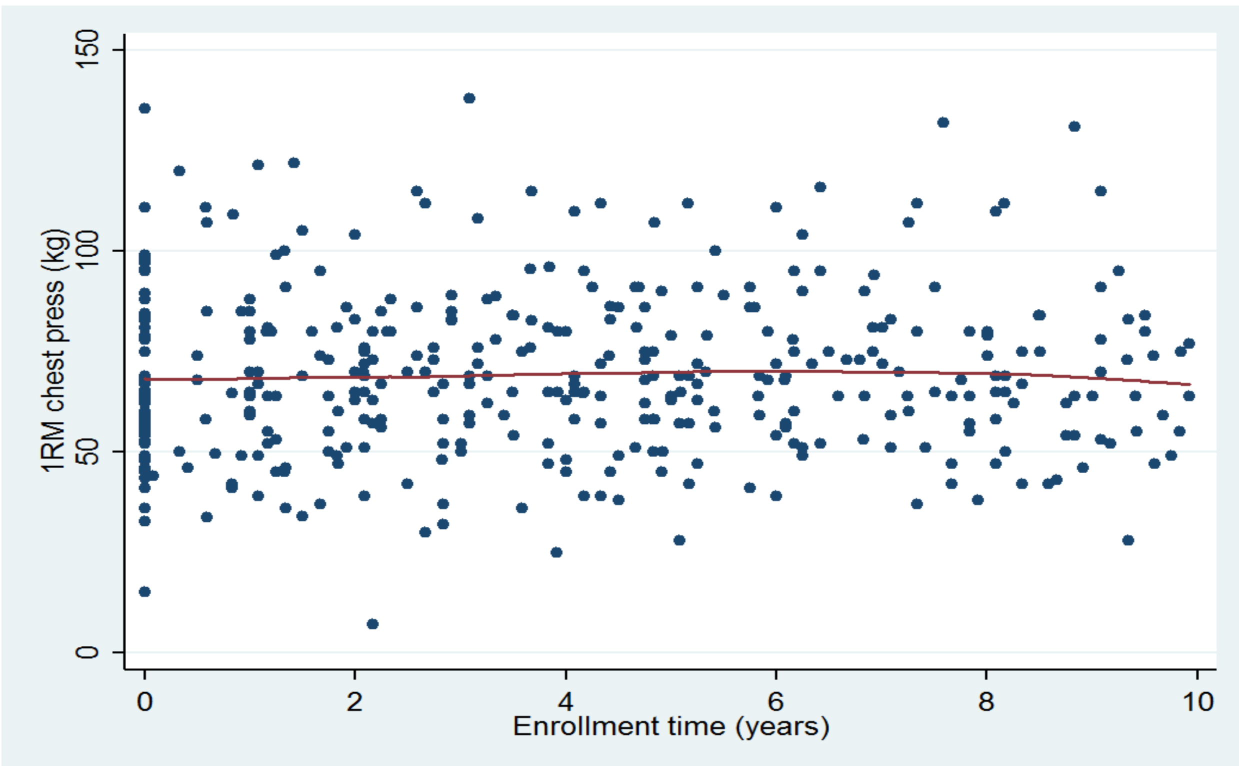


Figure 2.5. Trajectory of 1-repetition maximum seated back row in 70 men (n=411 observations), truncated at 10 years

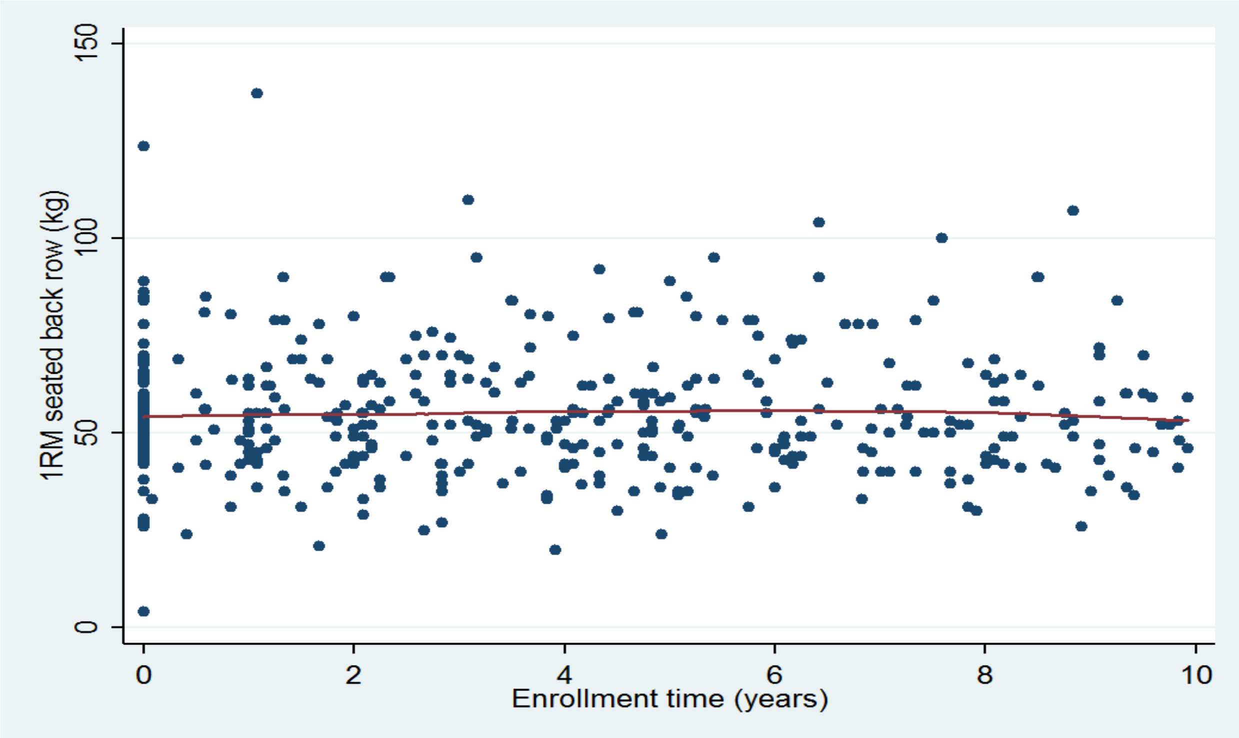


Figure 2.6. Trajectory of 1-repetition maximum knee extension in 70 men (n=408 observations), truncated at 10 years

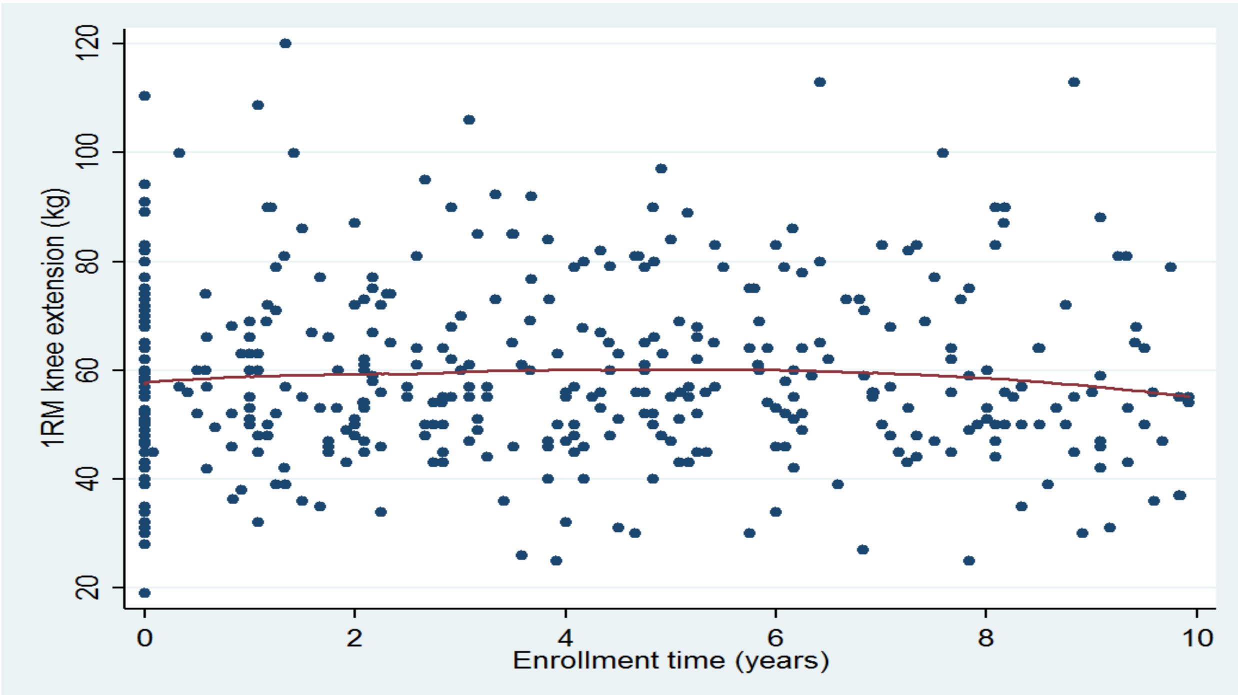


Table 2.4 presents mixed models results for these changes in 1RM chest press and seated back row using a random intercept model only. The rates of decline were lower, but not significantly different, compared to previously published rates (chest press: -0.65 vs. -2.36%/year, p=0.174; seated back row: -0.55%/year vs. -2.36%/year, p=0.161) (see Figure 2.8 and Table 2.5).

Table 2.4. Mixed model analysis on changes in muscle strength over 10 years of program members, after controlling for age (n=70, 411 observations)

Fixed and random effects components from 0-10 years of enrollment			
1. Chest press			
Fixed Effects Variables	*β (SE)*	*95% CI*	*p-value*
IV: Years	-0.448 (0.18)	(-0.79, -0.10)	0.011*
Covariate: Baseline Age	-1.21 (0.22)	(-0.1.63, -0.80)	<0.001*
Constant	146 (13)	(119, 173)	<0.001*
Random Effects Variance Components	*Estimate (SE)*	*95% CI*	
Intercept	203 (38)	(141, 295)	

Residual	94.0 (7.2)	(81, 109)	
Model Fit Statistics	*Statistic*		
-2 log likelihood	-1604.8		
Bayesian Information Criteria	3245.6		
2. Seated Back Row			
Fixed Variables	*β (SE)*	*95% CI*	*p-value*
IV: Years	-0.310 (0.15)	(-0.61, -0.01)	0.041*
Covariate: Baseline Age	-0.945 (0.17)	(-1.28, -0.61)	<0.001*
Constant	116 (11)	(94, 138)	<0.001*
Random Effects Variance Components	*Estimate (SE)*	*95% CI*	
Intercept	131 (24)	(91, 190)	
Residual	70.3 (5.4)	(61, 82)	
Model Fit Statistics	*Statistic*		
-2 log likelihood	-1540.4		
Bayesian information criteria	3110.9		
3. Knee extension			
Fixed Effects Variables	*β (SE)*	*95% CI*	*p-value*
IV1: Years	1.17 (0.41)	(0.36, 1.98)	0.007*
IV2: $Years^2$	-0.177 (0.04)	(-0.26, -0.09)	<0.001*
Covariate: Baseline Age	-0.960 (0.18)	(-1.32, -0.60)	<0.001*
Constant	120 (12)	(97, 143)	<0.001*
Random Effects Variance Components	*Estimate (SE)*	*95% CI*	
Intercept	151 (28)	(104, 218)	
Slope (years)	0.67 (0.35)	(0.25, 1.8)	
Residual	46.2 (4.0)	(39, 55)	
Model Fit Statistics	*Statistic*		
Log likelihood	-1477.5		
Bayesian Information Criteria	2997.1		

Abbreviations: IV independent variable; SE standard error; CI confidence interval

Figure 2.8. Mixed model graph of predicted trajectories in 1-repetition maximum muscle strength outcomes in men

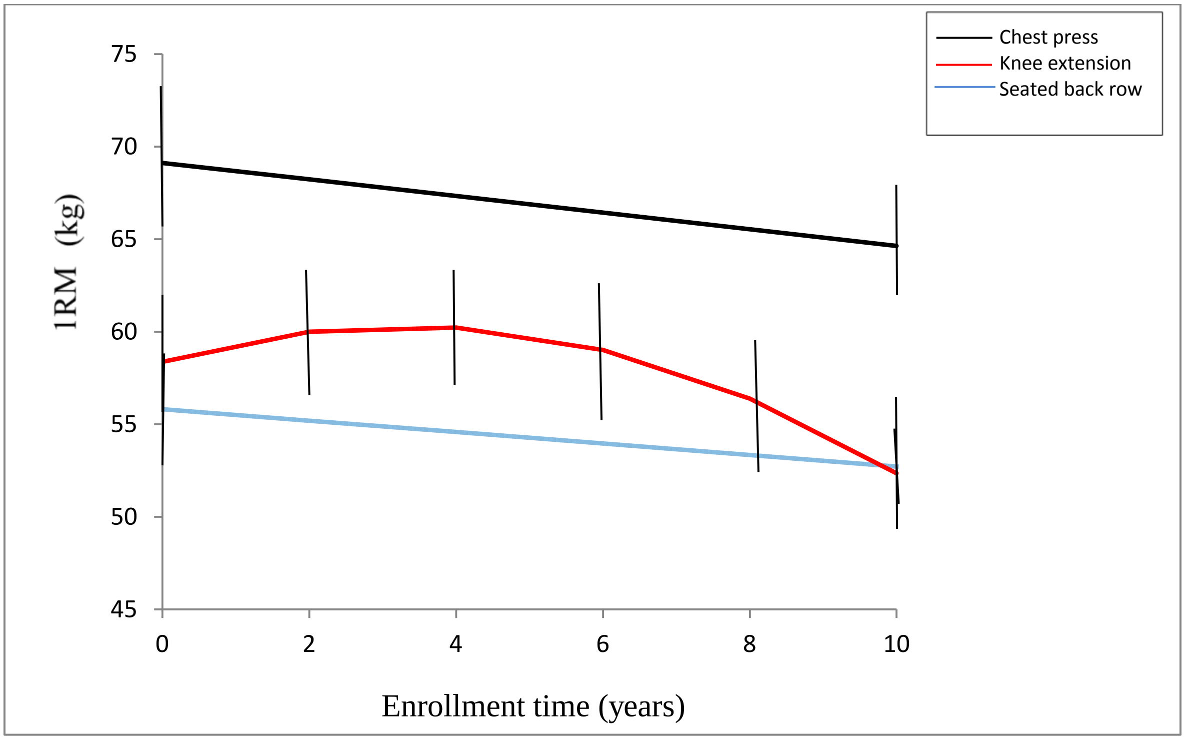


Table 2.5. Computed %/year changes in 1-repetition maximum muscle strength outcomes compared to calculated age-specific literature value (-2.36%/year)

Time	Observed change	Literature value	p-value
Chest press			
0-10 years	-0.7%/year	-2.36%/year	0.174
Seated Back Row			
0-10 years	-0.6%/year	-2.36%/year	0.161
Knee extension			
0-2 years	+1.4%/year	-2.36%/year	0.020*
>2-4 years	+0.2%/year		0.081
>4-6 years	-1.0%/year		0.227
>6-8 years	-2.2%/year		0.468
>8-10 years	-3.6%/year		0.251

Comparison rates from von Haehling, Morley, & Anker (2010) and Keller & Engelhardt (2014).

In contrast to upper body strength outcomes, a non-linear change in knee extension strength was observed over time, expressed as a function of years-years^2 (Table 2.4 and Figure 2.4). In this model, we identified a random intercept and random slope with an independent covariance structure. Knee extension strength showed an increase in the first four years of enrollment, followed by a decline at rates similar to those previously published (Table 2.5).

2.5 Discussion

Our retrospective analysis of long-term CR demonstrates that enrollment in a structured maintenance-phase, exercise-focused CR program, with individualized exercise prescriptions and supervision by trained staff, is associated with improved trajectories of change in fitness compared to previously published rates of decline in men. These findings support the use of long-term exercise opportunities as strategies for secondary CVD risk prevention in this high-risk population.

2.5.1 Limited research in long-term cardiac rehabilitation programs

There is a strong body of evidence supporting short-term (≤12 months) enrollment in CR programs for increasing CRF (Sumide et al., 2009; Ades, 2001; Sandercock, Hurtado, & Cardoso, 2013) and skeletal muscle strength (Nishitani et al., 2013; Yang et al., 2015; Yamamoto et al., 2016), but a paucity of analogous research for long-term enrollment in CR programs. Only one previous study to date has provided evidence of maintained fitness levels with long-term CR (Gayda et al., 2006). The lack of studies examining long-term CR may be attributed to the methodological challenges of conducting longitudinal research, but may also be a product of the barriers to CR service provision and low numbers. Low physician referrals, lack of financial assistance, and lack of available and accessible programs in the community have been contributed to low CR enrollment and utilization (Grace et al., 2012; Brady, Purdham, Oh, & Grace, 2012; Mampuya, 2012). Low rates of physician referrals are an important factor, whereby referral rates range from 30-52% in Canada (Aragam et al., 2011; Brady, Purdham, Oh, & Grace, 2012). Even among individuals who receive referrals to CR, less than 50% carry through to enroll in these programs (Grace et al., 2011) with one Ontario study citing a 22% enrollment rate (Swabey, Suskin, Arthur, & Ross, 2004). These low numbers in early phases of

CR can lead to even lower enrollment rates in maintenance-phase programs as fewer individuals can be followed over the long-term. Consequently, there is little research available on longer term outcomes of these programs. With early phases of CR typically lasting five months (Leon et al., 2005) the transition to maintenance-phase CR programs is critical for maintaining healthy, active lifestyles and thereby lowering the risk of future CVD events and mortality.

2.5.2 Effects of exercise-based cardiac rehabilitation programs on fitness

The current study offers novel insight into changes in CRF and skeletal muscle strength. Specifically, we were able to identify non-linear trajectories of change in some outcomes. We observed increases in CRF and lower body muscle strength (knee extension) for three and four years of program enrollment, respectively. These results suggest that the initial years of exercise-based CR programs may successfully counteract the expected age-related declines in fitness in individuals with CVD. Research shows cardiovascular and musculoskeletal system function diminishes with age, including reduced peripheral oxygen utilization and skeletal muscle oxidative capacity, reduced cardiac output and maximum heart rate (Betik & Hepple, 2008; Fleg, 2012) and sarcopenic muscle fibre loss and atrophy, decreased testosterone, and increased catabolic hormones (Zatsiorsky & Kreamer, 2008; Sharkley & Gaskill, 2007; Doherty, 2003). However, exercise improves fitness by improving coronary artery blood flow (Bruning & Sturek, 2015) via increased coronary artery compliance, endothelial-dependent vasodilation, and angiogenesis (Laughlin, Otman, & Bowles, 1998). Exercise-related preservations in muscle strength may be due to improved protein turnover, blood flow, and oxidative capacity of the working skeletal muscles, and reduced endothelial dysfunction and expression of myostatin (Yamamoto et al., 2016; Ades et al., 1996).

In addition to physiological mechanism, the influence of socio-psychological determinant of participation in CR programs must not be overlooked. Data from Brady, Thomas, Nolan, & Brooks (2005) identified location of residence, urbanicity, education level, and exercise self-efficacy as key social factors in CR enrollment and participation. These data were not available in the current study, but should inform future long-term CR programs to address. Indeed preserving CRF and muscle strength in CVD populations are important to reduce the risk of disease progression (Leon et al., 2000) mortality, and future CVD events (Kodama et al., 2009; Martin et al., 2013).

Of note, this study is the first to report that the CRF increased non-linearly up to three years of enrollment time. In contrast, Gayda et al. (2006), in a pre-post design, and reported a linear 2.2%/year decline in CRF. Arguably, the rate cited by Gayda et al. was under-estimated as the calculation included the initial 5.4% increase observed in the first year of their study. The current study adds to this previous work by including a larger sample size, more CRF assessment time points using the superior method of peak oxygen uptake with indirect calorimetry, and using mixed model analyses to account for random effects estimates and non-linear trajectories. Taken together, both of these studies suggest that it is important to use strategies to maintain exercise and physical activity behaviours in individuals with CVD over the long-term, which may translate into reduced mortality and improved quality of life in high-risk CVD populations (Kodama et al., 2009; Martin et al., 2013).

The comparison rates for changes in fitness from the literature were based on values observed in adults without history of CVD (Fleg et al., 2005; von Haehling, Morley, & Anker, 2010; Keller & Engelhardt, 2014) as there are no established analogous rates available in CVD populations. We postulated that at minimum, these comparisons would be conservative, as it is known that individuals with CVD engage in less physical activity and more sedentary behaviors and thus are less fit than their non-CVD counterparts (Gayda et al., 2006; Mora et al., 2007). Although early reports found faster rates of decline in CRF among individuals with CVD who were physically inactive compared to those who were active (Dehn & Bruce, 1972), more recent evidence suggests that there may be little association between physical activity levels and rate of change in CRF (Fleg et al., 2005; Stathokostas et al., 2004; Jackson, Sui, Hebert, Church, & Blair, 2009). A cohort study of 810 adults found that while higher levels of CRF were observed in those with higher self-reported physical activity at any given age, the rate of decline over 7.9-year follow up was the same across all physical activity groups (Fleg et al., 2005). Another cohort study (n=62) found that physical activity accounted for a small fraction of the changes observed in CRF over a 10-year follow-up, suggesting that the decline seen with aging is not simply due to reduced physical activity levels (Stathokostas et al., 2004). Thus, despite typically lower levels of physical activity observed among individuals with CVD, the comparison rates taken from the non-CVD literature would likely be similar.

2.5.3 Study limitations and strengths

The retrospective design of the current study prevented the examination causal links and mechanisms for the observed changes in fitness with program enrollment, or for insights to be gained through program attendance and physical activity records as this information was not available. There was a smaller sample size for muscle strength outcomes which somewhat limits the generalizability of these findings. However, the dataset provided a high number of observations over multiple time-points, thereby permitting mixed effects model analyses, and adding novel insights that were not possible in previous studies that used pre-post measurement designs. The current study analysis allowed for identification of random effects and a method of modeling a more complete picture of the non-linear changes over time, thus improving the interpretability and generalizability of the observations and conclusions.

2.5.4 Study conclusions

This was the first study to report increases in both CRF and muscular strength during the first several years of long-term, maintenance-phase CR program enrollment in men, and subsequent rates of decline that were comparable to, or slower than, age-adjusted literature values. Prospective cohort studies are warranted to confirm the observations, and to identify potential mechanisms underlying these changes.

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CHAPTER 3

THE ASSOCIATION OF AGE AND INITIAL FITNESS ON THE CHANGES IN FITNESS WITH LONG-TERM ENROLLMENT IN CARDIAC REHABILITATION IN MEN: A RETROSPECTIVE STUDY

3.1 Abstract

BACKGROUND: Cardiac rehabilitation (CR) programs provide important opportunities for individuals with cardiovascular disease to improve fitness and thus reduce the risk for recurrent events and mortality. The impact of age and initial fitness on trajectories of fitness with long-term CR has not been investigated, but may provide insight into the effects of exercise-based strategies for cardiovascular populations at different ages and starting fitness levels. The purpose of this retrospective study was to model the association of the baseline age and fitness on the changes in cardiorespiratory fitness (CRF) and skeletal muscle strength with long-term enrollment in CR in men.

METHODS: Data were extracted from program charts of 160 men (mean age 64 years) who were enrolled ≥1 year in a long-term, maintenance-phase CR program and who completed ≥2 cardiopulmonary exercise tests. CRF was represented by peak oxygen consumption (VO_2peak, ml.kg-1.min-1) and skeletal muscle strength was assessed using one-repetition maximum tests for chest press, seated row, and knee extension (kg). Mixed model analyses were used to model trajectories of CRF and muscle strength and their interactions between enrollment time, age, and initial fitness levels. Data were truncated at 5.5 years for CRF and 10 years for muscle strength in order to preserve ≥70% data and improve generalizability of the results.

RESULTS: In all models, enrollment time by age and enrollment time by initial fitness interactions were observed. Greater initial improvements and slower declines in fitness were observed in younger individuals and among those with low initial fitness (among low fitness: +7.6% to +1.3/year in age 50-59 years, +5.8 to 0% in age 60-69 years, and +3.9 to -1.8% in age 70-79 years; among high fitness: +2.8 to -0.8% in 50-59, +1.7 to -2%% in 60-69, and -0.5 to -3.3% in 70-79). An interaction was observed between age and initial fitness in models for CRF and back row muscle strength, where the differences in CRF and back row were increasingly larger over time between younger and older individuals who were fit at baseline in comparison to those with low initial fitness.

CONCLUSIONS: The benefits of long-term enrollment in CR on cardiorespiratory and musculoskeletal fitness are associated with baseline age and fitness levels. Importantly, fitness levels are higher at all time points among those with higher levels of baseline fitness regardless of age, compared to those with lower starting fitness. The importance of age and initial fitness levels extends beyond short-term exercise training programs in men with CVD.

3.2 Introduction

Over 422 million people are living with cardiovascular disease (CVD) worldwide (Roth et al., 2017). It is the leading cause of global mortality, currently accounting for 18 million or 33% of deaths and projecting to increase to over 22 million by 2030 (Roth et al., 2017). CVD remains a large economic burden, costing the global economy $863B USD (Bloom et al., 2017) and is projected to increase by 21% to $1.04T USD by 2030 (Bloom et al., 2017; Moran et al., 2014). CVD accounts for over 30% of the total global burden of disease in adults aged 60 years and older, the highest of all chronic diseases in older adults (Prince et al., 2015). In fact, over 80% of CVD-related deaths occur in adults aged 65 years and above, and the prevalence of hypertension, coronary heart disease, and heart failure is 40% in adults 40-59 years, but increases to 70-75% in 60-79 years and over 80% in 80 years and older (Lloyd-Jones et al., 2009).

Cardiac rehabilitation (CR) programs offer important opportunities for risk factor modification that can lower the burden of CVD by reducing cardiovascular (Anderson et al., 2016) and all-cause mortality (Taylor et al., 2004), and hospital admissions (Anderson et al., 2016). With exercise training as the core component of CR, these programs are effective in improving measures of fitness, including cardiorespiratory fitness (CRF) (Sumide et al., 2009; Sandercock, Hurtado, & Cardoso, 2013; Ades, 2001) and skeletal muscle strength (Nishitani et al., 2013; Yang et al., 2015; Yamamoto et al., 2016; Fragonli-Munn, Savage, & Ades, 1998), both of which are protective against CVD progression and all-cause mortality (Kodama et al., 2009; Martin et al., 2013; Celis-Morles et al., 2018).

CR programs were originally created to provide aerobic exercise training opportunities for younger and middle-aged adults, and solely after myocardial infarction or coronary artery bypass surgery (Schopfer & Forman, 2016). CR has since evolved and expanded to not also address and mediate challenges experienced by the large growing population of older adults with CVD, but also include a broader range of CVD common in older adults, including heart failure and valvular heart diseases.

It is known that fitness is lower in older adults with CVD compared to their younger counterparts (Anderson et al., 2016; Sumide et al., 2009; Laddu et al., 2018; Balady et al., 1996) and that fitness declines a faster rates in older adults compared to younger adults: >2%/year in those ≥60 years of age vs. 1-1.5%/year in those 40-59 years of age (Fleg et al., 2005; Jackson et al., 2009). Low fitness in older adults is a result of reduction in cardiovascular and physiological adaptability in response to exercise training (Sandercock, Hurtado, & Cordoso, 2013; Laddu et al., 2018) and historically, the extent to which exercise could improve fitness in older adults was thought to be limited due to their advanced age, presence of co-morbidities, and reduced ability to exercise at higher intensities (Fleg, 2012). In fact however, there is an extensive body of evidence of improvements in fitness following <12 months of exercise training in older adults (Seals et al., 1984; Vaitkevicius et al., 2002; Huang et al., 2005) and older CVD populations (Rees, Taylor, Singh, Coats, & Ebrahim, 2004; Laddu et al., 2018; Balady et al., 1996; Ades, Waldman, & Gillespie, 1995; Lavie & Milani, 1993). Improvements in fitness in older adults, especially in those with CVD, carry great functional importance because of the additive effects of aging and cardiovascular pathology on physical capacity and exercise training (Fleg, 2012). CR programs now provide a broader repertoire of exercise interventions, targeting muscle strength and balance as efforts to reduce aging-related vulnerabilities co-existing with CVD, such as frailty, falls, and disability (Schopfer & Forman, 2016).

The impact of initial fitness levels on changes in fitness following exercise training is critical to consider. Studies have shown that baseline levels of CRF was associated with mortality risk (Myers et al., 2002; Martin et al., 2013) and low physical function (Forman et al., 2017; Fletcher et al., 1995). Moreover, it is the strongest predictor of improvements in VO_2peak, where lower fitness levels were associated with greater improvement (Vaitkevicius et al., 2002; Laddu et al., 2018; Balady et al., 1996). After 10 weeks of CR, Balady et al. (1996) reported a 4.2-metabolic equivalent (MET) improvement in CRF in individuals with low baseline fitness (<5 METs), almost two-fold higher than those with fitness ≥5 METs. In a retrospective analysis of 10,700 adults with CVD who completed a 12-week CR program, Laddu et al. (2018) found that individuals with the lowest initial fitness (<5 METs) improved the most (by 1.3 METs or 35% from baseline) compared to those with higher fitness (improvements by 0.77-1.03 METs or 8-12% from baseline). While the lowest fitness group was the oldest, it also had higher prevalence of modifiable risk factors, co-morbidities, and more severe cardiac events (Laddu et al., 2018). These results are clinically significant given that individuals with CVD who have low CRF, regardless of age, have the greatest potential to increase physical function and reduce the risk of mortality after CR programs (Martin et al., 2013; Forman et al., 2017).

To date, two studies have focused on changes in fitness with long-term CR (Gayda et al., 2006; Belardinelli et al., 2012). Gayda et al. (2006) reported a 2.2%/year decline in METs over 10 years in a sample of older adults with a mean age of 72 years at entry, but this was under-estimated because the authors included the observed 5.4% increase within the first 12 months of enrollment in their calculation. Belardinelli et al. (2012) reported a 14.7% increase in CRF within 12 months, followed by a plateau up to 3 years, and a decline of 1.3%/year in 63 adults (mean age of 60 years) with recent diagnosis of chronic heart failure who enrolled at <5 METs, a threshold for increased risk of both mortality (Myers et al., 2002; Martin et al., 2013) and low physical function (Forman et al., 2017; Fletcher et al., 1995). There have been no studies that have examined the effects of initial fitness levels or aging on trajectories of CRF and muscle strength with long-term CR. Examining changes in long-term fitness across a broader range of age groups, cardiovascular diagnoses, and initial fitness levels can help identify potential differences in fitness trajectories and provide insight into the interaction between aging and exercise training in the CVD population.

The objective of this study was to model the association between the dependent variables of CRF (primary outcome) and skeletal muscle strength (secondary outcome) and independent variables of age at time of enrollment in long-term CR and initial CRF and muscle strength levels and in men following at least 12 months of enrollment. Based on previous literature that has reported accelerated declines in fitness with aging (Fleg et al., 2005; Keller & Engelhardt, 2013; von Haehling, Morley, & Anker, 2010) and greater improvements in fitness among individuals with lower initial fitness levels (Laddu et al., 2018; Balady et al., 2996), we hypothesized: 1) faster declines in CRF and muscle strength over enrollment time in older compared to younger adults, and 2) larger improvements and slower declines in CRF and strength in individuals with lower initial fitness levels compared to those with higher initial fitness.

3.3 Materials and Methods

This study was a retrospective chart review of data for members in a community-based, maintenance-phase CR program. The study was approved by the Hamilton Integrated Research Ethics Board (#2017-1248).

3.3.1 Study Eligibility

In order to examine changes in fitness over long-term enrolment in CR, Participants' data were included if they were enrolled for at least 12 months and had CRF data from at least two cardiopulmonary exercise tests (CPET).

3.3.2 Cardiac Rehabilitation Program

This maintenance-phase, exercise-based CR program was offered to community-dwelling individuals at least 18 years old with CVD. See Appendix 1 for supplemental information regarding participant intake package, health questionnaire, physiotherapist assessment, and exercise log sheets. Individuals were referred to the program by their cardiologist or family physician, and were required to complete a formal CPET prior to commencing in the program. Exercise prescription was individualized for each participant, developed based on the results of the CPET and physical assessments. Minor adjustments to the intensity and duration of exercise prescriptions were made over time as needed to accommodate for changes in health, fitness, and functional capacity. All members were prescribed a comprehensive program of aerobic training immediately upon program entry, but the initiation of upper body resistance training may have been delayed by 6-8 weeks in some individuals to allow sufficient time for healing and recovery following cardiac surgery.

Members were recommended to perform both aerobic and resistance training components at the program facility two times per week under staff supervision and encouraged to exercise outside the program as well. They were prescribed at least 30 minutes of aerobic training at 60-65% of heart rate reserve 3-5 days/week. Resistance training was prescribed twice weekly at 1-3 sets of 12 repetitions in all major muscle groups 30-40% and 50-60% of 1-repetition maximum (1RM) for upper and lower extremity, respectively.

Additionally, the program included regular blood pressure monitoring and education regarding heart-healthy living through educational brochures and knowledge translation seminars.

3.3.3 Cardiorespiratory Fitness and Skeletal Muscle Strength Outcomes

Assessments of VO_2peak, the primary outcome, were conducted annually at two testing sites. Testing equipment and protocols for VO_2peak assessment were standardized between the two sites. Medications were not withheld. VO_2peak (ml.kg-1.min-1) was measured using indirect calorimetry on the Ergoline cycle ergometer, and conducted by a cardiovascular technologist with physician supervision. The workload started at 100 kpm/min and increased by increments of 100 kpm/min every minute, where the average of the highest values of oxygen consumed over a 15 second period represented VO_2peak. Resting and peak heart rate (beats/minute) and systolic and diastolic blood pressure (mmHg), and peak aerobic power (kpm/min) were also assessed.

One of the testing sites was also equipped with equipment to assess muscle strength. Thus, strength results were available for a subset of the CRF data (n=70/160, 44%). Skeletal muscle strength assessments were performed 30-60 minutes before VO_2peak assessments. 1RM chest press, seated back row, and knee extension were assessed using standardized protocol and performed in a seated position on the Hydrafitness Omnikinetics strength machine (Hydrafitness Omnikinetics, Belton, Texas). The technician demonstrated the exercise motions, monitored the participant's form and effort, and adjusted the weight accordingly to achieve the highest lift (see Appendix 3 for a visual of the equipment). The Hydrafitness Omnikinetics machine was used throughout the study period and calibration was maintained.

3.3.4 Data extraction

Data from program member files dating from January 1985 to December 2016 were extracted during the period of January-April 2017 (see Appendix 4 for the data extraction document). Demographic information were extracted including age (years), height (cm), weight (kg), date of cardiovascular event or surgical procedure, time-post event (years), reason of enrollment, date of exercise test, and duration of enrollment (years). Fitness data were extracted for all available time points for VO_2peak (ml.kg-1.min-1), and 1RM (kg) for chest press, seated back row, and knee extension. Resting and peak heart rate (beats/minute) and blood pressure (mmHg) were also extracted. Two research assistants who completed training in retrospective chart review at McMaster University assisted with the data extraction. Weekly meetings with research assistants took place to ensure high quality data, and extracted data were reviewed and cross-referenced for errors.

3.3.5 Statistical Analysis

All analyses were performed using Stata 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). Descriptive statistics (means ±SD) and frequencies (n, %) were used to describe demographic information and baseline characteristics.

Mixed model analyses were applied to model the associations between the independent variables (age at enrollment and initial CRF levels) on changes in the dependent variables over enrollment time (relative VO_2peak for CRF (ml.kg-1.min-1), and 1RM chest press, seated back row, and knee extension for muscle strength (kg)). We also repeated the analysis of CRF using absolute VO_2peak (l/min); these results are presented in Tables 1-2 and Figures 1-3 of Appendix 8. Mixed model analyses are highly flexible and allow for analysis with missing data, unequal number of measurements per participant, and varying gaps in time between measurements from participant to participant (Snijders et al., 2012). To build the models according to standard methods of complex multi-level modelling, we first established the relationship between the dependent variables and the first independent variable enrollment time (i.e. linear or non-linear) via lowess smoother curves and mixed model analyses.

Secondly, we tested for 3-way interaction (Enrollment time X Age X Initial fitness) despite being underpowered, and for 2-way interactions between the independent variables (Enrollment time X Age, Enrollment time X Initial fitness**,** Age X Initial fitness) on changes in CRF and muscle strength. Since the literature has shown that declines in fitness accelerate with aging (Fleg et al., 2005; Jackson et al., 2009; von Haehling, Morley, & Anker, 2010; Keller & Engelhardt, 2013), and that individuals with lower initial fitness levels benefit more from exercise than those with higher initial fitness (Laddu et al., 2018; Balady et al., 1996), the interaction terms of Enrollment time X Age and Enrollment time X Initial fitness were of primary concern and maintained in the model regardless of statistical significance. There is no available literature to support or deny an Age X Initial fitness interaction, thus this was an exploratory secondary interaction.

Lastly, we identified relevant random effects and the most appropriate covariance structure after removing outlying observations with high influence (identified by residual plots). The log likelihood tests and Bayesian Information Criteria were used to identify the best fitting models. The analyses were performed with all participants, but interaction graphs were created to display trajectories for men from 50-79 years of age only, since participants from 40-49 and from >80 years of age represented a small (5-6%) proportion of the sample). Initial fitness levels were entered into the models as continuous variables, but values of 17.5 ml.kg-1.min-1 and 28.0 ml.kg-1.min-1 were selected to represent low and high initial CRF levels respectively for the interaction graphs. The value of 17.5 ml.kg-1.min-1 (or 5 METs) was chosen based on previous literature showing increased risk of mortality (Myers et al., 2002; Martin et al., 2013) and low physical function (Forman et al., 2017; Fletcher et al., 1995), while the value of 28 ml.kg-1.min-1 (or 8 METs) represents high fitness in aging population from these data. These values also coincided with the 25th and 75th percentiles of CRF in our data. For skeletal muscle strength, the 25th and 75th percentiles of initial strength values in our data were used to represent low and high strength respectively in the muscle strength interaction graphs (56 and 83 kg for chest press; 45 and 63 kg for seated back row; 47 and 69 kg for knee extension), as no literature were available.

3.4 Results

A flowchart representing the data extraction and inclusion process is displayed in Figure 3.1. Data from 599 member charts were extracted, of which 199 met the criteria to be included in the analyses (i.e., having available CPET records and having greater than 12 months of enrollment duration). Due to lower enrollment rates of women (n=39, 19.6%) and thus low availability of data that precluded mixed model analyses, women were not included. Thus, VO_2peak data from 160 men (160/199; 80.4%) were included for analysis of changes in the primary outcome of CRF, of which a subset of 70 men with available skeletal muscle strength data (44% of 160 with CRF data) was included for the analysis of changes in 1RM chest press, seated back row, and knee extension strength.

Figure 3.1. Flow of data extracted and included in the analysis

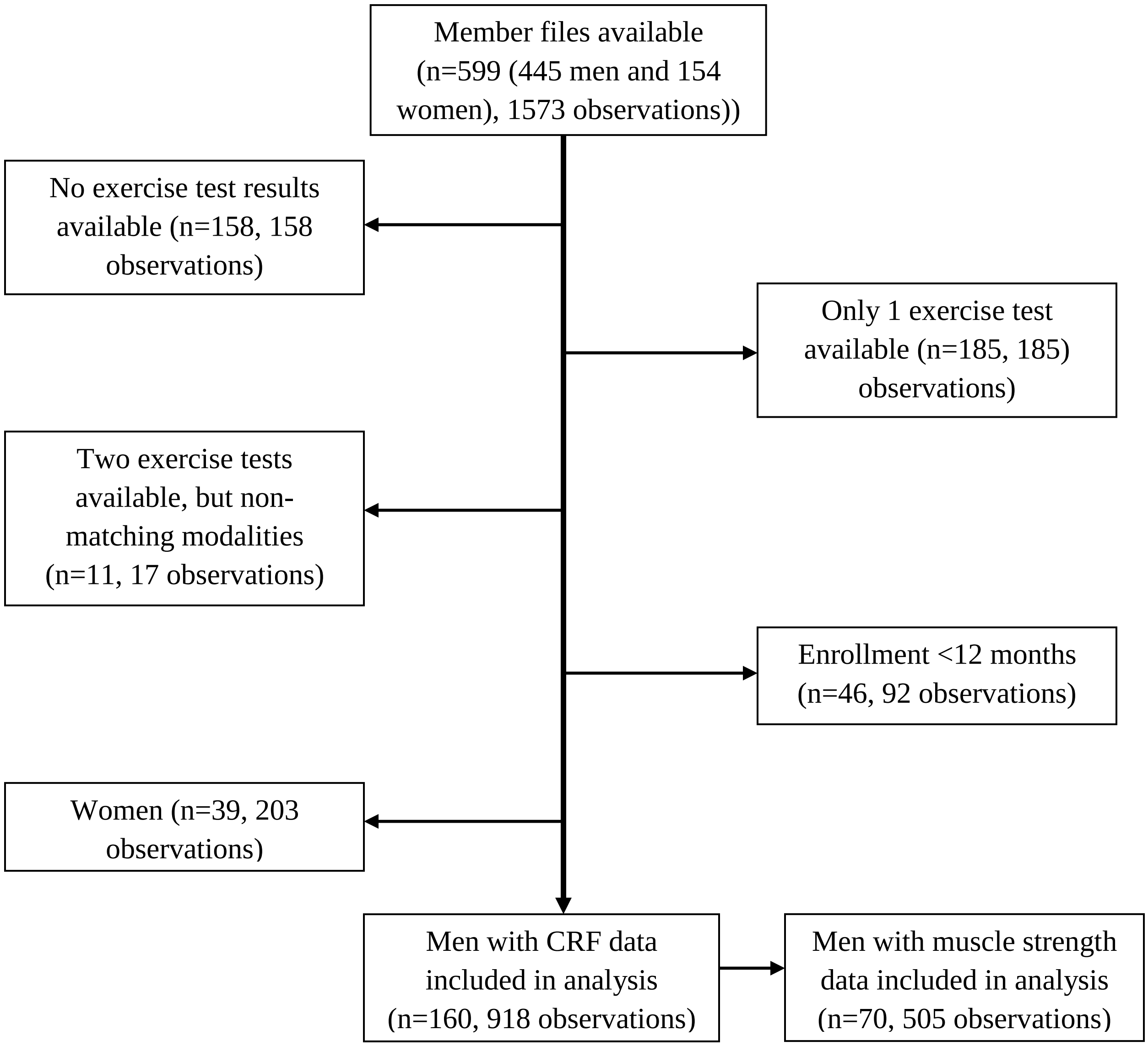


Table 3.1 summarizes the baseline characteristics of the 160 men included in the final analysis. Members started the CR program with an average VO_2peak of 22.7 ml.kg-1.min-1, which is lower than reference values for men without CVD (ranging from 32-34 ml.kg-1.min-1) (Heyward & Gibson, 2014), but comparable to individuals with CVD (Sumide et al., 2009; Nishitani et al., 2013; Laddu et al., 2018).

Table 3.1. Baseline characteristics of 160 men enrolled in the cardiac rehabilitation program

Variable	n	Value
Age (years)	160	64.3 ± 9.3
Weight (kg)	136	83.8 ± 13.1
Height (cm)	137	174.7 ± 7.2
Smoking history: n (%)	73	
Never smoked		23 (31.5)
Ever smoked		50 (68.5)
Reason for enrollment: n (%)	160	
CABG		63 (39.3)
Coronary angioplasty		36 (22.5)
Other heart surgery		9 (5.6)
Myocardial infarction		34 (21.3)
Cardiomyopathy		6 (3.8)
Other		12 (7.5)
Time post-event (years)	152	1.7 (3.0)
Enrollment duration (years)	160	6.6 ± 5.2
Resting heart rate (beats/min)	127	69 ± 12
Resting systolic BP (mmHg)	154	127 ± 18
Resting diastolic BP (mmHg)	154	77 ± 11
Peak heart rate (beats/min)	160	132 ± 23
Peak systolic BP (mmHg)	109	177 ± 32
Peak diastolic BP (mmHg)	108	80 ± 11
Relative VO_2peak (ml.kg-1.min-1)	160	22.7 ± 7.1
% of peak heart rate achieved	160	81 ± 12
Peak aerobic power (kpm/min)	152	915 ± 292
1RM chest press (kg)	70	68 ± 20
1RM seated backrow (kg)	70	54 ± 17
1RM leg extension (kg)	70	57 ± 17

Notes: Continuous variables are presented as means ± standard deviations. Categorical variables are presented as frequencies (percentage). Abbreviations: CABG coronary bypass grafting; BP blood pressure; 1RM one-repetition maximum.

3.4.1 Cardiorespiratory Fitness Results

Although mean program duration was 6.6 years for CRF, upon closer inspection, there were only 37 men (23%) with enrollment exceeding 10 years which resulted in fewer observations towards the upper limits of enrollment time. In order to minimize missing data, VO_2peak data were truncated at 5.5 years to preserve 75% available data (Figure 2.2). Similarly, muscle strength data, which contained more repeated observations and thus allowed for a longer truncation, were truncated at 10 years to preserve 75% available data. Scatter plots showed a non-linear increase in VO_2peak in the first 3 years of enrollment, followed by a non-linear decline (Figure 2.2).

To capture this polynomial shape of the data, we added a quadratic term in enrollment time ($time^2$) in the mixed model analyses (Table 3.2). VO_2peak changed as a function of both linear (time) and quadratic ($time^2$) terms. Three outlying observations with high influence on the model were excluded from the analyses. A significant 3-way interaction between enrollment time, age, and initial fitness was observed [estimate (SE) -0.001 (0.0003), 95% CI (-0.002, -0.0004), p=0.001]. All 2-way interactions (Enrollment time X Age, Enrollment time X Initial fitness, Age X Initial fitness) were significant in the model ($p<0.05$) and did not include zero within their 95% CIs. There were inter-individual variability in both initial level and rate of change in VO_2peak and as such, a random intercept and random slope model was used. A random effect on the enrollment $time^2$ term was also tested, but found not to be significant (estimate (SE) 0.012 (0.014), 95% CI (0.001, 0.125)), indicating similar non-linear VO_2peak growth and decline across individuals. An independent covariance structure was identified since it best fit the data.

Table 3.2. Mixed model analysis on changes in VO_2peak in 160 men, including age at enrollment and initial VO_2peak as interaction terms (592 observations)

Fixed and random effects components from 0-5.5 years of enrollment			
Fixed Effects Variables	*β (SE)*	*95% CI*	*p-value*
IV1: Enrollment Time	4.06 (1.26)	(1.59, 6.52)	0.001*
IV2: Enrollment Time^2	-0.124 (0.036)	(-0.19, -0.05)	0.001*
IV3: Age	-0.073 (0.04)	(-0.01, 0.16)	0.088
IV4: Initial VO_2peak	1.24 (0.18)	(1.01, 1.48)	<0.0001*
Constant	-3.60 (2.82)	(-9.13, 1.93)	0.202
Interaction terms			
Enrollment Time x Age	-0.033 (0.02)	(-0.06, -0.003)	0.029*
Enrollment Time x initial VO_2peak	-0.053 (0.02)	(-0.09, -0.01)	0.010*
Age x initial VO_2peak	-0.004 (0.002)	(-0.01, -0.001)	0.016*
Random Effects Variance Components	*Estimate (SE)*	*95% CI*	
Slope (enrollment time)	1.46 (0.24)	(1.04, 2.03)	
Intercept	0.18 (0.28)	(0.01, 3.70)	
Residual	4.13 (0.30)	(3.58, 4.77)	
Model Fit Statistics	*Statistic*		
Log likelihood	-1418.5		
Bayesian Information Criteria	2907.3		

Abbreviations: IV independent variable; SE standard error; CI confidence interval. Three outlying observations with high influenced removed. No observed random effects variance on the slope of enrollment time^2 (estimate (SE) 0.012 (0.014), 95% CI (0.001, 0.125)).

Figure 3.2 depicts the interactions between enrollment time, age at enrollment and initial VO_2peak levels from the mixed model analysis (computed %/year changes compiled in Table 3.3). The observed trajectories for VO_2peak were more favourable at younger ages at time of enrollment (Enrollment time X Age interaction) and at lower initial VO_2peak levels (Enrollment time X Initial VO_2peak interaction). Additionally, the differences in trajectories of VO_2peak between the ages 50-59, 60-69, and 70-79 years were consistently larger from baseline to 3 years of enrollment in individuals with higher starting fitness levels (Age X Initial VO_2peak interaction), suggesting a greater training effect for younger adults in this group. In contrast, these differences were much smaller among all ages for individual enrolled with low fitness.

Figure 3.2. Mixed model graph of predicted relative VO_2peak trajectories in men with added age and initial VO_2peak as interaction terms

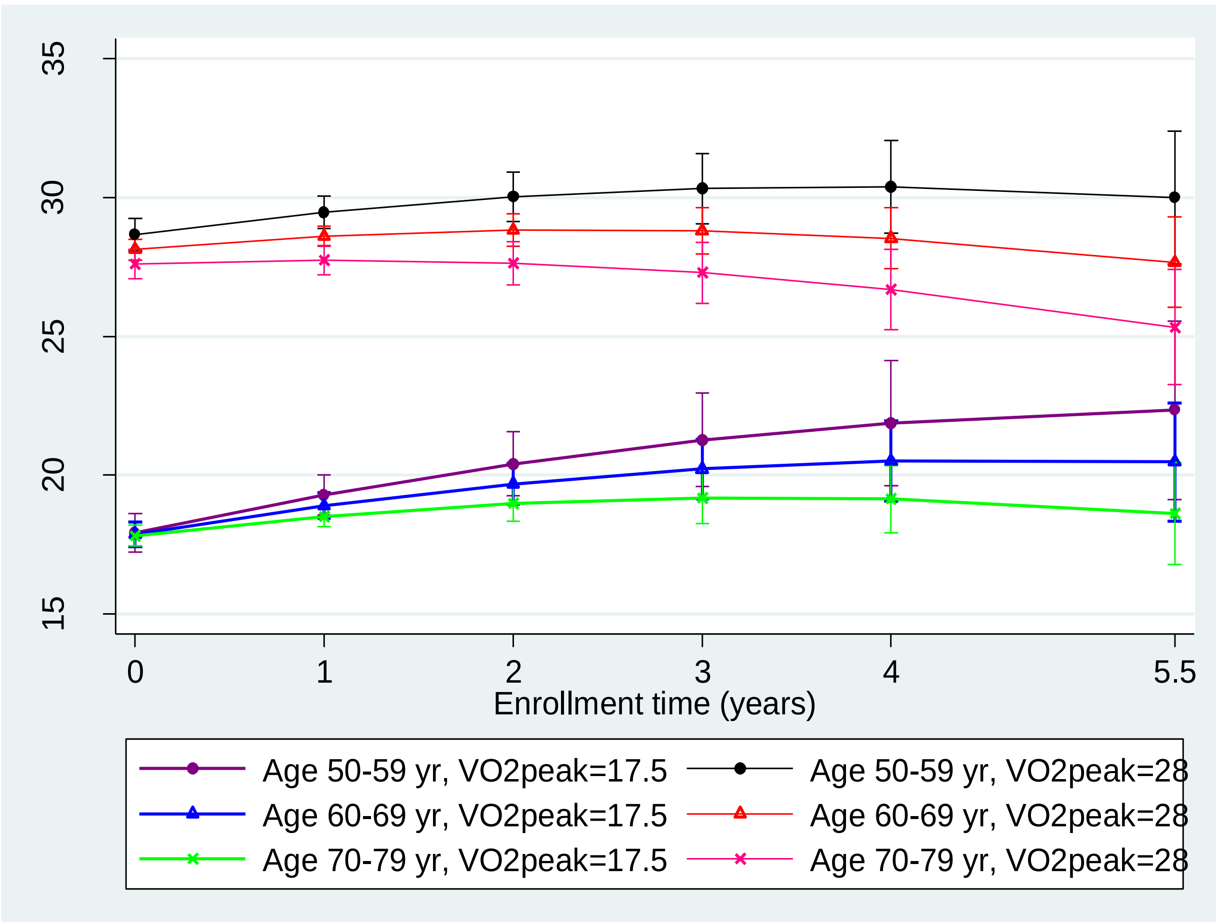


Table 3.3. Computed %/year changes in VO_2peak by age and initial fitness level

	Initial level of VO_2peak					
	Low (17.5 ml.kg-1.min-1)			High (28 ml.kg-1.min-1)		
Enrollment time	**Age at enrollment (years)**			**Age at enrollment (years)**		
	50-59	60-69	70-79	50-59	60-69	70-79
0 to 1 yr	7.6	5.8	3.9	2.8	1.7	-0.5
>1 to 2 yr	5.8	4.2	2.5	1.9	0.8	-0.4
>2 to 3 yr	4.2	2.6	1.1	1.0	0.0	-1.3
>3 to 4 yr	3.0	1.5	-0.2	0.2	-0.9	-2.2
>4 to 5 yr	1.3	0.0	-1.8	-0.8	-2.0	-3.3

3.4.2 Skeletal Muscle Strength Results

The 10-year trajectories of 1RM chest press and seated back row strength data show a relatively linear decline throughout enrollment (Figures 2.4 and 2.5), while knee extension strength data show a quadratic relationship with initial increases peaking at Year 2 followed by declines after Year 3 (Figure 2.6). See Appendix 7 for the non-truncated trajectories of the muscle strength outcomes.

3.4.2.1 One-Repetition Maximum Chest Press Results

Table 3.4 shows the mixed model analyses of the linear trajectory in 1RM chest press with the interaction terms. A significant 3-way interaction (Enrollment time by Age by Initial 1-RM chest press) was observed (estimate (SE) -0.0004 (0.0002), 95% CI (-0.0007, -0.0001), p=0.012). The interaction terms of Enrollment time X Age and Enrollment time X Initial chest press strength were significant ($p<0.05$) and did not contain zero in the 95% CIs. This was not the case for the interaction of Age X Initial chest press strength [estimate (SE) -0.007 (0.004), 95% CI (-0.015, 0.002), p=0.127), which reduced strength of the model (Bayesian information criteria and log likelihood values) and thus was removed. The most appropriate model was a linear term of enrollment time with the random effect variance components of a random intercept and slope with an independence covariance structure.

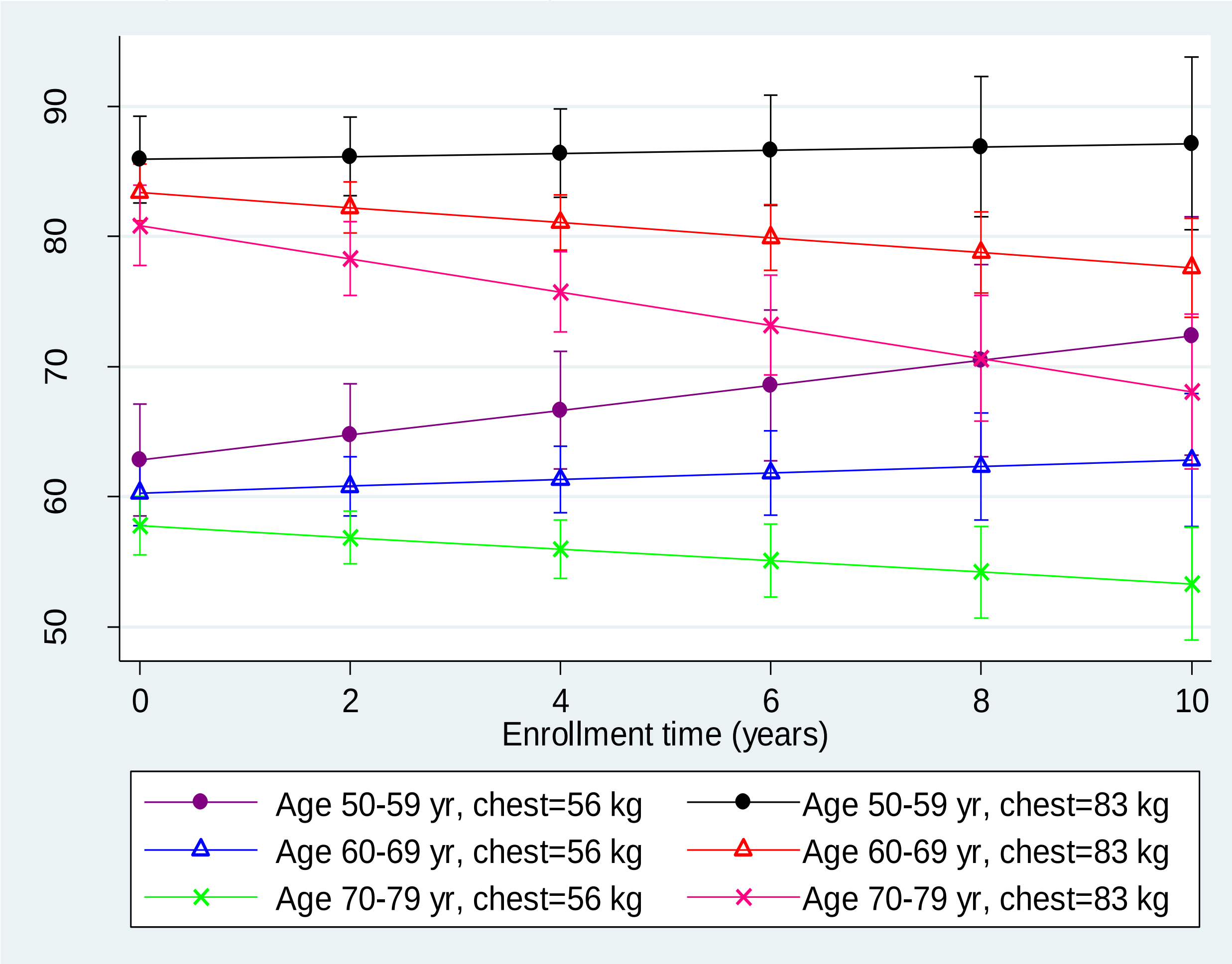
Table 3.4. Mixed model analysis on changes in chest press strength in 70 men, including age and initial chest press strength as interaction terms (406 observations)

Fixed and random effects components from 0-10 years of enrollment			
Fixed Effects Variables	*β (SE)*	*95% CI*	*p-value*
IV1: Time	6.18 (2.29)	(1.69, 11)	0.007*
IV2: Age	-0.253 (0.12)	(-0.49, -0.02)	0.036*
IV3: Initial chest press	0.855 (0.03)	(0.76, 0.95)	<0.0001*
Constant	27.6 (9.8)	(8.2, 47)	0.005*
Interaction terms			
A) Time X age	**-0.070 (0.03)**	**(-0.13, 0.01)**	**0.013***
B) Time by initial chest press	**-0.031 (0.01)**	**(-0.05, -0.01)**	**0.003***
Random Effects Variance Components	*Estimate (SE)*	*95% CI*	
Slope (time)	0.63 (0.39)	(0.19, 2.1)	
Intercept	27 (8.2)	(15, 49)	
Residual	58 (4.7)	(50, 68)	
Model Fit Statistics	*Statistic*		
Log likelihood	-1461.2		
Bayesian Information Criteria	2976.5		

Abbreviations: 1RM 1 repetition maximum; IV independent variable; SE standard error; CI confidence interval. Five outlying observations with high influence removed.

Figure 3.3 depicts the trajectories for 1RM chest press with interactions of Enrollment time X Age and Enrollment time X Initial chest press strength. The negative beta-coefficients for both interaction terms indicate less favourable trajectories in older participants compared to younger participants, and in individuals with higher baseline 1RM chest press values compared to those with lower values. The absence of an interaction of Age X Initial chest press (tested but removed) is explained visually by similar differences in 1RM chest press over any point in enrollment time between individuals aged 50-59, 60-69, and 70-79 years regardless of initial levels of chest press strength (1RM 56 vs. 83 kg). Table 3.7 outline the computed %/year changes in all muscle strength outcomes by age and initial strength levels.

Figure 3.3. Mixed model graph of predicted 1-repetition chest press strength trajectories in men with added age and initial chest press strength as interaction terms



3.4.2.2 One-Repetition Maximum Seated Back Row Results

Table 3.5 shows the mixed model analyses of the non-linear trajectory in 1RM seated back row with the interaction terms. A significant 3-way interaction (Enrollment time by Age by Initial 1-RM back row) was observed (estimate (SE) -0.0006 (0.0001), 95% CI (-0.0009, -0.0003), $p<0.0001$). All interactions of Enrollment time X Age, Enrollment time X Initial back row strength, and Age X Initial back row strength were significant and improved the model. The most appropriate model included a non-linear term of enrollment time ($time^2$) with the random effect variance components of a random intercept and slope (enrollment time) with an independence covariance structure. No random effects of enrollment $time^2$ were observed.

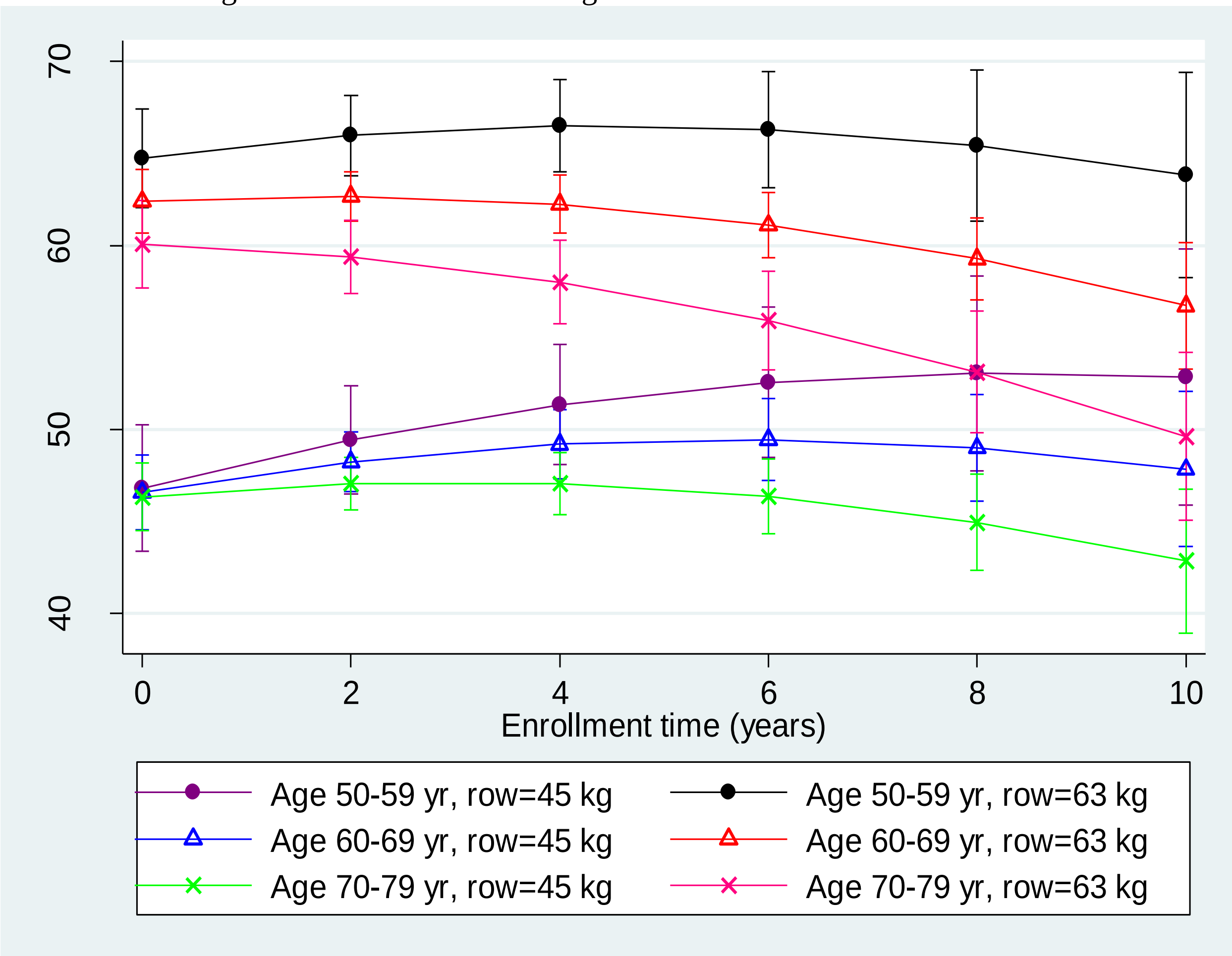
Table 3.5. Mixed model analysis on changes in seated back row strength in 70 men, including age and initial back row strength as interaction terms (406 observations)

Fixed and random effects components from 0-10 years of enrollment			
Fixed Effects Variables	*β (SE)*	*95% CI*	*p-value*
IV1: Enrollment time	5.60 (1.8)	(2.16, 9.03)	0.001*
IV2: Enrollment time^2	-0.088 (0.04)	(-0.18, -0.0003)	0.049*
IV3: Age	0.503 (0.20)	(0.11, 0.89)	0.011*
IV4: Initial back row	1.58 (0.21)	(1.18, 1.99)	<0.0001*
Constant	-23.1 (13)	(-49, 2.9)	0.081
Interaction terms			
Enrollment time x Age	-0.048 (0.02)	(-0.09, -0.004)	0.032*
Enrollment time x Initial back row	-0.039 (0.01)	(-0.06, -0.02)	<0.0001*
Age x Initial back row	-0.012 (0.003)	(-0.02, -0.005)	<0.0001*
Random Effects Variance Components	*Estimate (SE)*	*95% CI*	
Slope (time)	0.30 (0.17)	(0.10, 0.96)	
Intercept	8.4 (4.1)	(3.2, 21)	
Residual	49 (3.8)	(42, 57)	
Model Fit Statistics	*Statistic*		
Log likelihood	-1401.7		
Bayesian Information Criteria	2869.5		

Abbreviations: 1RM 1 repetition maximum; IV independent variable; SE standard error; CI confidence interval. Five outlying observations with high influence removed. No random effect of enrollment time^2 (estimate (SE) 2.3 x10^{-20} (0), 95% CI (0, 0)).

Figure 3.4 depicts the interactions of Enrollment time X Age, Enrollment time X Initial back row strength, and Age X Initial back row strength on trajectories of 1RM seated back row. The observed trajectories for 1RM back row were more favourable at younger ages at time of enrollment (Enrollment time X Age interaction) and at lower initial 1RM back row levels (Enrollment time X Initial back row strength interaction). Additionally, the differences in trajectories between the ages 50-59, 60-69, and 70-79 years were consistently larger throughout 10 years of enrollment in individuals with higher starting 1RM back row levels (Age X Initial back row strength interaction), suggesting a greater training effect for the younger adults in this group. In contrast, these differences were much smaller among all ages for individual enrolled with low levels of back row strength.

Figure 3.4. Mixed model graph of predicted 1-repetition seated back row strength trajectories in men with added age and initial back row strength as interaction terms



3.4.2.3 One-Repetition Maximum Knee Extension Results

Table 3.6 shows the mixed model analyses of the non-linear trajectory in 1RM knee extension strength with the interaction terms. A significant 3-way interaction (Enrollment Time X Age X Initial knee extension) was observed (estimate (SE) -0.001 (0.0002), 95% CI (-0.001, -0.0006), $p<0.0001$). However, the interaction of Age X Initial knee extension strength was not significant, contained zero within the 95% CI, and thus was removed as it reduced the strength of the model (estimate (SE) -0.003 (0.004), 95% CI (-0.01, 0.004), $p=0.301$). The 2-way interactions of Enrollment time X Age and Enrollment time X Initial knee extension strength were significant, had larger beta-coefficients, and added strength to the model. Overall, the most appropriate model included a non-linear term of enrollment time ($time^2$) with the random effect variance components of a random intercept and slope (enrollment time) with an independence covariance structure. No random effects of enrollment $time^2$ were observed.

Table 3.6. Mixed model analysis on changes in knee extension strength in 70 men, including age and initial knee extension strength as interaction terms (404 observations)

Fixed and random effects components from 0-10 years of enrollment			
Fixed Effects Variables	*β (SE)*	*95% CI*	*p-value*
IV1: Enrollment time	10.0 (2.4)	(5.2, 15)	<0.0001*
IV2: Enrollment time^2	-0.124 (0.04)	(-0.20, -0.05)	0.001*
IV3: Age	-0.093 (0.09)	(-0.27, 0.08)	0.285
IV4: Initial knee extension	0.882 (0.04)	(0.80, 0.97)	<0.0001*
Constant	13.3 (7.1)	(-0.57, 27)	0.060
Interaction terms			
Enrollment time x Age	-0.088 (0.03)	(-0.15, -0.03)	0.004*
Enrollment time x Initial knee extension	-0.063 (0.01)	(-0.09, -0.04)	<0.0001*
Random Effects Variance Components	*Estimate (SE)*	*95% CI*	
Slope (time)	1.5 (0.4)	(0.81, 2.6)	
Intercept	14 (4.4)	(7.2, 25)	
Residual	32 (2.6)	(27, 38)	
Model Fit Statistics	*Statistic*		
-2 log likelihood	-1354.4		
Bayesian Information Criteria	2774.8		

Abbreviations: 1RM 1 repetition maximum; IV independent variable; SE standard error; CI confidence interval. Four outlying observations with high influence removed. No random effect of enrollment time^2 (estimate (SE) 2.2 x10^{-4} (0.004), 95% CI (1.9 x10^{-20}, 2.7 x10^{12})).

Figure 3.5 depicts the interactions of Enrollment time X Age and Enrollment time X Initial knee extension strength on 1RM seated knee extension trajectories. The negative beta-coefficients for both interaction terms indicate less favourable trajectories in older compared to younger participants, and in individuals with higher baseline 1RM knee extension values compared to those with lower values. The absence of an interaction of Age X Initial knee extension strength (tested but removed) is explained visually by similar differences in 1RM knee extension over any time-point between individuals aged 50-59, 60-69, and 70-79 years regardless of initial levels of knee extension strength (1RM 56 vs. 83 kg).

Figure 3.5. Mixed model graph of predicted 1-repetition knee extension strength trajectories in men with added age and initial knee extension strength as interaction terms

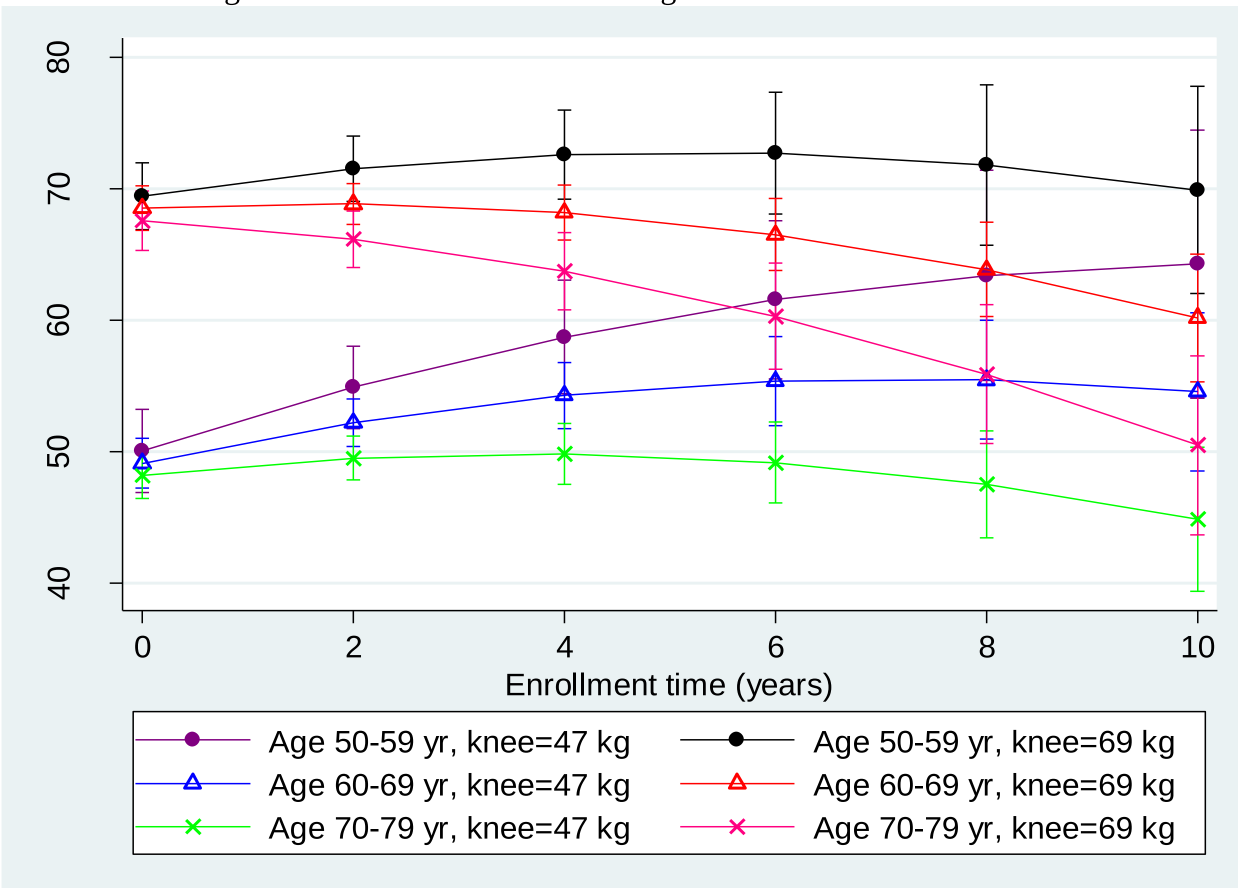


Table 3.7. Computed %/year changes in muscle strength outcomes by age and initial strength levels for 1-repetition maximum i) chest press, ii) seated back row, and iii) knee extension

i) 1RM chest press

	Initial level of 1RM chest press					
	Low (56 kg)			High (83 kg)		
Enrollment time	**Age at enrollment (years)**			**Age at enrollment (years)**		
	50-59	60-69	70-79	50-59	60-69	70-79
0 to 10 yr	1.5	0.4	0.8	1	-0.7	-1.5

ii) 1RM seated back row

	Initial level of 1RM seated back row					
	Low (45 kg)			High (63 kg)		
Enrollment time	**Age at enrollment (years)**			**Age at enrollment (years)**		
	50-59	60-69	70-79	50-59	60-69	70-79
0 to 2 yr	2.6	1.8	0.8	1.0	0.2	-0.6
>2 to 4 yr	1.9	1.0	0.0	0.4	-0.4	-1.2
>4 to 6 yr	1.1	0.3	-0.7	-0.1	-1.0	-1.8
>6 to 8 yr	0.5	-0.5	-1.5	-0.7	-1.5	-2.5
>8 to 10 yr	-0.2	-1.2	-2.3	-1.2	-2.2	-3.3

iii) 1RM knee extension

	Initial level of 1RM knee extension					
	Low (47 kg)			High (69 kg)		
Enrollment time	**Age at enrollment (years)**			**Age at enrollment (years)**		
	50-59	60-69	70-79	50-59	60-69	70-79
0 to 2 yr	4.8	3.2	1.4	1.5	0.2	-1.0
>2 to 4 yr	3.5	2.0	0.4	0.8	-0.5	-1.9
>4 to 6 yr	2.4	1.0	-0.7	0.1	-1.2	-2.7
>6 to 8 yr	1.4	0.1	-1.7	-0.6	-2.0	-3.7
>8 to 10 yr	0.7	-0.8	-2.7	-1.3	-2.9	-4.8

3.5 Discussion

3.5.1 The importance of exercise training in cardiovascular disease

Individuals with CVD, regardless of age, are at high risk of recurrent CVD events and mortality (Kaasenbrood et al., 2016; Martin et al., 2013). With early phases of CR typically lasting just five months (Leon et al., 2005), the transition to long-term, maintenance-phase CR programs is critical for maintaining a healthy, active lifestyle over the lifespan. Results from this study suggest that baseline age and fitness levels are associated with observed impoved fitness trajectories in long-term CR in men.

CR is an effective model of care for secondary prevention through risk factor modification (Anderson et al., 2016), and a strong body of evidence supports short-term (≤12 months) enrollment in CR programs for increasing CRF (Sumide et al., 2009; Lazzeroni et al., 2017; Ades, 2001; Greco, Guardini, & Citelli, 1998) and skeletal muscle strength (Sumide et al., 2009; Nishitani et al., 2013; Fragnoli-Mun, 1998). Results from the current study corroborate these earlier findings of short-term improvement, but also suggest that the trajectories can extend over 3 years regardless of age and initial fitness levels.

3.5.2 Interactions between time, age, and starting fitness levels on the changes in fitness during cardiac rehabilitation

The current study offers novel insight into relationships between age, initial fitness, and changes in fitness with long-term CR. Similar to previous studies, we observed that CRF and muscle strength were higher at any point in time in younger participants (Fleg et al., 2005; Heyward & Gibson, 2014; Keller & Engelhardt, 2014) and for individuals with high initial fitness levels (Laddu et al., 2018; Vaitkevicius et al., 2002; Balady et al., 1996). Importantly, our data show that all fitness outcomes increased at faster rates and declined at slower rates in younger individuals and those with lower initial fitness levels. Interestingly, older adults with higher baseline levels of CRF and 1RM seated back row strength experienced smaller improvements and steeper declines over time, whereas their counterparts who presented with lower baseline fitness levels showed greater improvements and were more stable over time. While individuals with CVD can achieve improvements in fitness from exercise training, it is remains critical for all individuals to capitalize on strategies to improve fitness at any time (even prior to onset of CVD) to reduce the impact on physical function and risk of cardiovascular events and mortality.

Age-associated changes in cardiovascular and musculoskeletal systems are well established and help to explain why greater improvements and slower declines in fitness were observed in younger individuals. Reductions in maximum heart rate, cardiac output, peripheral oxygen capacity and utilization, and testosterone levels, and increased catabolic hormones and muscle fibre loss and atrophy are physiological changes typically seen with aging (Ho, Beard, & Farrell, 1997; Sharkley & Gaskill, 2007; Hakola et al., 2011; Grimby & Saltin, 1983; Williams et al., 2006). These changes, combined with the presence of CVD co-morbidities, contribute to the ability for older adults to exercise (Sandercock, Hurtado, & Cardoso, 2013; Laddu et al., 2018).

Moreover, our data support earlier studies that have also shown that baseline fitness is inversely associated with improvements in fitness, and indeed is often a stronger predictor than age, gender, and co-morbidities (Laddu et al., 2018; Vaitkevicius et al., 2002; Balady et al., 1996). Individuals with CVD who have low baseline fitness not only have the most potential to improve in fitness, they also present with more health issues (e.g. more severe cardiac events, cardiovascular pathology, and modifiable cardiovascular risk factors) than those with high fitness

(Laddu et al., 2018; Bruning & Sturek, 2015; Martin et al., 2013). As such, persons with CVD and lower baseline fitness levels have greater potential to improve modifiable risk factors with participation in CR as a result of both exercise training, increased physical activity levels, and optimization of other secondary prevention strategies (Brunin & Sturek, 2015; Gayda et al., 2006). Indeed, participants in our sample with lower initial fitness levels presented with higher body mass index, blood pressure, and proportions of more severe cardiac events (e.g. requiring coronary artery bypass graft surgeries) and medication use for hypertension, dyslipidemia, and diabetes, yet demonstrated greater improvement and slower declines in fitness compared to those with higher baseline fitness. It is unclear from our data if the observed improvements were influenced by increased physical activity since this data was not available, but should be incorporated into future prospective designs. While our findings may suggest that those with lower fitness levels benefit more from CR, it is important to note that fitness levels were still higher at all time points in those who were fitter at entry into the program.

3.5.3 Study limitations and strengths

We acknowledge the limitations of this study. As a retrospective analysis, we could not examine direct causal links between CR program enrollment and changes in CRF and skeletal muscle strength, and could not address any insights to be gained through program attendance and physical activity records as this information was not consistently recorded. It was uncertain whether the declines in fitness outcomes were due to aging or reduced physical activity and attendance. In addition, early initiation of CR is also a strong predictor of improvement in fitness (McPhee, Winegard, MacDonald, McKelvie, & Millar; 2015; Valkeinen, Aaltonen, & Kujala, 2010), but given the sample size, we selected age and baseline fitness variables in our mixed models and argue that baseline fitness is more important to investigate due its risk association with both mortality (Myers et al., 2002; Martin et al., 2013) and low physical function (Forman et al., 2017; Fletcher et al., 1995). Future research with larger sample sizes may explore additional variables, such as early initiation of CR.

Nonetheless, there were strengths in the statistical analyses used in this study, as the results were made more generalizable by appropriately truncating the data to minimize the effect of missing observations. Moreover, the dataset provided a high number of observations over multiple time points, thereby permitting identification of random effects through mixed model analyses. This contributed to a more complete picture of the non-linear trajectories that were not possible in previous studies that used pre-post measurement designs.

3.5.4 Study conclusions

This was the first study to report on the association of age and initial fitness and trajectories of fitness in men with CVD enrolled in long-term CR. We observed benefits to CRF and skeletal muscle strength in participants as a group. While our data showed greater improvements and slower declines in younger individuals and those with low initial fitness, fitness levels remained higher over time for individuals with higher fitness at baseline at any comparative age. These findings support the use of long-term exercise opportunities for individuals of all ages with CVD regardless of initial fitness levels.

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CHAPTER 4

LONG-TERM ENROLLMENT IN CARDIAC REHABILITATION ALSO BENEFITS CARDIORESPIRATORY FITNESS AND SKELETAL MUSCLE STRENGTH IN WOMEN WITH CARDIOVASCULAR DISEASE: A RETROSPECTIVE STUDY

4.1 Abstract

BACKGROUND: Despite known the benefits of cardiac rehabilitation (CR) and associations between fitness and recurrent cardiovascular events and mortality, changes in cardiorespiratory fitness (CRF) and muscle strength with long-term CR have never been examined in women, a population under-researched and under-represented. The purpose of this study was to: 1) Examine changes in CRF and muscle strength in women over long-term CR program enrollment

METHODS: Data were extracted from the program charts of 39 women (mean ± SD age 65 ± 9 years) who were enrolled ≥1 year in a maintenance-phase CR program and who completed ≥2 exercise tests. CRF was represented by peak oxygen consumption (VO_2peak, ml/min/kg). Skeletal muscle strength (kg) was assessed using one-repetition maximum tests for chest press, seated row, and knee extension. Mixed models analyses were used to determine changes in CRF (up to 5 years) and muscle strength (up to 6 years).

RESULTS: CRF and muscle strength linearly increased throughout enrollment at 1.5%/year and 0.6-2.1%/year, respectively, opposite to expected age-relate declines.

CONCLUSIONS: Despite being under-researched and under-represented, our data show that long-term, maintenance-phase CR enrollment can benefit fitness outcomes in women with CVD. These findings support the use of long-term exercise opportunities as strategies for secondary prevention in this high-risk population of women. Larger prospective cohort studies are warranted to confirm the observations, and to identify potential mechanisms underlying these changes.

4.2 Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide, accounting for over 33% of global deaths (18 million) annually (Roth et al., 2017). Due to advancements in diagnosis and treatment of CVD, CVD-related mortality rates have declined from 1990-2015 (Roth et al., 2017), yet still are projected to increase to 22 million deaths annually by 2030 (Roth et al., 2017). The effects of CVD contribute to a large economic burden, currently costing the global economy $863 billion USD and projected to increase by 21% to over $1 trillion USD by 2030 (Bloom et al., 2017).

CVD is diagnosed 10-20 years earlier in men than women, but the incidence is similar between the sexes when women enter menopause and experience large reductions in the cardio-protective hormone estrogen (Wei, George, Chang, & Hicks, 2017). Moreover, while the age-adjusted prevalence of CVD and related mortality statistics have historically been higher in men than women, the sex gap in these rates is narrowing. In 2015, global data now show similar statistics between sexes: 205 of 420 million of all prevalent cases of CVD and 8.5 of 18 million CVD-related deaths occur in women (Roth et al., 2017). The Canadian data show similar trends, such that the age-standardized prevalence rates in in women are approaching similar numbers to men with respect to CVD (women 5,812 vs. men 6,833 cases per 100,000) and CVD-related mortality (women 23,000 vs. men 26,000 annually) (Statistics Canada, 2016). Women have more severe CVD and thus experience poorer prognoses (Garuba et al., 2018; Finks, 2010). Women have higher short- and long-term mortality rates from myocardial infarction compared to men, independent of age and co-morbidities (Finks, 2010) and especially under the age of 55 years (Go et al., 2014; Roger et al., 2011). One- and 5-year rates of fatal recurrent myocardial infarction are 23% and 42% in women ≥40 years of age, respectively, compared to 18% and 33% in men (Roger et al., 2011).

Furthermore, it was previously assumed that the development, diagnosis, and management of CVD in women were the same as in men, but recent evidence is now suggesting otherwise (Sanghavi & Gulati, 2015). This gender bias has led to many issues, such as under-representation of women in CVD research studies (<30% women) (Garcia et al., 2016; Mikail, 2005) and greater risk of adverse health outcomes resulting from misdiagnosis, mismanagement (under-prescription of medications for hypertension, hypercholesterolemia, and diabetes), under-treatment, and lack of support and awareness of CVD (Yentl's syndrome (Johnston, Schenck-Gustafsson, & Lagerqvist, 2011)) (Heart and Stroke, 2018; Merz, 2011). Compared to men, women are four times more likely to be readmitted to hospitals for angina after normal angiograms, less likely to receive necessary surgical interventions and cardiac medications, less likely to survive after CV events, and more likely to experience delays in treatment (Garcia et al., 2016; Makail, 2005).

The first part to understanding this problem is recognizing the sex differences in the anatomy of the heart and surrounding vasculature. Women's hearts are still not well understood, a consequence of under-representation of women in CVD research (Garcia et al., 2016; Mikail, 2005). Computed tomography shows that women have smaller hearts and coronary arteries compared to men (Dickerson, Nagaraja, & Raman, 2010), however with aging, cardiac muscle around the chambers atrophies in women and grows larger and thicker in men (Eng et al., 2016). Also, the reduction in filling capacity of the heart with advancing age is more pronounced in women than men (Dickerson, Nagaraja, & Raman, 2010). These sex-differences with aging have important clinical implications.

Women also present with CVD differently than men. They are more likely to experience diffuse coronary artery disease with less extensive and obstructive lesions, and more likely to develop heart failure or experience a stroke after a myocardial infarction, with more debilitating effects compared to men (Finks, 2010). Women have a higher incidence of unrecognized and silent myocardial infarction with non-ST-segment elevation acute coronary syndrome and normal tropinon levels (Finks, 2010). Cardiac Syndrome X describes patients with myocardial ischemia without evidence of obstructive coronary artery disease, which is more commonly reported in women (Sanghavi & Gulati, 2015; Kemp,Vokonas, Cohn, & Gorlin, 1973). Indeed, women also typically present with CVD at older ages and with more co-morbidities, which contributes to misdiagnoses and greater complexities in management (Finks, 2010). Some atypical symptoms of acute coronary syndrome in women include dyspnea, indigestion, middle back pain, vomiting and nausea, and unexplained fatigue.

There are important differences in risk factors for CVD between men and women. Emerging evidence recognizes ovulation and pregnancy-related issues, such as pre-eclampsia, gestational diabetes, and hypertension, as risk factors for CVD unique to women (Bellamy, Casas, & Hingorani, 2007; Mannisto et al., 2013). The development of CVD in women is delayed at 10-20 years likely due to the anti-atherosclerotic and anti-inflammatory effects of estrogen (Sanghavi & Gulati, 2015), but after menopause, protection against traditional CVD risk factors is greatly reduced. A meta-analysis by Wei et al. (2017) showed that the risk of CVD was 10% higher in women than men for each 10-mmHg increment of systolic blood pressure, despite a higher prevalence of hypertension in men. Although smoking is more prevalent in men, a previous study has shown a stronger association with risk of CVD diagnosis and mortality in women (Shaw et al., 2006). Diabetes, dyslipidemia, and obesity are more prevalent in women after menopause, and the associations between these risk factors and CVD are stronger in women after menopause than men (Shaw et al., 2006; Peters, Huxley, & Woodward, 2014; Sanghavi & Gulati, 2015; Kanaya, Grady, & Barrett-Connor, 2002). Understanding sex differences in CVD and its risk factors is important for researchers and clinicians for establishing targeted secondary prevention strategies, such as exercise interventions.

Exercise-focused cardiac rehabilitation (CR) is an effective, well-established, and cost-effective strategy for secondary prevention, and a key component of the continuum of care for both men and women living with CVD (Anderson et al., 2016). Numerous health benefits have been reported after short-term (<12 months) CR studies sampling men and women, including reduced risk of cardiovascular mortality and hospital admissions (Anderson et al., 2016). Previous studies have also found improvements in CRF and muscle strength outcomes after these programs in both men and women (Nishitani et al., 2013; Sumide et al., 2009; Sandercock, Hurtado, & Cardoso, 2013; Anderson et al., 2016; Santos et al., 2014; Yang et al., 2015), although arguably the proportion of women sampled was typically only 15% and the studies were too small or did not report the results disaggregated by sex subgroups to determine if the effect sizes were similar between sexes (Anderson et al., 2016; Yamamoto et al., 2016; Heart and Stroke, 2018; Mikail, 2005).

With growing awareness and recognition of the importance of sex considerations in health research, a very recent meta-analysis was attempted to compare the effects of CR on mortality and morbidity between women and men, but ultimately not undertaken because only 2 of 80 studies included in the review had data in women available (Ghishi, Chaves, Bennett, Lavie, & Grace, 2019). However, individual studies have reported equal if not greater benefits in women after short-term CR programs. In a very early study by Balady, Jette, Scheer, & Downing (1996), larger improvements in exercise tolerance were observed after 10 weeks of CR in women up to the age of 75 years compared to men, but comparable findings beyond 75 years of age. More recently, in a large study of over 25,000 individuals with CVD (of which 24% were women), women who completed a three-month out-patient CR program experienced greater reduction in the risk of all-cause mortality compared to men (64% in women vs. 49% in men) (Colbert et al., 2015). In early CR (two weeks post-event), women achieve benefits in clinical outcomes, such as reduced anxiety and improved physical functioning, mobility, and independence to a similar degree as men (Feola et al., 2015). Other studies have shown similar (Gupta, Sanderson, & Bittner, 2007; O'Farrell, Murray, Huston, LeGrand, & Adamo, 2000) and greater (Wise & Patrick, 2012; Cannistra, Balady, O'Malley, Weiner, & Ryan, 1992) improvements in CRF in women after completion of short-term CR programs. These improvements in CRF are equally important in both sexes as they translate into similar reductions in risk of CV events and CVD mortality in both men and women (Roger et al., 1998; Kavanagh et al., 2002; Kavanagh et al., 2003).

Despite the health benefits of short-term CR programs, CR remains under-utilized in women to an even greater extent than men (Anderson et al., 2016). The age-standardized prevalence of CVD in women is similar to men (women 5,812 vs. men 6,833 per 100,000; Roth et al., 2017), yet a meta-analysis showed that only 15% of members in CR programs are women (Anderson et al., 2016). Compared to men, women are 47% less likely to be referred to CR programs, 36% less likely to enroll once referred, and 37% less likely to complete (Supervia et al., 2017; Samayo et al., 2014). There are many barriers to CR utilization in women, such as under-referral by health professional, lack of awareness of the benefits of CR, caregiver and family responsibilities, and negative perceptions of exercise (Supervia et al., 2017; Grace et al., 2009). In spite of these barriers, women who do enroll in CR achieve at least equivalent gains in fitness as men after short-term programs (Balady, Jette, Scheer, & Downing, 1996; Gupta, Sanderson, & Bittner, 2007; O'Farrell, Murray, Huston, LeGrand, & Adamo, 2000; Wise & Patrick, 2012; Cannistra, Balady, O'Malley, Weiner, & Ryan, 1992).

There is a paucity of evidence of trajectories of fitness over the long term with ongoing participation in CR, yet understanding these changes over time are important to establish. To date, only two studies have examined CRF changes over long-term CR program enrollment. Of these, one study did not include women (Gayda et al., 2006) and the other included a small proportion of women (14/63, 22%) and did not disaggregate results by sex (Belardinelli, Georgiou, Cianci, & Purcaro et al., 2012). Importantly, there has been no research that has reported long-term changes in fitness with CR in women.

Thus, the objective of this retrospective study was two-fold: To identify changes in CRF and upper and lower body skeletal muscle strength in women after ≥12 months of enrollment in a maintenance-phase CR program

4.3 Methods

This study was a retrospective chart review of data for members in a community-based, maintenance-phase, exercise-focused CR program. The study was approved by the Hamilton Integrated Research Ethics Board (#2017-1248).

4.3.1 Study Eligibility

Participants' data were included in this analysis if they were women, had CRF data from at least two cardiopulmonary exercise tests (CPET) conducted using matching modalities. Since we were interested in the effects of long-term membership in CR, data were only included for women with at least 12 months of membership.

4.3.2 Cardiac Rehabilitation Program

The CR program is maintenance-phase, exercise-based program offered to community-dwelling individuals ≥18 years old with CVD. Participants were referred to the program through their attending cardiologist or family physician. See Appendix 1 for supplemental information regarding participant intake package, health questionnaire, physiotherapist assessment, and exercise log sheets.

The initial exercise prescription was based on the results of the CPET and physical assessments. All members were prescribed a comprehensive program of aerobic training immediately upon program entry, but the initiation of the upper body resistance training component was typically delayed by 6-8 weeks in individuals post-surgery to allow sufficient time for healing and recovery. Members were instructed to attend the program twice weekly and encouraged to exercise three days/week outside the program. They were prescribed 30 minutes of aerobic training at 60-65% of heart rate reserve. For the resistance training component, members were encouraged to perform 1-3 sets of 12 repetitions in all major muscle groups two days/week while being supervised by staff. Resistance training loads were prescribed at 30-40% and 50-60% of 1-repetition maximum (1RM) for upper and lower extremity, respectively, and adjusted as needed. The exercise program was progressed in terms of intensity and duration recommendations during membership. Blood pressure, heart rate, and rate of perceived exertion were regularly monitored, and self-management and heart-healthy living education was provided via brochures and knowledge translation seminars.

4.3.3 Outcomes: cardiorespiratory fitness and skeletal muscle strength

CRF was the primary outcome of interest, evaluated from the results of annual CPET. CPET were conducted using cycle ergometry or treadmill, where VO_2peak (ml.kg-1.min-1) was measured using indirect calorimetry. The tests were performed by a cardiovascular technologist with physician supervision. Resting and peak heart rate (beats/minute) and systolic and diastolic blood pressure (mmHg) were also measured.

Upper and lower body Skeletal muscle strength was quantified using 1-repetition maximum (1RM, units) for chest press, seated back row, and knee extension. Muscle strength outcomes were available for a subset of members (n=19/39, 49%) who attended assessments at one testing site that possessed the necessary equipment (Hydrafitness Omnikinetics, Belton, Texas) to conduct the tests (see Appendix 3 for a visual of the equipment). The Hydrafitness Omnikinetics machine was used throughout the study period and calibration was maintained.

4.3.4 Data extraction

Data from member files dating from January 1985 to December 2016 were extracted during the period of January-April 2017 (see Appendix 4 for the data extraction document). Demographic information included age (years), height (cm), weight (kg), date of cardiovascular event or surgical procedure, time-post event (years), reason of enrollment, date of exercise test, and duration of membership (years). VO_2peak (ml.kg-1.min-1), and 1RM (kg) for chest press, seated back row, and knee extension were extracted for all available time points. Resting and peak heart rate (beats per minute) and blood pressure (mmHg), and test modality (treadmill or cycle) were also extracted. Two research assistants who completed training in retrospective chart review at McMaster University assisted with the data extraction. Weekly meetings with research assistants took place to ensure high quality data, and extracted data were reviewed and cross-referenced for errors.

4.3.5 Statistical Analysis

All analyses were performed using Stata 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). Descriptive statistics (means ±SD) and frequencies (n, %) were used to describe demographic information and baseline characteristics. The frequency of new members, by sex (regardless of meeting study inclusion criteria), enrolled in the CR program at each 5-year interval over the past 30 years was also analyzed (see Figure 1 of Appendix 9 for the frequency of new members).

Mixed model analyses for longitudinal data were applied to address the relationship between changes in the dependent variables (relative VO_2peak, 1RM chest press, 1RM seated back row, and 1RM knee extension) and the independent variable membership time (years). The changes in absolute VO_2peak were also analyzed and presented in Figures 14-15 and Table 4 of Appendix 9. Mixed model analyses were used as they are highly flexible and allow for analysis of data with missing data, unequal number of measurements per participant, and varying gaps in time between measurements within each participant (Snijders et al., 2012). To build the models according to standard methods of complex multi-level modelling, we first established the relationship (i.e. linear or non-linear) between the dependent variable and membership time via lowess smoother curves and mixed model analyses. We later tested for an interaction between membership time and age at enrollment, and finally, identified relevant random effects and the most appropriate covariance structure. The Bayesian Information Criteria was used to identify the best fitting model.

Influencing observations with high level I and II residuals (r>3 or r<-3) were identified using residual plots. Literature comparison values for CRF and muscle strength were determined to be -1.73%/year and -1.90%/year. The comparisons were created to identify visual differences, in lieu of performing hypothesis testing as there was inadequate statistical power.The calculation of these rates involved age-specific values of change (by decade) in CRF (Fleg et al., 2005) and muscle strength (Keller & Engelhardt, 2014; von Haehling, Morley, & Ankler, 2010) from the general population, as data in the CVD population is not available. Specifically, our rates were weighted by applying decade-specific literature rates to the relative contribution of participants observed within each decade of age (40s, 50s, 60s, and ≥70s) in our data set. These calculations are outlined in Tables 1-2 of Appendix 9. For example, a specific CRF literature value of -13.5%/decade was applied to the 10/39 women in the dataset who enrolled at 50-59 years of age, while -16.6%/decade was applied to the 14/39 women aged 60-69 years. The four weighted, decade-specific components (40s, 50s, 60s, and ≥70s) were then summed to calculate the overall weighted rate of change relevant to our sample of women.

4.4 Results

Data from 599 members' charts were extracted (n=445 men, n=154 women), of which 39/154 women (25.3%) met the eligibility criteria of having ≥12 months of enrollment time and CPET records available (Figure 4.1). CRF data for all 39 women were included in the analysis, and data for muscle strength was available for 19 women.

Baseline characteristics for the 39 women included in the study are presented in Table 4.1. Members were mean age 65.0 years old and mean baseline VO_2peak was 16.8 ml.kg-1.min-1, lower than reference values for age-matched average women without CVD (ranging from 24-26 ml.kg-1.min-1) (Heyward & Gibson, 2014) but similar to women with CVD (Wise & Patrick, 2012; O'Farrell et al., 2000).

Overall, mean program membership duration was 6.2 years but upon closer inspection, there were only 9 women (23%) with membership durations exceeding 10 years and thus fewer observations towards the upper limits of membership time. As such, data were truncated to preserve ≥70% available data and improve the generalizability of the mixed models at 5 and 6 years for CRF and muscle strength, respectively. All data points and the overall, non-truncated trajectory for change in VO_2peak are presented in Figure 2 of Appendix 9. Figures 3 and 4 of Appendix 9 also displays spaghetti and fitted plots over non-truncated and truncated membership time, which visualize each individual's separate trajectory of VO_2peak. Figure 4.2 below shows the lowess smoother curve depicting the overall trajectory of VO_2peak over the truncated 5 years of membership time. The data show an approximately linear increase in VO_2peak from baseline to 5 years of enrollment.

Figure 4.1. Flow of data extracted and included in the analysis

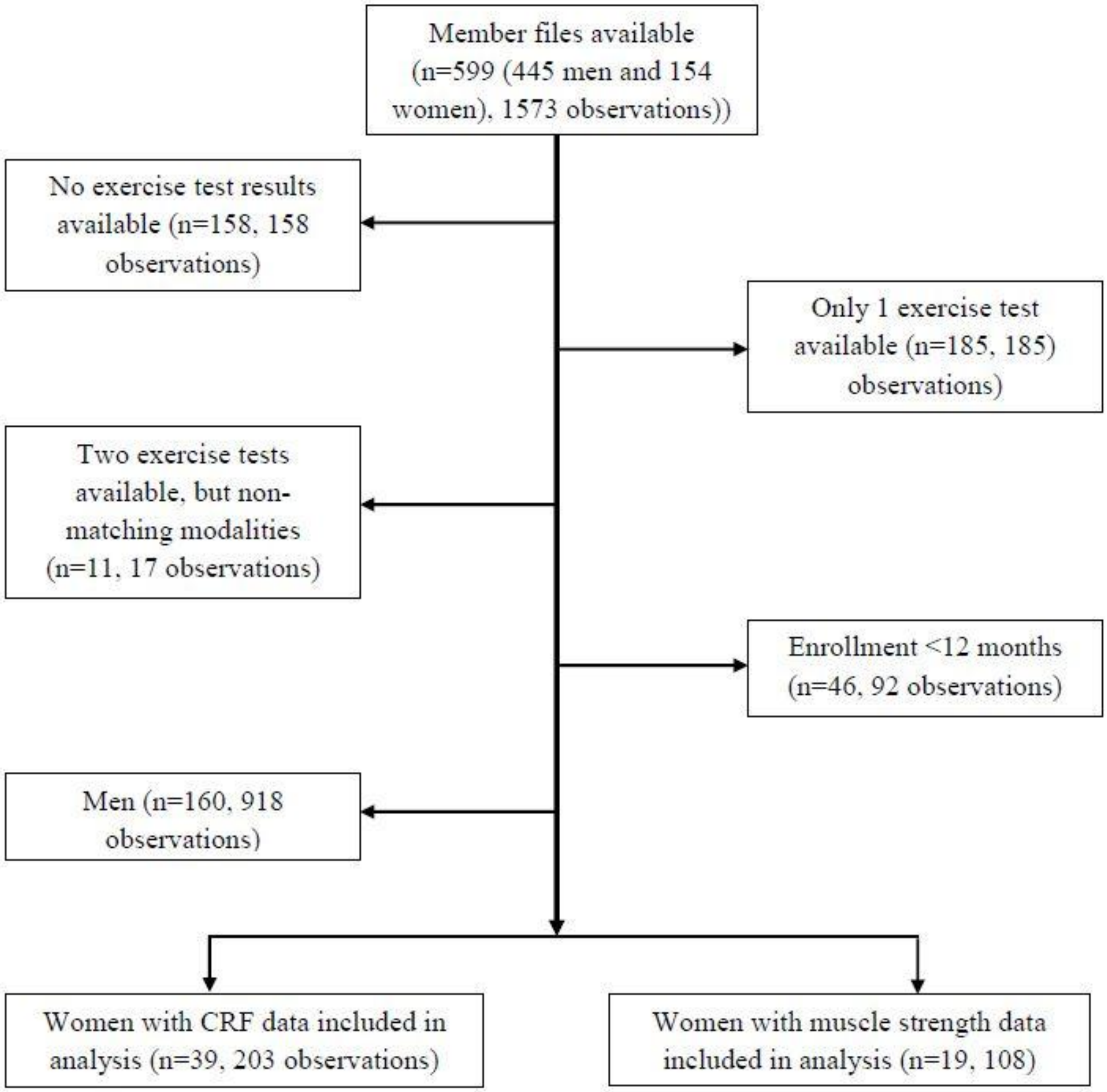
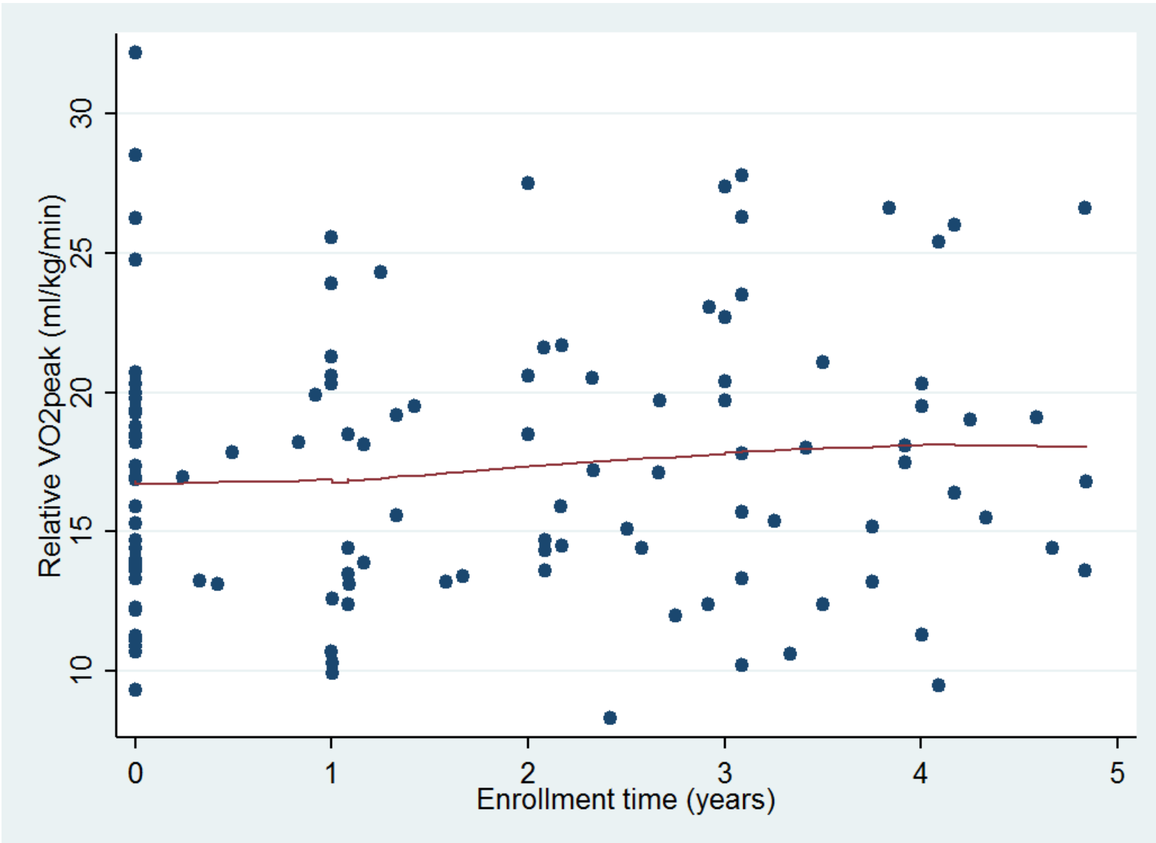


Table 4.1. Baseline characteristics of 39 women enrolled in the cardiac rehabilitation program

Variable	n	Value
Age (years)	39	65.0 ± 8.7
Weight (kg)	33	74.0 ± 19.7
Height (cm)	33	160.5 ± 6.6
Reason for enrollment: n (%)	39	
CABG		12 (30.8)
Coronary angioplasty		5 (12.8)
Valve surgery		4 (10.3)
Myocardial infarction		8 (20.5)
Other		10 (25.6)
Time post-event (years)	32	1.3 (1.7)
Enrollment duration (years)	39	6.2 ± 4.8
Resting heart rate (beats/min)	34	71 ± 11
Resting systolic BP (mmHg)	39	135 ± 20
Resting diastolic BP (mmHg)	39	77 ± 8
Peak heart rate (beats/min)	39	129 ± 25
% predicted peak heart rate achieved	39	80 ± 14
Peak systolic BP (mmHg)	28	172 ± 21
Peak diastolic BP (mmHg)	28	84 ± 24
VO_2peak (ml.kg-1.min-1)	39	16.8 ± 5.1
1RM chest press (kg)	19	39 ± 14
1RM seated back row (kg)	19	33 ± 11
1RM leg extension (kg)	19	32 ± 11

Notes: Continuous variables are presented as means ± standard deviations. Categorical variables are presented as frequencies (percentage). Abbreviations: CABG coronary bypass grafting; BP blood pressure; 1RM one-repetition maximum.

Figure 4.2. Trajectory of VO_2peak in women over 5 years of CR enrollment (n=39, 123 observations)



In the mixed model analysis, we added a quadratic term in enrollment time (years^2) to capture the possible polynomial shape of the data, but year^2 was not significant (β (SE) -0.134 (0.12), 95% CI (-0.35, 0.08), p=0.224) and increased the log likelihood and Bayesian Information Criteria of the model. Other attempts, such as spline analyses were conducted but conferred the same result. Based on the Bayesian model statistics, the linear model with random intercept only best captured the trajectory of VO_2peak observed in the lowess curve after adjusting for age. No effect of a random slope was identified which is consistent with the fairly similar individual linear trajectories observed the spaghetti plots of Figures 3-4 of Appendix 9. Table 4.2 shows this age-adjusted, linear change in VO_2peak for the truncated enrollment time

(Years 0-5). The random effects variance components included only the random intercept. Since the initial CRF levels varied between participants, a random intercept was included (variance estimate (SE) 14.8 (3.8), 95% CI 8.89, 24.5). The rate of change in CRF after baseline did not vary between participants and as such, a random slope was not included. No interactions between enrollment time and age at enrollment were found, and there were no influencing observations with high level I and II residuals.

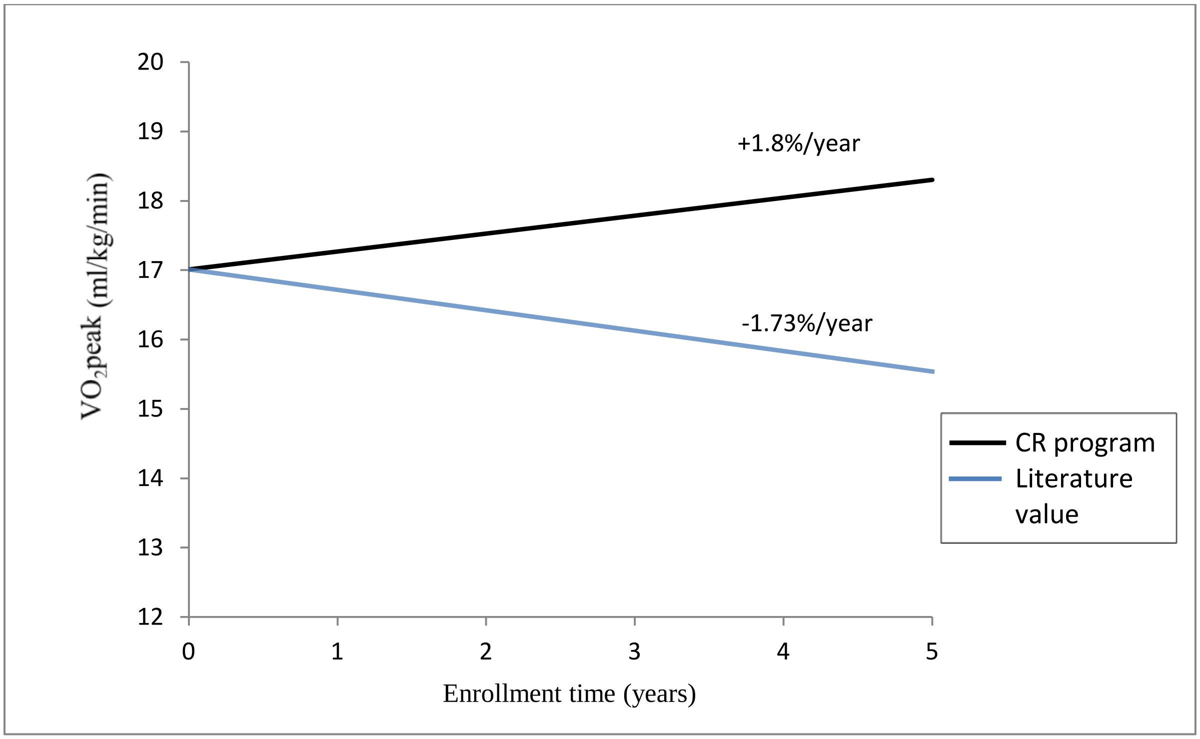
Figure 4.3 depicts the comparison between the linear change in VO_2peak over enrollment time and the literature value of -1.73%/year (Fleg et al., 2005). VO_2peak increased over enrollment time, in contrast to the decline expected based the aging literature comparison value (+1.8%/year vs. -1.73%/year). The trajectory of CRF over time was similar using absolute VO_2peak (L/min), which is displayed in Figures 14-16 and Table 4 of Appendix 9.

Table 4.2. Mixed model analysis on changes in VO_2peak levels in women over 5 years of CR enrollment after controlling for age (n=39, 123 observations)

Fixed and random effects components from 0-5 years of enrollment			
Fixed Effects Variables	*β (SE)*	*95% CI*	*p-value*
IV1: Years	0.257 (0.14)	(-0.02, 0.54)	0.072
IV2: Age at enrollment	-0.248 (0.08)	(-0.40, -0.10)	0.001*
Constant	33.1 (5.0)	(23.3, 43.0)	<0.0001*
Random Effects Variance Components	*Estimate (SE)*	*95% CI*	
Intercept	14.9 (3.9)	(8.9, 24)	
Residual	5.2 (0.8)	(3.9, 7.1)	
Model Fit Statistics	*Statistic*		
Log likelihood	-319.8		
Bayesian Information Criteria	663.6		

Abbreviations: IV independent variable; SE standard error; CI confidence interval.

Figure 4.3. Comparison of predicted change in VO_2peak in the 39 women over 5 years of enrollment compared to the literature value (Fleg et al., 2005)



Figures 4.4-4.6 show lowess smoother curves depicting the trajectories of overall change in skeletal muscle strength over the truncated 6 years of enrollment time (non-truncated data is presented in Figures 5-8 of Appendix 9). The smoothness of these curves is reduced compared to the primary outcome VO_2peak, as data were only available for a subset of participants (19/39 women, 48.7%). Nonetheless, the data resembled relatively linear patterns of little to no change in 1RM chest press and knee extension, and a slight linear increase in 1RM seated back row. Spaghetti and fitted plots displaying both non-truncated and truncated (at 6 years) trajectories of strength outcomes are displayed in Figures 9-13 of Appendix 9. These figures helped to inform which possible random effects (random intercepts and random slopes) could likely be tested for in the mixed model analyses.

Figure 4.4. Trajectory of 1RM chest press data in women over 6 years of CR enrollment (n=19, 66 observations)

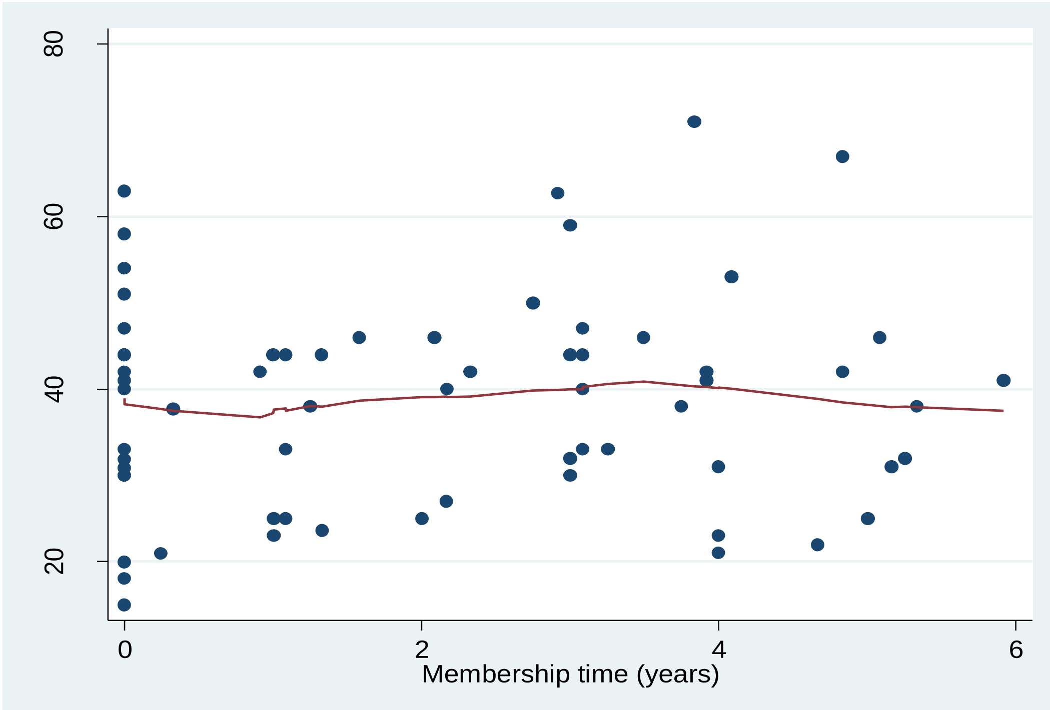


Figure 4.5. Trajectory of 1RM seated back row data in women over 6 years of CR enrollment (n=19, 66 observations)

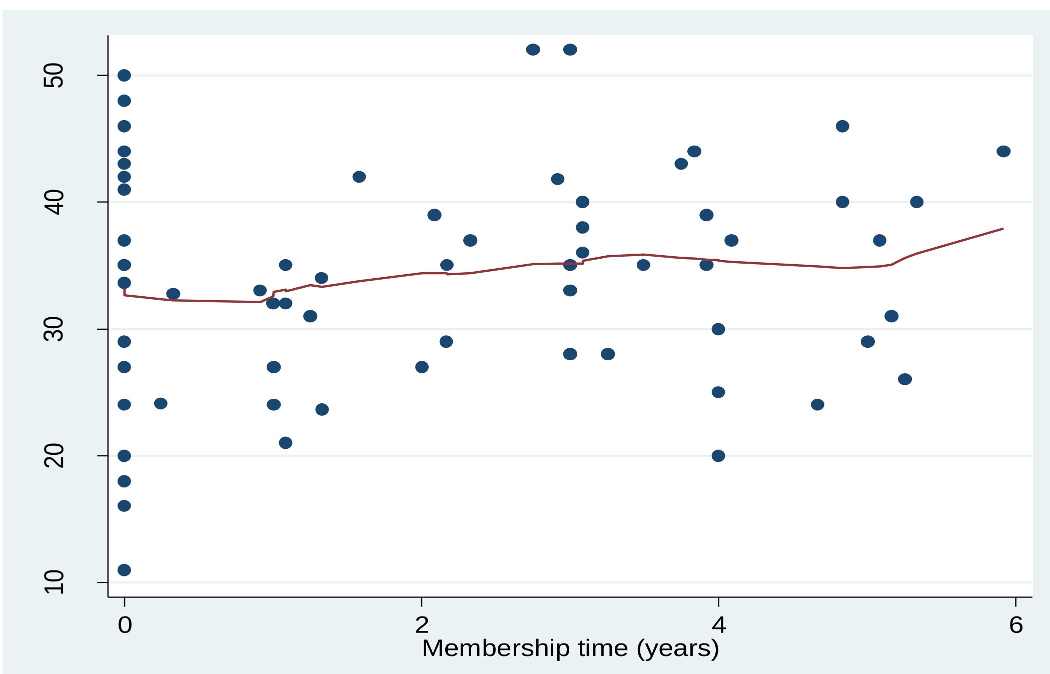
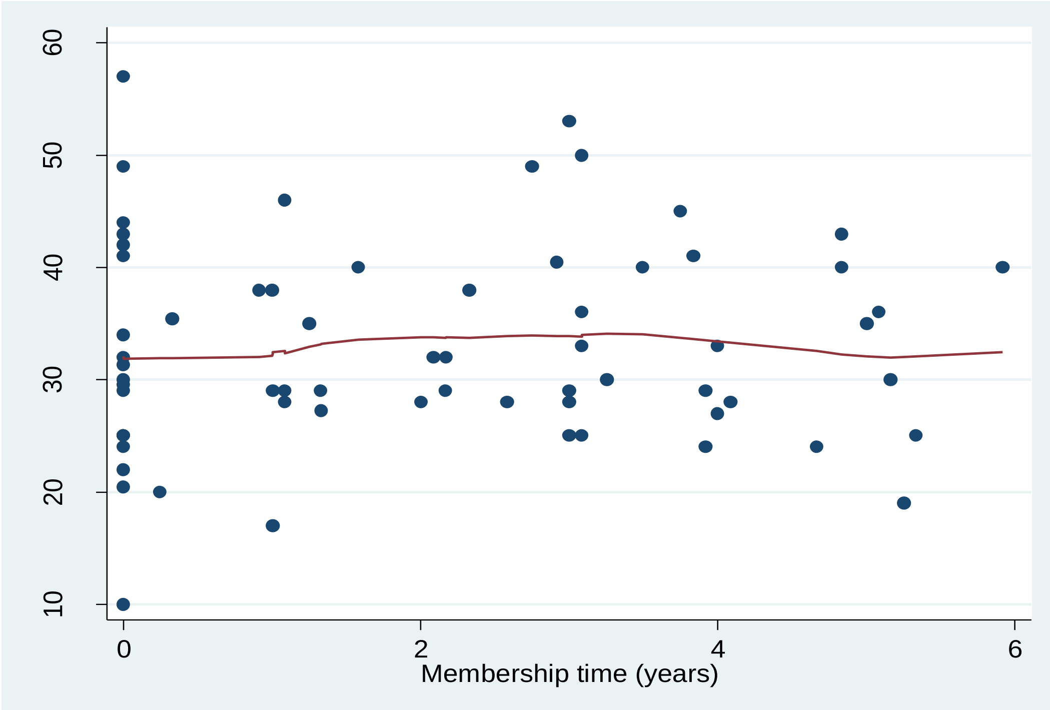


Figure 4.6. Trajectory of 1RM knee extension data in women over 6 years of CR enrollment (n=19, 66 observations)



Polynomial terms of enrollment time (quadratic years^2 and cubic years^3) were tested in the mixed model analyses to potentially capture non-linear patterns of change in muscle strength, but were removed from the models as all were non-significant (see Table 3 of Appendix 9 for tests of polynomial terms) and increased the log likelihood and Bayesian Information Criteria of the model. Based on the Bayesian model statistics, the linear models with random intercepts best captured the change in seated back row and knee extension over 6 years of enrollment time, whereas the linear model with a random intercept, random slope, and an unstructured covariance structure best fitted the change in chest press (Table 4.3). There were no influencing observations with high level I and II residuals, and no interactions between enrollment time and age at enrollment in all strength outcomes.

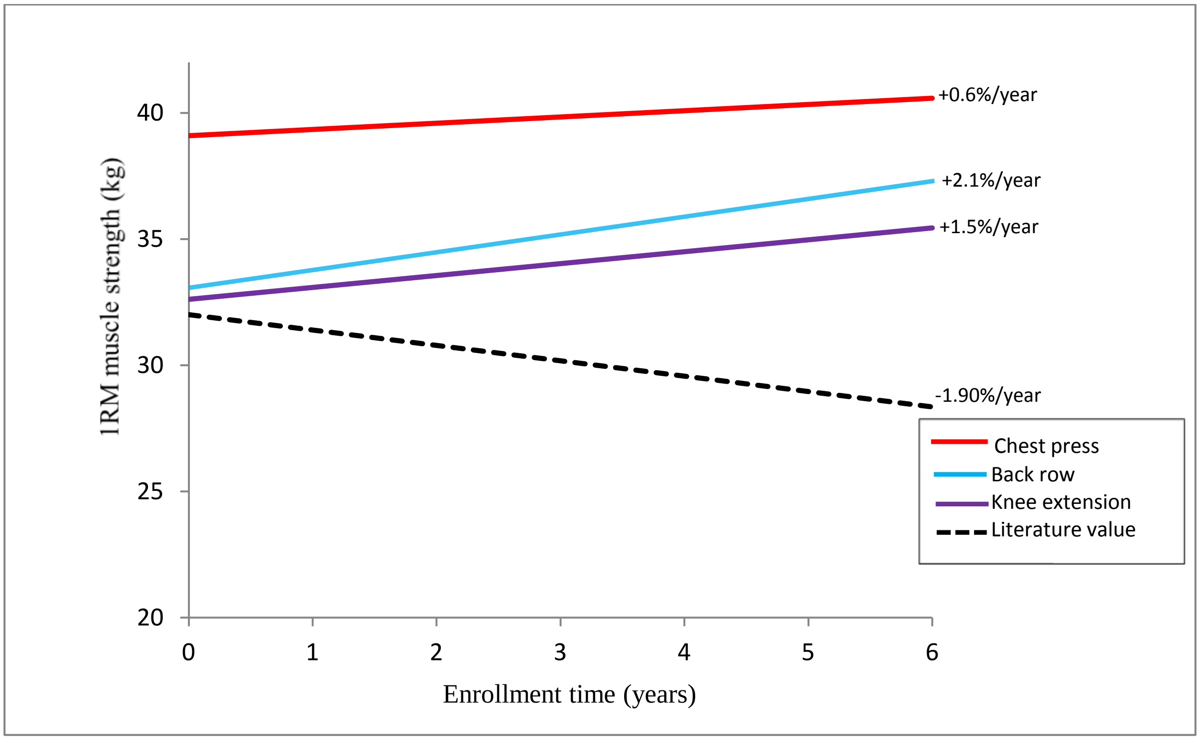
The age-adjusted linear slopes of enrollment time showed that muscle strength outcomes increased (from 0.63 to 2.13%/year) over 6 years, but only reached statistical significance for seated back row (Table 4.3). These slopes increased throughout enrollment, opposite of reported aging-related declines of 1.90%/year from previously published studies (Keller & Engelhardt, 2014; von Haehling, Morley, & Ankler, 2010) (Figure 4.7).

Table 4.3. Mixed model analysis on changes in muscle strength in women over 6 years of CR enrollment after controlling for age (n=19, 66 observations)

Fixed and random effects components from 0-6 years of enrollment			
1. Chest press			
Fixed Effects Variables	*β (SE)*	*95% CI*	*p-value*
IV: Years	0.246 (0.70)	(-1.13, 1.62)	0.725
Covariate: Baseline age	-0.845 (0.20)	(-1.24, -0.45)	<0.0001*
Constant	93.6 (14)	(66.0, 121)	<0.0001*
Random Effects Variance Components	*Estimate (SE)*	*95% CI*	
Intercept	120.3 (44)	(58.7, 247)	
Slope (years)	6.88 (3.1)	(2.87, 16.5)	
Covariance (slope, intercept)	-22.1 (10)	(-42.0, -2.14)	
Residual	16.3 (4.2)	(9.92, 26.9)	
Model Fit Statistics	*Statistic*		
-2 log likelihood	-222.8		
Bayesian Information Criteria	474.9		
2. Seated Back Row			
Fixed Variables	*β (SE)*	*95% CI*	*p-value*
IV: Years	0.705 (0.32)	(0.08, 1.33)	0.026*
Covariate: Baseline Age	-0.554 (0.16)	(-0.87, -0.24)	0.001*
Constant	68.8 (10)	(48.6, 89.1)	<0.0001*
Random Effects Variance components	*Estimate (SE)*	*95% CI*	
Intercept	29.7 (12)	(13.3, 66.3)	
Residual	20.0 (4.1)	(13.4, 30.0)	
Model Fit Statistics	*Statistic*		
-2 log likelihood	-208.8		
Bayesian information criteria	438.6		
***3.* Knee extension**			
Fixed Effects Variables	*β (SE)*	*95% CI*	*p-value*
IV: Years	0.471 (0.31)	(-0.13, 1.07)	0.122
Covariate: Baseline Age	-0.644 (0.21)	(-1.05, -0.24)	0.002*
Constant	74.0 (13)	(47.9, 100)	<0.0001*
Random Effects Variance Components	*Estimate (SE)*	*95% CI*	
Intercept	53.8 (21)	(24.8, 117)	
Residual	18.2 (3.9)	(12.0, 27.6)	
Model Fit Statistics	*Statistic*		
Log likelihood	-211.4		
Bayesian Information Criteria	443.7		

Abbreviations: IV independent variable; SE standard error; CI confidence interval

Figure 4.7. Comparison of predicted changes in muscle strength outcomes in the 19 women over 6 years of enrollment compared to the literature values (Keller & Engelhardt, 2014; von Haehling, Morley, & Ankler, 2010)



4.5 Discussion

This study provides important preliminary knowledge required to help fill gaps in the sex and CR research. The current analysis demonstrated that women enrolled in a structured maintenance-phase CR program demonstrate trajectories of improvement in fitness over 5-6 years of enrollment, contrasting previous research which suggests that fitness would decline over time. These findings provide further evidence to support CR for women living with CVD, but particularly for long-term, ongoing opportunities for exercise.

4.5.1 Effects of exercise-based cardiac rehabilitation programs on fitness

Women enrolled in a maintenance-phase CR program demonstrated increases in fitness throughout 5-6 years of enrollment time (1.5%/year for CRF and 0.6-2.1%/year for muscle strength). Given that CRF and muscle strength tend to decline with typical aging and that little was previously known about the changes in fitness in women after completion of short-term programs, the trajectories of continued positive gains in fitness over multiple years are clinically meaningful. Our previous work conducted in men with CVD (Pryzbek et al., 2019) showed that CRF increased for only 3 years of enrollment of long-term CR and subsequently declined. The more positive findings observed in women in the current study aligns with previous work that reported greater improvements in fitness in women participating in short-term CR programs compared to men (Wise & Patrick, 2012; Cannistra et al., 1992), although this was the first study to examine changes in fitness in women after several years of long-term CR.

The mechanisms underlying the differential effects on fitness between men and women after long-term CR programs are unknown, but may be related to sex differences in physiology and program attendance and exercise adherence.

It must be noted that aerobic fitness levels are higher for men than women at any given age. This is explained by sex differences in the anatomy and physiology of the lungs and airways, musculoskeletal system, and the myocardium and its surrounding blood vessels (LoMaura & Aliverti, 2018; Dickerson, Nagaraja, & Raman, 2010; Finks, 2010; Eng et al., 2016). Men have more muscle mass (Fleg et al., 2005; Goodpaster et al., 2005), higher cardiac index values (cardiac output adjusted for body surface area), and better cardiovascular responses at rest and during sub-maximal exercise, which leads to their higher CRF levels at any age compared to women (Wheatly, Synder, Johnson, & Olson, 2014; Finks, 2010). While men remain more fit than then women, there are several physiological reasons that suggest faster reductions in fitness in men.

The reduction in sex hormones, testosterone and estrogen, plays an important role in the aging effects on the heart, lungs, and skeletal muscle (Brown, 2008; Parker, Kalasky, & Proctor, 2010). It is known that women do not experience a large, abrupt loss in estrogen levels until menopause, but men lose testosterone continuously after the age of 40 years which is associated with their faster loss in skeletal muscle mass (Brown, 2008; Goodpaster et al., 2005). Men do have more muscle mass than women, but the research shows that fat-free mass decreases at faster rates in men with aging (Hughes et al., 2002; Visser et al., 2002). The greater improvements in fitness observed in women in the current study could partially be due to sex differences in reductions in fat-free mass with aging. We measured relative VO_2peak (ml.kg-1.min-1), which only considers total body mass, and is known to decline at slower rates than fat-free mass (Hughes et al., 2002). In addition to fat-free mass, the research shows that women may be more able to achieve greater fitness improvements in women with aging resulting from less steep declines in cardiac output and left ventricular mass (Weiss et al., 2006; Goldspink et al., 2009), stronger flow-mediated vasodilatation effects after exercise training (Black et al., 2009), and slower losses in muscle mass and strength (Goodpaster et al., 2005).

In addition to sex differences in physiology, data on sex differences in program attendance, adherence to exercise prescription, and total physical activity levels are also important variables to consider, but were unavailable in our retrospective data. Historically, women are less likely to attend and complete short-term CR programs (Supervia et al., 2017; Samayo et al., 2014), but are more likely than men to engage in adequate levels (≥150 minutes/week) of physical activity after completion of CR programs (Wise & Patrick, 2012). Future prospective studies of long-term CR programs must collect these data to order to identify potential mechanisms for sex differences in the fitness results.

4.5.2 Under-representation of women in cardiac rehabilitation

Women have been historically under-represented in CR research and have significantly lower referral and enrollment rates compared to men (Anderson et al., 2016; Supervia et al., 2017; Samayo et al., 2014). The CR program at PACE is starting to move away from this by showing a positive trend of increasing enrollment in women over the last 30 years (the trend is shown in the supplemental Figure 1 of Appendix 9). In the current dataset, 20% (39/199) of women were included in the analysis, and 26% (154/599) were enrolled at PACE but not included. These values are higher than the 15% reported the meta-analysis by Anderson et al. (2016). While the increased number of women in our data conveys a positive message of increased utilization of CR in women, the proportion of enrollment still falls far below expected rates that would reflect the prevalence of CVD in women.

The long-standing issue of low referral and under-utilization of CR is common to both men and women, but more so in women (Anderson et al., 2016; Grace et al., 2009). The body of CVD literature is predominantly consisted the data from men, with studies sampling less than 30% women (Mikail, 2005; Garcia et al., 2018) despite comparable rates of prevalence and mortality between men and women (Roth et al., 2017). Under-representation of women is a consequence of many interacting factors, such as how researchers conduct CVD health research and sex biases CVD diagnosis and management (Grace et al., 2009). This under-representation is exacerbated in CR research as even fewer women (15%) are enrolled in CR programs (Anderson et al., 2016). For instance, a recent meta-analysis attempted to compare the effects of CR on mortality and morbidity between women and men but ultimately was not undertaken due to insufficient data in women (Ghishi, Chaves, Bennett, Lavie, & Grace, 2019). These problems exist in CR research because compared to men, women are 47% less likely to be referred to CR which leads to their 36% lower chance of enrollment (Supervia et al., 2017; Samayo et al., 2014). Under-diagnosis and mismanagement of CVD from physicians, lack of strong support once referred, negative perceptions of exercise, family responsibilities, and multiple co-morbidities are barriers to CR utilization in women (Grace et al., 2009; Supervia et al., 2017; Finks, 2010). A key strategy to increase CR utilization in women is to increase referrals. Combined automatic and liaison referral (personal discussion with a nurse or physiotherapist) has increased CR referral and enrollment in Ontario (Grace et al., 2011). This approach may provide a different avenue to CR for women with CVD who would otherwise not likely be referred by their physician.

4.5.3 Study limitations and strengths

The relatively small sample size of 39 women was a limitation to the generalizability of the findings. There was not enough statistical power to perform comparison tests between the observed changes in fitness and aging-related changes from previous studies. However, this was the first study to report on fitness trajectories over 5-6 years of CR in women, which was not possible in the two only other study conducted in long-term CR study which did not disaggregate data by sex (Gayda et al., 2006; Belardinelli et al., 2012). The richness of our dataset also provided a high number of observations over multiple time-points in women, thereby permitting mixed model analyses, and adding novel insights superior to conventional pre-post measurement studies. The data further allowed for identification of random effects and a method of modeling a more complete picture of changes in fitness over time, thus improving the interpretability and generalizability of the findings.

Due to the retrospective nature of this analysis, we could not examine causal links for the observed changes in fitness with exercise training. Also, insights could not to be gained through program attendance, physical activity, healthy eating and diet, and smoking cessation records as this information was not available.

4.5.4 Study conclusions

Although faced with low numbers and significant under-representation in CR compared to men (Anderson et al., 2016), our results offer new evidence of improved fitness trajectories in women after long-term enrollment in supervised, maintenance-phase CR.These findings support the use of long-term exercise opportunities as strategies for secondary prevention in this high-risk population of women. Larger prospective cohort studies are warranted to confirm the observations, and to identify potential mechanisms underlying these changes.

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CHAPTER 5

DISCUSSION

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide, carrying a large global economic burden (Roth et al., 2017). Individuals living with CVD are at elevated risk of mortality and recurrent events (Anderson et al., 2016; Clark, Hartling, Vandermeer, & McAlister, 2005; Taylor et al., 2004). Exercise-based cardiac rehabilitation (CR) programs are well-established secondary prevention programs for persons with CVD that facilitate short-term improvements in fitness (<12 months). To date however, the evidence in long-term CR is very limited. The three studies that form this thesis provide additional support of the benefits of long-term CR on cardiorespiratory fitness (CRF), and also establish a new body of knowledge showing benefits to skeletal muscle strength in both men and women with CVD.

There is a wealth of evidence from previous studies of short-term CR (<12 months) that have established large improvements in CRF (10-30%) (Sandercock, Hurtado, & Cardoso, 2013; Ades, 2001; Laddu et al., 2018; Sumide et al., 2009) and skeletal muscle strength outcomes (Nishitani et al., 2013; Yamamoto et al., 2016; Yang et al., 2015). Improvements in fitness are important for reducing the risk of recurrent events and mortality in this high-risk population (Martin et al., 2013; Hulsmann et al., 2004; Beatty, Schiller, & Whooley, 2012), but ongoing opporutnities for exercise beyond short-term CR are necessary to ensure that the benefits are sustained in the long-term.

Previously, only two studies (Gayda et al., 2006; Belardinelli et al., 2012) had examined changes in fitness after long-term CR. The paucity of long-term CR studies may be due to methodological challenges associated with longitudinal study designs as well as the under-utilization of CR. There is limited availability of early CR programs in Canada with only 220 sites nationwide, the equivalent of one spot per 4.55 patients with CVD (Tran et al., 2018)). Further, only 30-52% of eligible individuals are referred by physicians, fewer than 50% of these actually enroll (Brady, Purdham, Oh, Grace, 2012; Grace et al., 2011; Aragam et al., 2011), and only 20-34% participate and complete early-phase CR (Grace, Bennett, Ardern, Clark, 2014; Ades et al., 2018). Analagous data on availability, enrollment and completion rates of long-term CR programs are not known, but it is likely that due to limited access to early programs, there is even lower enrollment in long-term programs and thus, limited long-term research studies.

Taken together, the three studies that comprise this thesis contribute to our understanding of trajectories in fitness outcomes in individuals enrolled in CR. Our findings in Chapter 2 add to the sparse body of literature supporting CRF benefits after long-term exercise-based CR enrollment in men and created a new body of evidence supporting improvements in skeletal muscle strength (Pryzbek et al., 2019). This study builds upon the earlier work of Gayda et al. (2006) by sampling more participants and employing more advanced statistical models of non-linear trajectories of changes in fitness in 160 men and reporting a quadratic relationship between time and CRF over 5.5 years. However, a limitation of the retrospective design used in both the current study and the previous study by Gayda et al. (2006) was reduced methodological control, such as lack of data on attendance and exercise protocol adherence.

Belardinelli et al. (2012) was able to enact greater methodological control through a prosecptve study that examined changes in CRF among 63 individuals with chronic heart failure. Similar to the current study, Belardinelli and colleagues also found a non-linear trajectory of change, but differed in the rates of change with an initial 14.7% increase in CRF at 12 months of enrollment, a plateau until 3 years, and a linear decline of 1.5%/year until 10 years (Belardinelli et al., 2012). While the magnitude of initial increase was larger and subsequent decline was less than that found in our study, this may have been due to their sample being 5 years younger in age, were earlier post-diagnosis (within 3 months), and had lower baseline levels of CRF (<5 metabolic equivalents). Larger improvements in CRF are expected during earlier phases of CR (Sandercock, Hurtado, & Cardoso, 2013) and among individuals enrolled in CR programs with CRF <5 metabolic equivalents (Laddu et al., 2018; Balady et al., 1996).

Chapter 2 also provided the first evidence of the benefits to skeletal muscle strength after long-term enrollment in maintenance-phase CR in men with CVD. While studies of short-term CR have reported improvement in skeletal muscle strength early after CV events (Nishitani et al., 2013; Yamamoto et al., 2016; Yang et al., 2015), it is also critical to maintain these benefits in the long-term to reduce the risk of recurrent events and mortality in the years that follow (Martin et al., 2013; Hulsmann et al., 2004; Gary et al., 2012). We observed a quadratic relationship in lower body strength (knee extension) with a small 0.18-1.40% increase in the first year of enrollment followed by non-linear declines ranging from 1.00-3.58%/year, which were similar to previously published rates (von Haehling, Morley, & Anker, 2010; Keller & Engelhardt, 2014). We also observed slower linear declines (<1%/year) in upper body strength (chest press and seated back row). While age-associated losses in upper and lower body muscle strength have been attributed to reduced muscle mass, motor unit activation, and muscle quality (Jakobi & Rice, 2002; Frontera et al., 2000; Keller & Engelhardt, 2014), it has also been reported that there is a preferential decline in lower body strength. This may be a result of functional and physiological factors, such as reductions in walking or running activity over time, greater use of upper body support to compensate for weaker lower limbs (Candow & Chilibeck, 2005), and a greater reduction in myosin heavy chain IIb content with age in muscles of the lower body (Jubrias, Odderson, Esselmand, & Conley, 1997).

The richness of data allowed us to explore additional analyses of fitness trajectories in Chapter 3. That CRF and skeletal muscle strength were lower across all time points for older men and those with lower baseline fitness was not surprising, given the literature on aging and fitness in non-CVD populations (Fleg et al., 2005; Keller & Engelhardt, 2014; von Haehling, Morley, & Ankler, 2010). The mechanisms underlying the accelerated declines in CRF and muscle strength with aging, such as reductions in cardiac output, maximum heart rate, skeletal muscle size and function, and peripheral oxygen utilization, are well established (Williams et al., 2006; Sharkley & Gaskill, 2007; Ho, Beard, & Farrell, 1997). Moreover, low baseline fitness is a stronger predictor of improvements in fitness than age, gender, and co-morbidities (Laddu et al., 2018; Baladay et al., 1996), a product of these individuals having more severe cardiovascular pathologies or low physical activity levels, which allows for greater potential to improve modifiable risk factors with long-term exercise (Bruning & Sturek, 2015; Laddu et al., 2018).

While we observed slower rates of improvements and faster rates of decline in fitness outcomes in older participants and those with higher baseline fitness, this should not discourage these individuals from joining long-term CR programs. In fact, their fitness trajectories were at least similar, if not better, to expected declines from the non-CVD aging literature (Fleg et al., 2005; Keller & Engelhardt, 2014; von Haehling, Morley, & Ankler, 2010). These data may suggest stronger responses to exercise training for individuals who were less fit upon program entry, and despite subsequent decline in fitness levels over time, fitness outcomes were higher at every given point for those who were more fit at baseline. Having higher fitness levels are important to reduce risks of recurrent events and morality in high-risk CVD populations (Martin et al., 2013; Hulsmann et al., 2004).

Chapter 4 of this thesis contributes new and novel information regarding the benefits to CRF and skeletal muscle strength after long-term enrollment in maintenance-phase CR in a sample of women. Women showed increases in CRF of 1.5%/ for five years and 0.6-2.1%/year in skeletal muscle strength outcomes throughout six years, despite age-expected declines in fitness (Fleg et al., 2005; Keller & Engelhardt, 2014; von Haehling, Morley, & Ankler, 2010). Although the objective of this study was not to compare trajectories of fitness in men to those of women, the preservations in fitness outcomes in women suggest that they may benefit differently with long-term exercise training compared to men. These findings are consistent with studies of short-term CR programs that did disaggregate their data by sex, which reported greater improvements in fitness in women compared to men (Feola et al., 2015; Balady, Jette, Scheer, & Downing, 1996; Wise & Patrick, 2012; Cannistra, Balady, O'Malley, Weiner, & Ryan, 1992). These sex-related differences may be related to faster losses in testosterone levels (Brown, 2008; Parker, Kalasky, & Proctor, 2010), fat-free mass (Fleg et al., 2012; Goodpaster et al., 2005), cardiac output and left ventricular mass (Weiss et al., 2006; Goldspink et al., 2009), and flow-mediated vasodilatation in men with aging (Black et al., 2009). Nonetheless, this was the first study to report changes in fitness after long-term CR in women and provides a foundation for future prospective studies to confirm our findings and explore potential mechanisms of change.

Barriers to the utilization of CR in men and women are well established (Supervia et al., 2017; Resurreccion et al., 2017; Finks, 2010), but the work by Grace et al. (2009) provided a deeper understanding of the barriers. While both sexes experienced the same total number of barriers to participation in CR, men and women differed in the nature of these barriers (Grace et al., 2009). Challenges with accessing transportation, the presence of more co-morbidities, perceiving exercise as tiring or painful, lack of awareness of CR programs, and family responsibilities were stronger predictors in women for not enrolling in CR, whereas men reported lower self-efficacy in managing CVD alone and that they were already exercising at home or gym as reasons for not enrolling in CR (Grace et al., 2009).

Women are under-represented in CR, and less likely to utilize CR services than men (Anderson et al., 2016). Notably, while women have only slightly lower CVD prevalence and mortality rates compared to men, they make up just 15% of the CR program population (Anderson et al., 2016). In the two previous studies examining changes in fitness with long-term CR, neither had sufficient data to perform separate analyses in women (5/43 in Gayda et al. (2006) and 14/63 in Belardinelli et al. (2012)). Our dataset benefitted from having fitness data for 39 women, enabling us to examine trajectories of fitness with long-term CR separately in women. Interestingly, we noted that an additional 17 women had enrolled in the last 6 months leading up to data extraction, and while they were not included in our analyses as they did not meet enrollment eligibility criteria, this suggests a trend of increasing numbers of women enrolled in long-term CR program (supplemental enrollment data shown in Figure 1 of Appendix 9). Similarly, an additional 40 men enrolled in the last 6 months, but did not meet study eligibility criteria. Interestingly, these data show an increasingly higher proportion of new enrollers in women (30%, 17/57), approximately 2-fold greater than the currently reported 15% (Anderson et al., 2016). The growing proportion of women enrolled in our long-term CR program is indeed promising, and represents important steps towards a better balance between the sexes in CVD research and community programs.

Obtaining enough data in women remains a major challenge for CR research, as evidenced by an attempted meta-analysis to examine sex differences in the effects of exercise on mortality and morbidity but only 2 of 80 studies had data available in women (Ghishi, Chaves, Bennett, Lavie, & Grace, 2019). Our study was the first with sufficient data to conduct separate analyses in 39 women. Earlier studies of long- (Gayda et al., 2006; Belardinelli et al., 2012) and short-term CR studies (Nishitani et al., 2013; Sumide et al., 2009; Sandercock, Hurtado, & Cardoso, 2013; Anderson et al., 2016; Santos et al., 2014; Yang et al., 2015) reported results with both sexes combined, likely because of small samples of women or that the importance of examining sex and gender differences were not known or understood (Anderson et al., 2016; Yamamoto et al., 2016; Heart and Stroke, 2018; Mikail, 2005). Understanding potential differences in how men and women respond differently to exercise training can help better deliver effective secondary prevention CR programs.

Overall, the observed trajectories in fitness reported in this thesis following long-term enrollment in CR among men and women provide positive support to the CR literature. We acknowledge the limitations of the data and as such, the findings must be interpreted cautiously. The retrospective design of the studies does not permit us to examine causal links and identify mechanisms, nor for potential insights to be gained through program attendance, exercise adherence, and physical activity records, as this information was not available. There was a smaller sample size for muscle strength outcomes which limits the generalizability of these findings. Nonetheless, the dataset provided a high number of observations over multiple time-points, thereby permitting mixed effects analyses and adding novel insights that were not possible in previous studies that used pre-post measurement designs. Moreover, the analyses allowed for identification of random effects and a method of modeling a more complete picture of the non-linear changes over time, thus improving the interpretability and generalizability of the observations and conclusions.

We acknowledge that there were limitations in selecting literature comparison rates for changes in fitness. Firstly, we chose to use comparison values reported in adults without history of CVD (Fleg et al., 2005; von Haehling, Morley, & Anker, 2010; Keller & Engelhardt, 2014) as there are no established analogous rates available in CVD populations, but postulated that at minimum, these were conservative comparisons. Although fitness levels are higher across all age groups among persons without CVD compared to those with CVD (Gayda et al., 2006; Marin et al., 2013; Mora et al., 2007), the rates of decline associated with aging are likely similar (Fleg et al., 2005; Stathokostas et al., 2004; Jackson, Sui, Hebert, Church, & Blair, 2009). Secondly, we did not apply sex-specific rates of declines in skeletal muscle strength. Some studies have reported faster rates of decline in muscle strength among men compared to women (Goodpaster et al., 2005; Doherty, 2003) but we selected rates reported by Keller & Engelhardt (2014) and von Haehling, Morley, & Ankler (2010), which while were not sex-specific, were more conservative and representative of the age distribution in our data.

In summary, our data provide evidence of benefits to CRF and skeletal muscle strength in men and women after long-term enrollment in maintenance-phase CR. CR programs remain under-utilized, especially in women, and the opportunities for long-term exercise training are very limited in CVD yet important for reducing the risks of recurrent events and mortality. Future prospective work is warranted with larger sample sizes to confirm the benefits observed in fitness trajectories and identify potential mechanisms underlying these changes.

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APPENDIX 1

The Physical Activity Centre of Excellence Cardiac Rehabilitation Program

Ivor Wynne Centre
1280 Main Street West
Hamilton, ON L8S 4L8
T: 905-525-9140 ext. 24877
F: 905-525-7629

McMaster University

PACE
McMaster Physical Activity Centre of Excellence

CLIENT INFORMATION

NAME:			DATE:
ADDRESS:			
CITY:	PROVINCE:		POSTAL CODE:
FAMILY PHYSICIAN: PHYSICIAN CONTACT INFO:		HEALTH CARD NUMBER:	
HOME PHONE:	CELL PHONE:		WORK PHONE:
DATE OF BIRTH: YYYY-MM-DD	OCCUPATION:		EMPLOYER:
HOW DID YOU HEAR ABOUT US?			
WHAT PROGRAM ARE YOU CONSIDERING? (PLEASE CHECK ONE) ☐MACSENIOR ☐MACCARDIAC ☐MS-FITT ☐MACWHEELER'S ☐MACWARRIORS			
EMAIL:			
EMERGENCY CONTACT:	RELATION:		PHONE:

Ivor Wynne Centre
1280 Main Street West
Hamilton, ON L8S 4L8
T: 905-525-9140 ext. 24877
F: 905-525-7629

CONSENT TO RELEASE INFORMATION

NAME:	DATE OF BIRTH: YYYY-MM-DD

I hereby give my permission to the Physical Activity Centre of Excellence to release my personal information as per my request. I understand that this form is in accordance with the Privacy Act and that my personal information will not be used for secondary purposes.

I consent to the release of my information to be shared with all members of the PACE team. This includes, but is not limited to; Director, Program Coordinator, Registered Kinesiologists, Registered Physiotherapists, Placement Students, Staff, and Volunteers. I give my permission to PACE to contact physicians within my circle of care to obtain information that could directly impact my activities at the PACE.

Furthermore, on occasion, the McMaster community may have media present within the facility to educate and promote current and future programs. Pictures, video, and other media forms may be taken at this time for use within the community. By signing this form you consent to having your photo or video taken and used in accordance with the Privacy Act.

PARTICIPANT NAME (PRINTED) ______________________

SIGNATURE OF PARTICIPANT ______________________

WITNESS NAME (PRINTED) ______________________

SIGNATURE OF WITNESS ______________________

DATE ______________________

Ivor Wynne Centre
1280 Main Street West
Hamilton, ON L8S 4L8
T: 905-525-9140 ext. 24877
F: 905-525-7629

Extended Health Care Coverage Form

NAME:	DATE:
DATE OF BIRTH: YYYY-MM-DD	
EXTENDED HEALTH CARE COMPANY: Contact Information:	POLICY #:
	MEMBER ID:

Please specify what amount of third-party medical coverage you are entitled to under your current insurance policy.

*Failure to provide details will result in the impression that there is no coverage

	Does your insurance company cover? (Y/N)	Maximum number of visits	Maximum coverage per visit	% Covered	Annual Max
Physiotherapy					
Exercise therapy					
Cardiac Rehabilitation					
Registered Kinesiologist					

Extended Health Care Coverage Form Continued

	Does your insurance company cover? (Y/N)	Maximum number of visits	Maximum coverage per visit	% Covered	Annual Max
Braces & Pressure Stockings					
Chiropractic					
Osteopathy					
Massage Therapy					
Orthotics					
Other: please specify					

What does your insurance company require from us?

____
____
____
____
____

Medical History Questionnaire

NAME:	DATE:
DATE OF BIRTH: YYYY-MM-DD	HEIGHT:__________ WEIGHT:__________ BMI: __________

1. MEDICAL HISTORY

Have you ever been diagnosed as having any of the following conditions?			If yes, year of diagnoses;
Cardiac Event (MI/PTCA/CABG/other)	☐ Yes	☐ No	__________
Stroke/Transient ischemic attack (TIA)	☐ Yes	☐ No	__________
Angina (chest pain)	☐ Yes	☐ No	__________
Arthritis	☐ Yes	☐ No	__________
Peripheral vascular disease	☐ Yes	☐ No	__________
Osteoporosis	☐ Yes	☐ No	__________
Neuropathies (problems with sensations)	☐ Yes	☐ No	__________
If yes, describe: __________			
Respiratory disease	☐ Yes	☐ No	__________
Parkinson's disease	☐ Yes	☐ No	__________
Multiple sclerosis	☐ Yes	☐ No	__________
Polio/post-polio syndrome	☐ Yes	☐ No	__________
Epilepsy/seizures	☐ Yes	☐ No	__________
Visual (glaucoma, macular degeneration, etc.)	☐ Yes	☐ No	__________
Inner ear problems/recurrent ear infections	☐ Yes	☐ No	__________
Other movement disorders	☐ Yes	☐ No	__________
Depression/Anxiety/Other Mental Illness	☐ Yes	☐ No	__________

2. CARDIOVASCULAR RISK FACTORS

High Blood Pressure	☐ Yes	☐ No	____________
Elevated Cholesterol	☐ Yes	☐ No	____________
Diabetes (Type 1 or 2) or Metabolic Disease	☐ Yes	☐ No	____________
Physical Inactivity (<150 min. per week of moderate intensity exercise)	☐ Yes	☐ No	____________
Chemical dependency (alcohol or drugs)	☐ Yes	☐ No	____________
Kidney Disease	☐ Yes	☐ No	____________
Known Cardiovascular Disease(CVD)	☐ Yes	☐ No	____________
Smoking	☐ Yes	☐ No	____________

3. Have you ever been diagnosed with cancer? ☐ Yes ☐ No
   If yes, please specify type and any treatment past and present: ____________

   ____

   ____

   ____

   ____

4. Have you had a joint Replacement: ☐ Yes ☐ No

   If yes, please specify:

   ☐ Right hip Date: ____________

   ☐ Left hip Date: ____________

   ☐ Right knee Date: ____________

   ☐ Left knee Date: ____________

5. Please list any injuries you have had (past or present) and how they may limit your physical activity (if applicable)

   ____

   ____

   ____

6. Have you been diagnosed with a cognitive disorder: ☐ Yes ☐ No
   If yes, please describe: ____

   ____

   ____

7. Any other health concerns? ☐ Yes ☐ No
   If yes, please describe: ____

   ____

   ____

   ____

8. List all medications that you currently take (including all over-the-counter and alternative medicines)

Type of Medication (and dose)	*For what condition?*
____________________	____________________
____________________	____________________
____________________	____________________
____________________	____________________
____________________	____________________
____________________	____________________
____________________	____________________
____________________	____________________
____________________	____________________
____________________	____________________

9. Do you require the use of (please check):

	Yes	No
a. Hearing aid	☐	☐
b. Eyeglasses	☐	☐
c. Walking aid		
i. Cane	☐	☐
ii. Walker	☐	☐
iii. Other: ___________	☐	☐

MOBILITY & FALLS

10. Have you ever had any condition or experience any injury that has affected your balance or ability to walk without assistance?

☐ Yes ☐ No

If yes, please describe: ______________________________

____

____

11. How many times have you fallen *within the past 6 months?*__________

a. Date: ____________________

b. Location:____________________

c. Reason for fall: ______________________________

____

____

____

d. Did you require medical treatment? ☐ Yes ☐ No

e. Please provide some details for any additional fall you may have had in the past 6 months:

____

____

____

12. How concerned are you about falling?

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Not at all	A little	Moderately	Very	Extremely

13. As a result of this concern, have you stopped doing some of the things you used to do or liked to do?

☐ Yes ☐ No

14. In general, do you currently require household or nursing assistance to carry out daily activities? ☐ Yes ☐ No

If yes, please describe the assistance needed/received: ____________________

____

____

____

____

ACTIVITY

15. Do you currently participate in regular physical activity (such as walking, sports, exercise classes, housework, or yardwork)?
☐ Yes ☐ No

If yes, please describe type of activity and duration: ______________________

____

____

____

If yes, how many times per week?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

16. How would you describe your overall health?

☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor

17. In general, how would you rate the quality of your life?

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Very low	Low	Moderate	High	Very high

---

18. Please indicate your ability to do each of the following (Please check all those that apply):

	Can do	Can do with difficulty or with help	Cannot do	Comments
a. Take care of own personal needs (e.g., dressing yourself, toileting, upkeep of personal hygiene)	☐ 2	☐ 1	☐ 0	
b. Bathe yourself, using tub or shower	☐ 2	☐ 1	☐ 0	
c. Climb up and down a flight of stairs (e.g., second story)	☐ 2	☐ 1	☐ 0	
d. Do light household activities (e.g., cooking, dusting, washing dishes, sweeping a walkway)	☐ 2	☐ 1	☐ 0	
e. Do heavy household activities (e.g., scrubbing floors, vacuuming, raking leaves)	☐ 2	☐ 1	☐ 0	
f. Do own shopping for groceries	☐ 2	☐ 1	☐ 0	
g. Walk outside (one or two blocks)	☐ 2	☐ 1	☐ 0	
h. Walk ½ mile	☐ 2	☐ 1	☐ 0	
i. Walk 1 mile	☐ 2	☐ 1	☐ 0	
j. Lift and carry 10 pounds	☐ 2	☐ 1	☐ 0	
k. Lift and carry 25 pounds	☐ 2	☐ 1	☐ 0	
l. Do strenuous activities	☐ 2	☐ 1	☐ 0	

Health Questionnaire

1. Past Surgeries
   Have you ever undergone any major elective/emergency operative procedure?
   Yes____ No____
   (i) When? ________________________________
   (ii) Specify surgery(ies) ________________________________

2. General Health
   Have you, or do you currently suffer from…
   a) Heart or lung problems? Yes_____No____
      Comment:
   b) Stroke? Yes_____No____
      Comment:
   c) Cancer? Yes_____No____
      Comment:
   d) Parkinson's Disease? Yes_____No____
      Comment:
   e) Arthritis or joint problems? Yes_____No____
      Comment:
   f) Severe Osteoporosis? Yes_____No____
      Comment:
   g) Nerve injury in the legs? Yes_____No____
      Comment:
   h) Any congenital hip/knee/ankle/foot
      Or orthopaedic condition or disease? Yes_____No____
      Comment:
   i) Foot deformities or podiatric conditions
      requiring orthotics or special footwear? Yes_____No____
      Comment:
   j) Diabetes or circulatory problems? Yes_____No____
      Comment:
   k) Blindness? Yes_____No____
      Comment:
   l) Fainting or dizzy spells? Yes_____No____
      Comment:

Additional Comments:
____
____

3. Medications
   Are you currently taking any medication(s)? Yes___ No ___
   List: ____
   ____
   ____

4. Do you regularly consume alcohol? Yes___ No___
   Number of drinks a day: ___________

5. Do you smoke Yes____ No____

CURRENT PHYSICAL ACTIVITIES

List all sport and leisure time activities:

____

____

____

____

____

CURRENT GOALS:

1.

2.

3.

4.

McMaster University

PACE McMaster Physical Activity Centre of Excellence

Name: ______________________________

Date: ______________________________

Age: ____________ DOB: ____________

Phone (c): __________ (h):____________

☐ Mac Seniors ☐ Mac Cardiac

PACE PHYSIOTHERAPY INTAKE ASSESSMENT

Summary of Medical History/Diagnoses from Health Questionnaire	

Social History

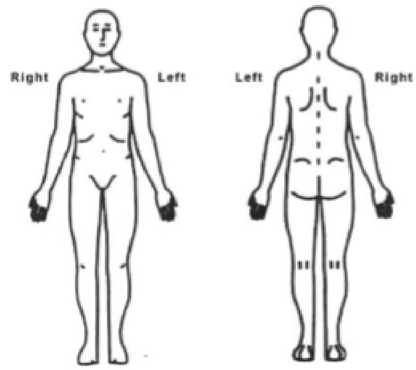
		Range of Motion and Strength (manual muscle testing) Completed as indicated by reports of pain, impairment, medical history or diagnosis				
Movement		Right ROM	Right MMT	Left ROM	Left MMT	Comments
Shoulder	AB Flex Ext IR ER					
Elbow	Flex Ext					
Wrist	Flex Ext					
Hip	AB Flex Ext IR ER					
Knee	Flex Ext					
Ankle	DF PF					

Name: ______________________

Date: ______________________

Age: __________ DOB: __________

PACE PHYSIOTHERAPY INTAKE ASSESSMENT
Continued



Special Tests	Posture

Sensation	Edema/Other Observations

Myotomes

- C3 neck side flex
- C4 sh. elevation
- C5 elbow flex/wrist ext
- C6 elbow ext./wrist flex
- C7 thumb ext/ulnar deviation
- C8 finger ab/add'n
- L2 Hip flexion
- L3 knee extension
- L4 Ankle dorsiflexion
- L5 Great toe extension
- S1 Ankle plantar flexion, ankle eversion, hip extension
- S2 Knee flexion

Senior Fitness Test		
Test Item	**Score**	**Rating and Comments**
30s Chair Stand		
Arm Curl	Right Left	
2 min. Step in Place		
Chair Sit and Reach (cm)	Right Left T_1 T_2	
Back Scratch (cm)	Right Left T_1 T_2	
8 foot Up and Go (s)	T_1 T_2	
6 min. Walk (km)		

PACE PHYSIOTHERAPY INTAKE ASSESSMENT
Continued

Name: ____________________
Date: ____________________
Age: __________ DOB: __________

Balance and Mobility		
Test Item	**Score**	**Rating and Comments**
Fullerton Advanced Balance Scale – short form	/16	
Berg Balance Scale – short form	/28	
30-foot walk Preferred speed	# steps ________ Time (s) ________ Velocity: ________ Stride length: ________ Cadence: ________	
Maximum speed	# steps ________ Time (s) ________ Velocity: ________ Stride length: ________ Cadence: ________	

Assessment/Plan/Goals

PACE PHYSIOTHERAPY INTAKE ASSESSMENT
Continued

Name: ______________________
Date: ______________________
Age: ____________ DOB: ____________

Exercise Precautions/Recommendations **(e.g. rotator cuff injury – no overhead lifting, hip replacement – avoid deep squats, etc.)**
1.
2.
3.
4.
5.
6.

☐ Appropriate for independent exercise program

☐ Supervision or light assistance by student/volunteer recommended due to ____________

____

____

____

☐ Consent obtained for assessment

____
Physiotherapist's Signature

<u>**Exercise Training Log**</u>

DATE	Treadmill	Bike	Arm Cycle	Stairs/Nu-Step	RT
WT. _____ HR _____ BP ______	___MIN@ ___MPH___%=_____ ___MIN@ ___MPH___%=_____	___MIN@___=____ ___MIN@___=____ ___MIN@___=____ ___MIN@_____=____	___MIN@___=____ ___MIN@___=____ ___MIN@___=____	___MIN@___=____ ___MIN@___=____ ___MIN@___=____	
WT. _____ HR _____ BP ______	___MIN@ ___MPH___%=_____ ___MIN@ ___MPH___%=_____	___MIN@___=____ ___MIN@___=____ ___MIN@___=____ ___MIN@___=____	___MIN@___=____ ___MIN@___=____ ___MIN@___=____	___MIN@___=____ ___MIN@___=____ ___MIN@___=____	
WT. _____ HR _____ BP ______	___MIN@ ___MPH___%=_____ ___MIN@ ___MPH___%=_____	___MIN@___=____ ___MIN@___=____ ___MIN@___=____ ___MIN@___=____	___MIN@___=____ ___MIN@___=____ ___MIN@___=____	___MIN@___=____ ___MIN@___=____ ___MIN@___=____	
WT. _____ HR _____ BP ______	___MIN@ ___MPH___%=_____ ___MIN@ ___MPH___%=_____	___MIN@___=____ ___MIN@___=____ ___MIN@___=____ ___MIN@_____=____	___MIN@___=____ ___MIN@___=____ ___MIN@___=____	___MIN@___=____ ___MIN@___=____ ___MIN@___=____	
WT. _____ HR _____ BP ______	___MIN@ ___MPH___%=_____ ___MIN@ ___MPH___%=_____	___MIN@___=____ ___MIN@___=____ ___MIN@___=____ ___MIN@___=____	___MIN@___=____ ___MIN@___=____ ___MIN@___=____	___MIN@___=____ ___MIN@___=____ ___MIN@___=____	
WT. _____ HR _____ BP ______	___MIN@ ___MPH___%=_____ ___MIN@ ___MPH___%=_____	___MIN@_____=____ ___MIN@_____=____ ___MIN@_____=____ ___MIN@_____=____	___MIN@___=____ ___MIN@___=____ ___MIN@___=____	___MIN@___=____ ___MIN@___=____ ___MIN@___=____	

Training Heart Rate Range _______________ beats per minute

Note: All cycling to be done at 50-60 RPM

APPENDIX 2

Additional Analyses of Changes in Cadiorespiratory Fitness in Men using Absolute VO_2peak

Figure 1. Non-truncated trajectory of absolute VO_2peak in 160 men (n=918 observations)

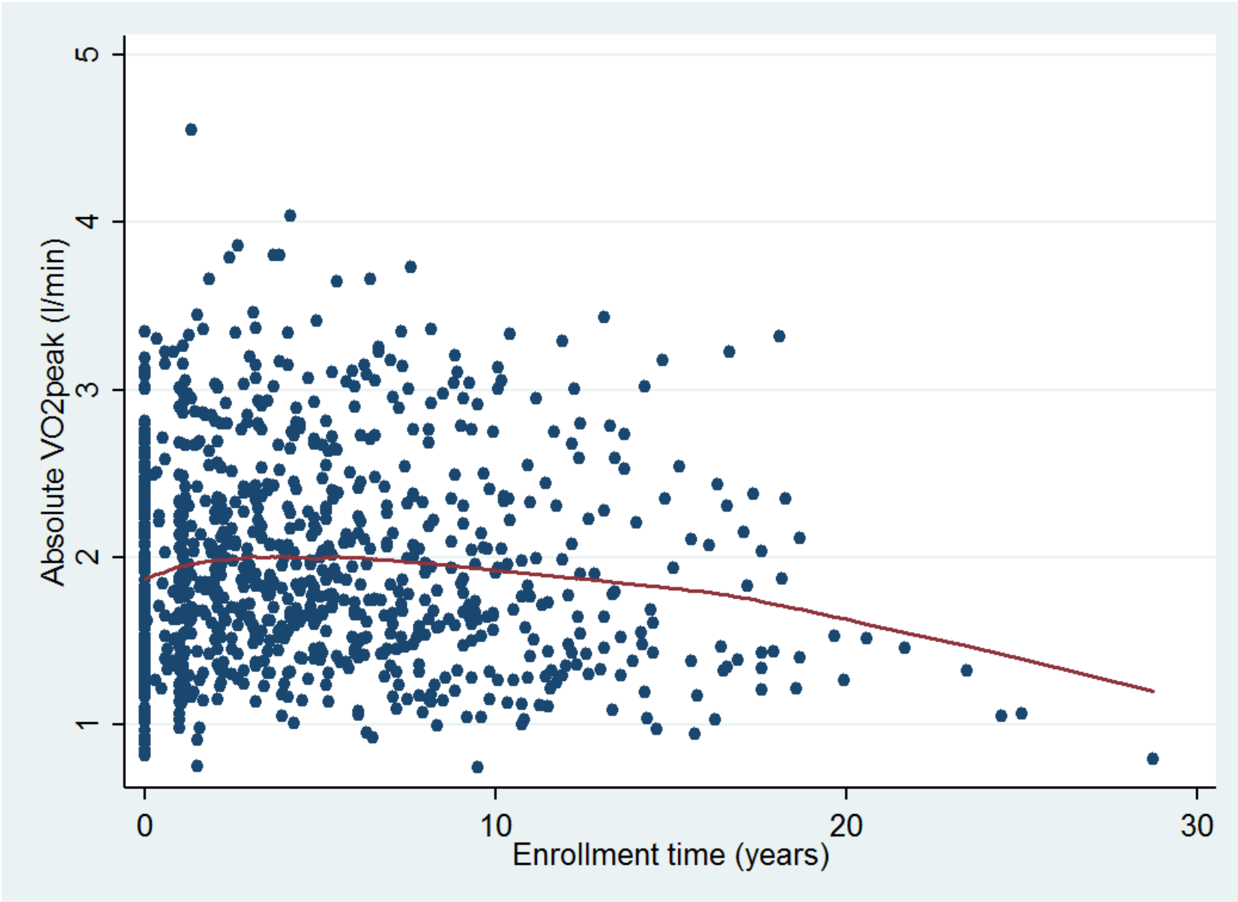


Figure 2. Truncated trajectory of absolute VO_2peak in 160 men (n=599 observations)

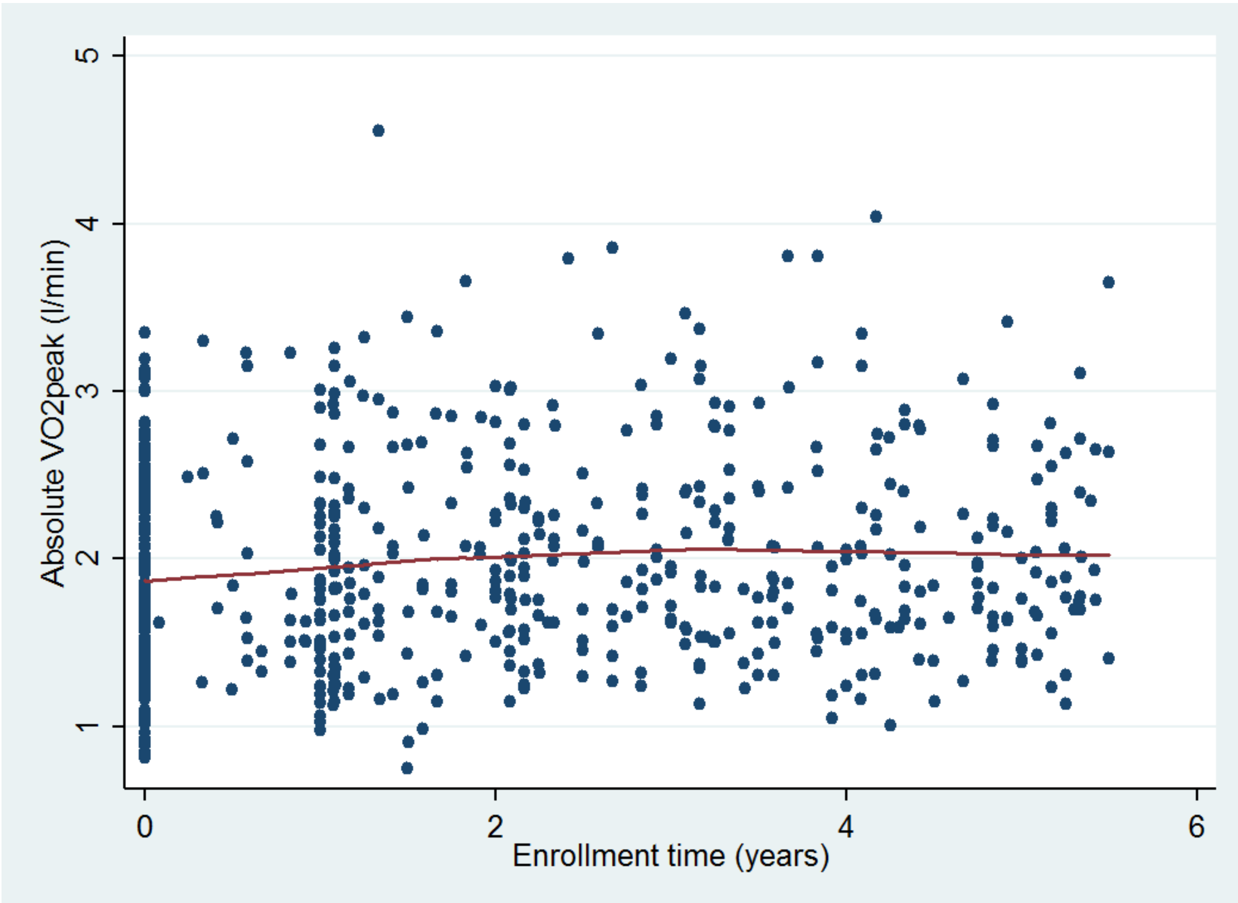


Table 1. Mixed model analysis on changes in absolute VO_2peak levels over 5.5 years after controlling for age (n=160, 594 observations)

Fixed and random effects components from 0-5.5 years of enrollment			
Fixed Effects Variables	*β (SE)*	*95% CI*	*p-value*
IV1: Years	0.080 (0.02)	(0.05, 0.11)	<0.001*
IV2: Years^2	-0.014 (0.003)	(-0.02, -0.01)	<0.001*
Covariate: Baseline Age	-0.034 (0.004)	(-0.04, -0.03)	<0.001*
Constant	4.05 (0.26)	(3.53, 4.56)	<0.001*
Random Effects Variance Components	*Estimate (SE)*	*95% CI*	
Slope (years)	0.004 (0.001)	(0.003, 0.007)	
Intercept	0.208 (0.025)	(0.163, 0.264)	
Residual	0.037 (0.003)	(0.031, 0.043)	
Model Fit Statistics	*Statistic*		
-2 log likelihood	-155.3		
Bayesian Information Criteria	355.3		

Abbreviations: IV independent variable; SE standard error; CI confidence interval. Four outlying observations with high influence removed. No observed random effects variance on the slope years^2 (estimate (SE) 5.76×10^{-26} (2.04×10^{-25}), 95% CI (5.64×10^{-29}, 5.89×10^{-23})).

Figure 3. Mixed model graph of predicted absolute VO_2peak trajectory in men

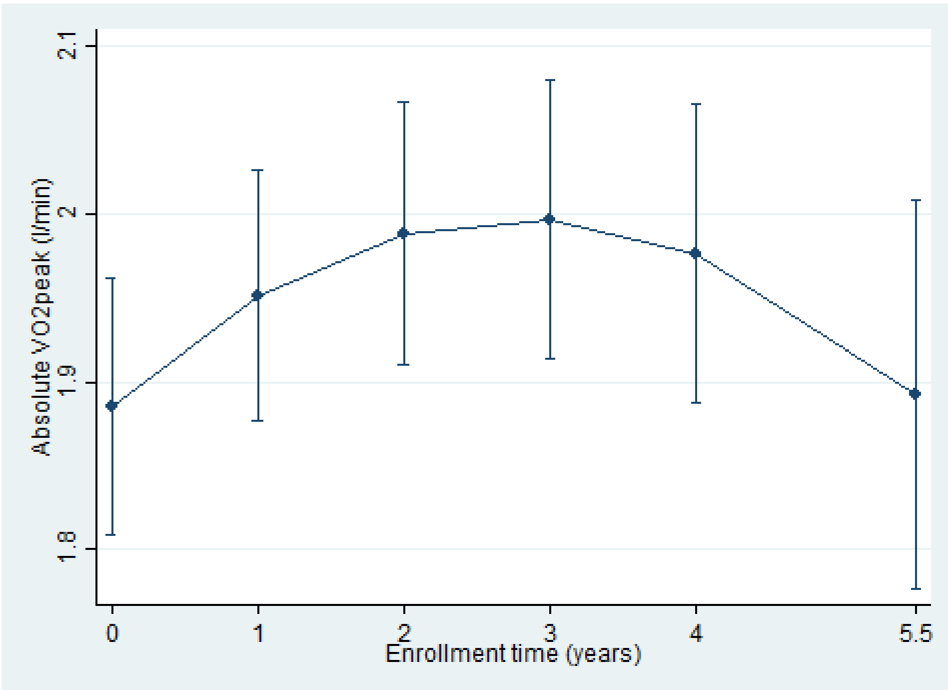


Table 2. Computed %/year changes in absolute VO_2peak by enrollment time interval compared to calculated age-specific literature value (-2%/year)

Time	Observed change	Literature value	p-value
0-1 years	+3.49%/year		<0.001*
>1-2 years	+1.91%/year		<0.001*
>2-3 years	+0.43%/year	-2%/year	0.017*
>3-4 years	-1.07%/year		0.246
>4-5.5 years	-2.84%/year		0.208

Literature comparison value from Fleg et al. (2005)

APPENDIX 3

Visual of Hydrafitness Omnikinetics Machine for Skeletal Muscle Strength Testing

Source: Texas Health Resources Stephenvile-Fort Worth Texas (2010)

APPENDIX 4

Data Extraction Information and Codebook

<u>Data extraction variables and code information</u>

<u>Variable</u>	**<u>Code Information</u>**
ID	
Initials of individual's name	
Background variables	
Reason excluded	1 – no CPET 2 – only 1 CPET 3 – <1 year enrolled 4 – non-matching modalities (i.e. treadmill and bicycle) 999 – included for analysis
Gender	1 – male 2 – female
Age	Years
Enrollment time	Years
CPET date	Month and year (i.e. January 2010)
Date of condition or event	Month and year
Enrollment reason	CABG, MI, heart failure, ect…
Time since enrollment reason	Years
Smoking history	0 – never smoked 1 – current smoker 2 – former smoker 3 – ever smoked (could be current or former) 4 – either never smoked or former smoker
Quit smoking among ever smokers	0 – no 1 – yes
Date quit	Month and year
Pack-year exposure	Years
Weight	Kg
Height	Cm
Body fat	%
Hemoglobin	mg/dl
Medications use: Blood pressure Cholesterol Diabetes	0 – no 1 – yes
Exercise variables	
CPET modality	1 – bicycle 2 – treadmill
Metabolic equivalents	METS

Absolute VO_2peak	l/min
Relative VO_2peal	ml.kg-1.min-1
Peak aerobic power	kpm/min
Resting heart rate	Beats per minute
Resting systolic blood pressure	mmHg
Resting diastolic blood pressure	mmHg
Peak heart rate	Beats per minute
Peak systolic blood pressure	mmHg
Peak diastolic blood pressure	mmHg
1RM chest press	Kg
1RM seated back row	Kg
1RM knee extension	Kg

Abbreviations: CPET cardiopulmonary exercise test; 1RM 1-repetition maximum

APPENDIX 5

Calculation of Literature Comparison Values in Men

Calculation of age-specific cardiorespiratory fitness literature comparison values in men

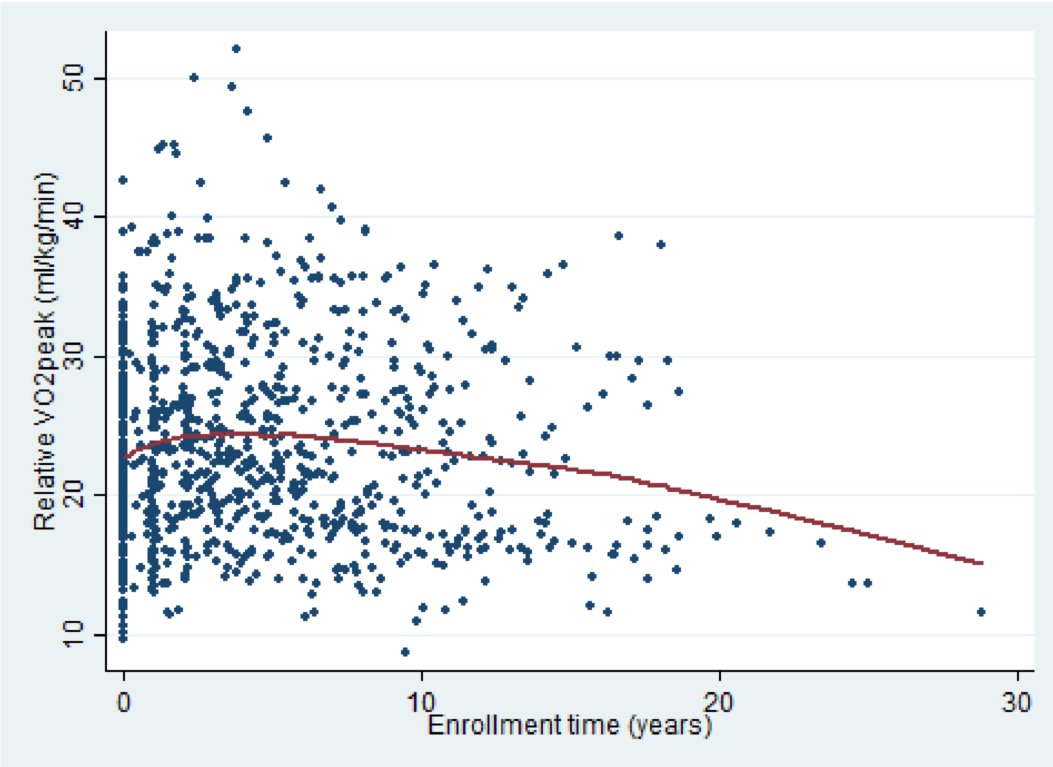
Decade	n	Literature Decline	Computing the comparison value*
40s	10	-10.3%/decade	10/160 x -10.3%= -0.64%
50s	40	-15.7%/decade	40/160 x -15.7%= -3.93%
60s	57	-19.8%/decade	57/160 x -19.8% = -7.05%
70s +	53	-24.3%/decade	53/160 x -24.3%= -8.05%
ALL	**160**		**= -20%/decade or -2.0%/year**

*Decade-specific %/decade decline values from Fleg et al. (2005)

APPENDIX 6

Lowess Curves of Non-Truncated Relative VO_2peak Outcome in Men

Non-truncated trajectory of relative VO_2peak in 160 men (n=918 observations)



APPENDIX 7

Supplemental Skeletal Muscle Strength Results in Men

Figure 1. Non-truncated trajectory of 1RM chest press in 70 men (n=505 observations)

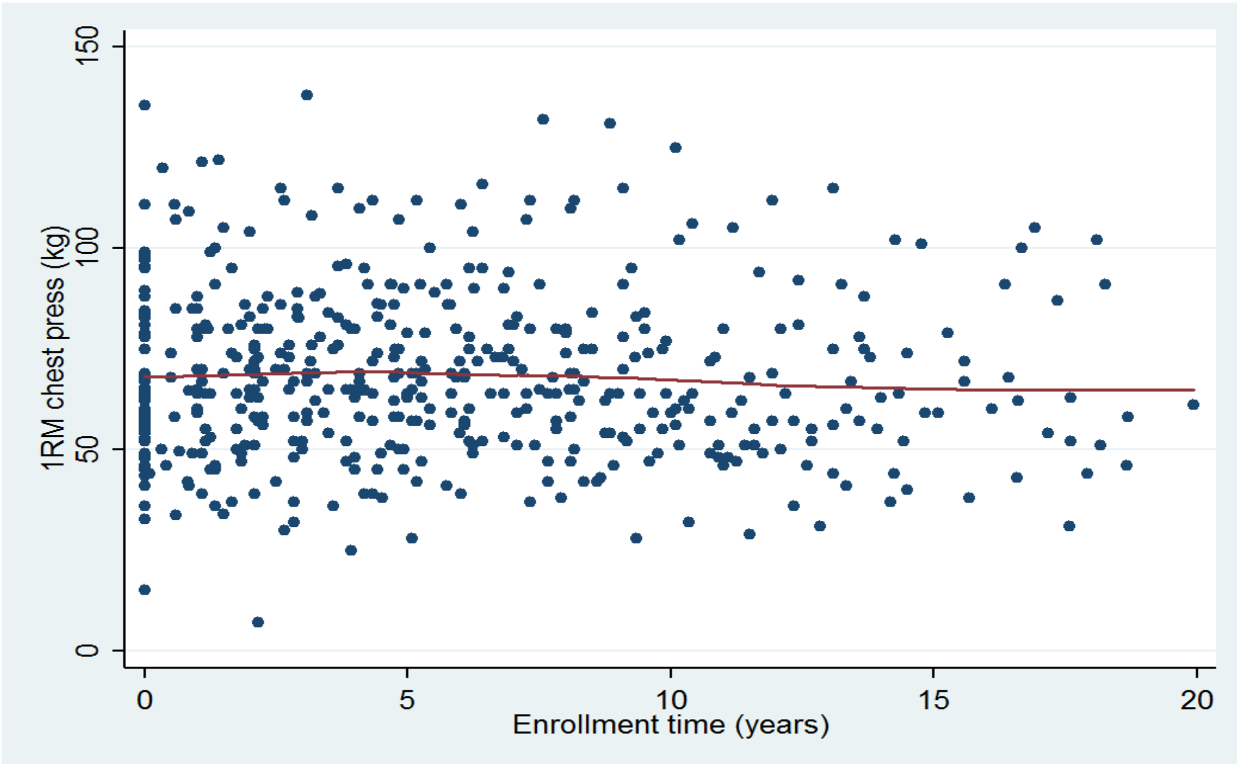


Figure 2. Non-truncated trajectory of 1RM seated back row in 70 men (n=505 observations)

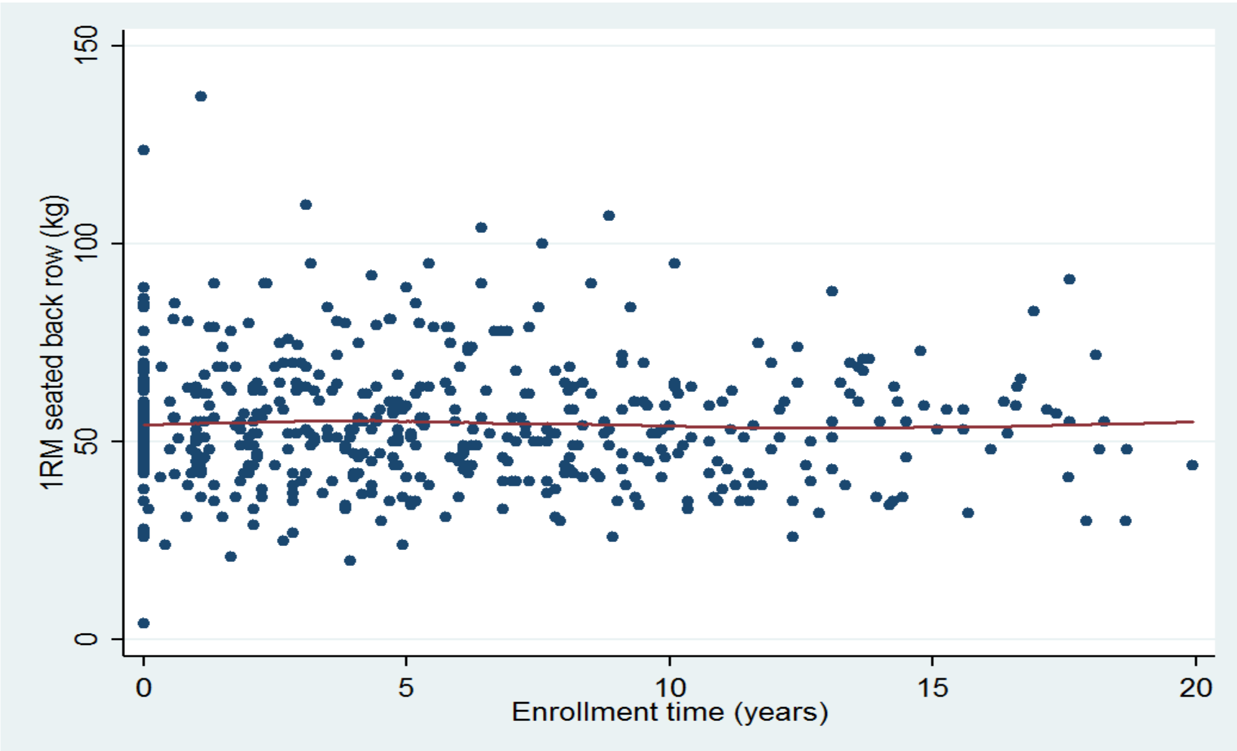
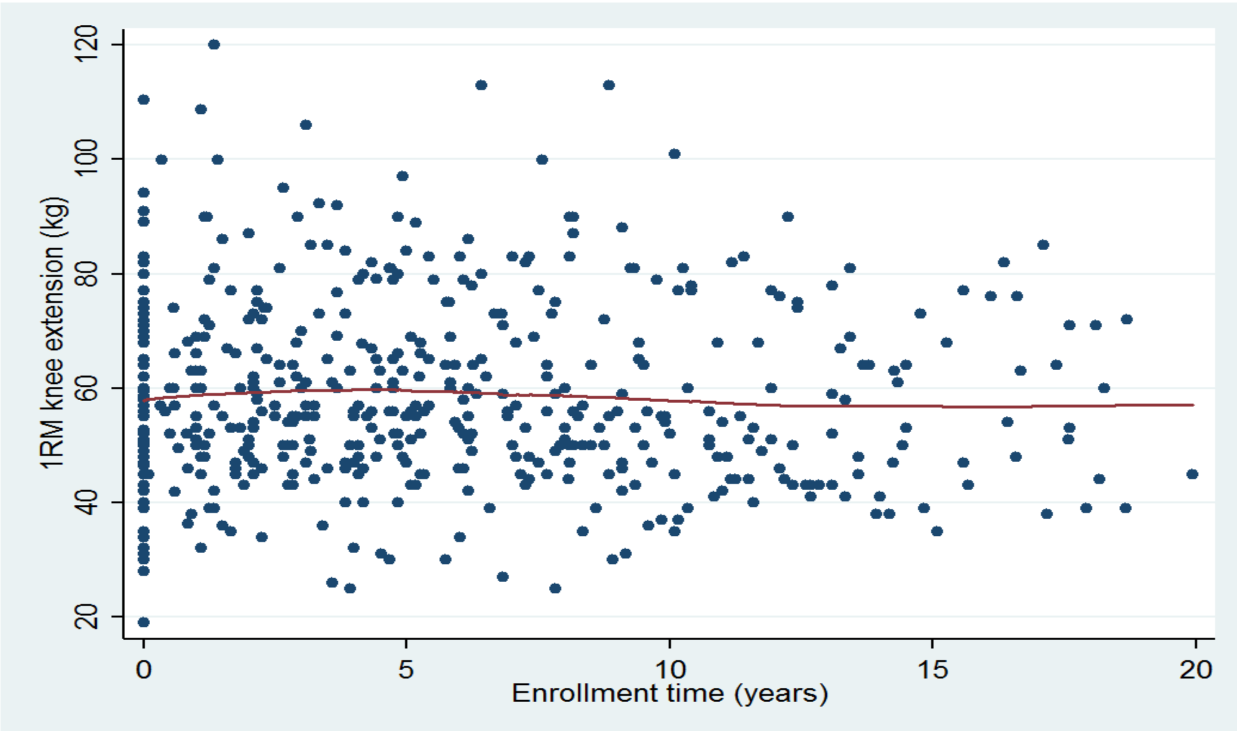


Figure 3. Non-truncated trajectory of 1RM knee extension in 70 men (n=503 observations)



APPENDIX 8

Additional Analyses of the Association between Age and Changes in Cardiorespiratory Fitness in Men using Absolute VO_2peak for Chapter 3

Figure 1. Non-truncated trajectory of absolute VO_2peak in 160 men (n=918 observations)

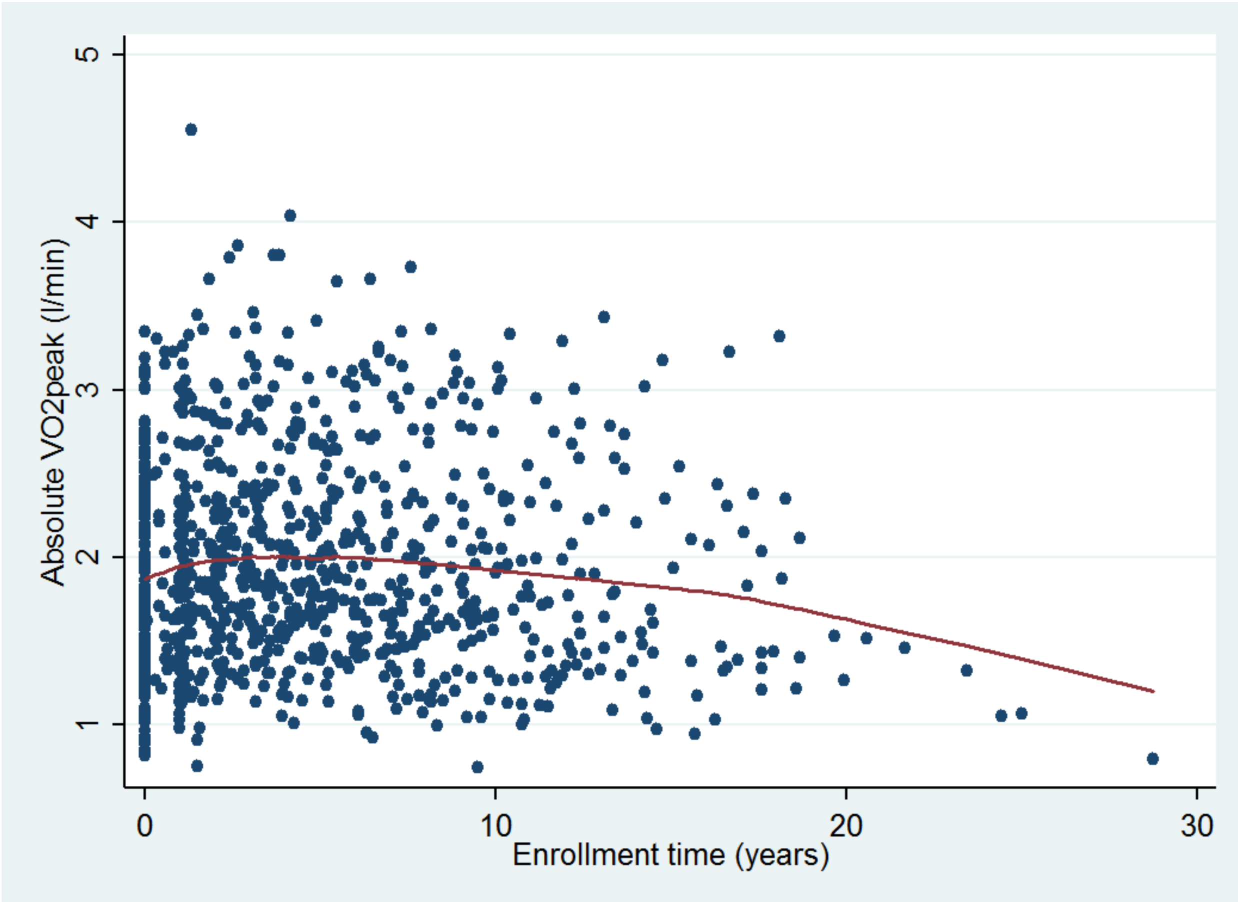


Figure 2. Truncated trajectory of absolute VO_2peak in 160 men (n=599 observations)

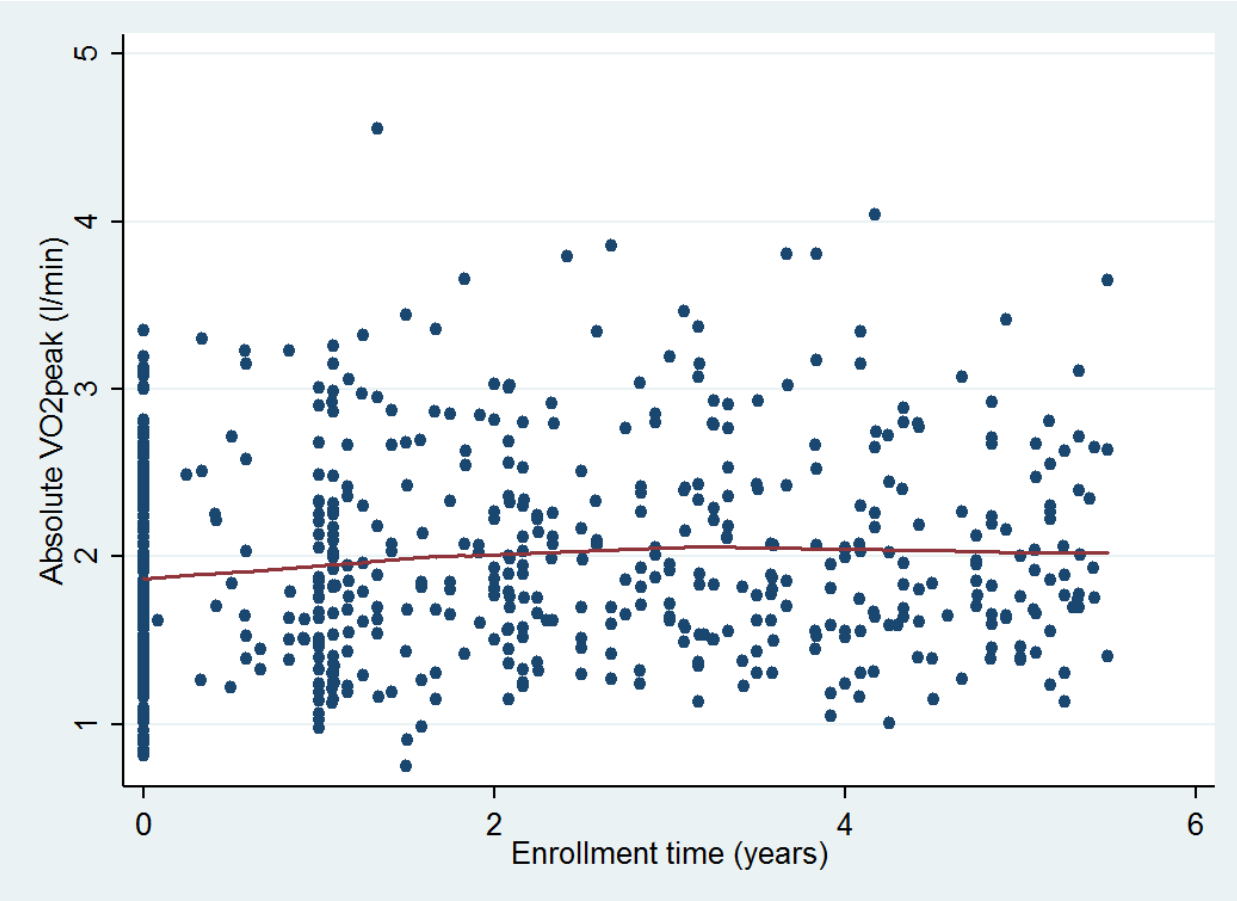


Table 1. Mixed model analysis on changes in absolute VO_2peak in 160 men, including age at enrollment and initial absolute VO_2peak interaction terms (589 observations)

Fixed and random effects components from 0-5.5 years of enrollment			
Fixed Effects Variables	*β (SE)*	*95% CI*	*p-value*
IV1: Time	0.578 (0.11)	(0.36, 0.78)	<0.0001*
IV2: $Time^2$	-0.013 (0.003)	(-0.02, -0.01)	<0.0001*
IV3: Age	0.002 (0.003)	(-0.005, 0.01)	0.617
IV4: Initial VO_2peak	1.12 (0.11)	(0.91, 1.32)	<0.0001*
Interaction terms			
A: Time x age	**-0.005 (0.001)**	**(-0.01, -0.002)**	**<0.0001***
B: Time x VO_2peak	**-0.092 (0.02)**	**(-0.13, -0.05)**	**<0.0001***
C: Age x VO_2peak	-0.002 (0.001)	(-0.006, 0.01)	0.183
Constant	-0.044 (0.215)	(-0.47, 0.38)	0.838
Random Effects Variance Components	*Estimate (SE)*	*95% CI*	
Slope (years)	0.009 (0.001)	(0.007, 0.013)	
Intercept	0.001 (0.002)	(8.5 $x10^{-6}$, 0.07)	
Residual	0.026 (0.002)	(0.022, 0.030)	
Model Fit Statistics	*Statistic*		
-2 log likelihood	85.5		
Bayesian Information Criteria	-100.8		

Abbreviations: IV independent variable; SE standard error; CI confidence interval. Seven outlying observations with high influenced removed. No observed random effects variance on the slope $time^2$ (estimate (SE) 7.6 $x10^{-5}$ (8.3 $x10^{-5}$), 95% CI (8.8 $x10^{-6}$, 6.5 $x10^{-4}$)).

Figure 3. Mixed model graph of predicted absolute VO_2peak trajectory in men with added age and initial VO_2peak interaction terms

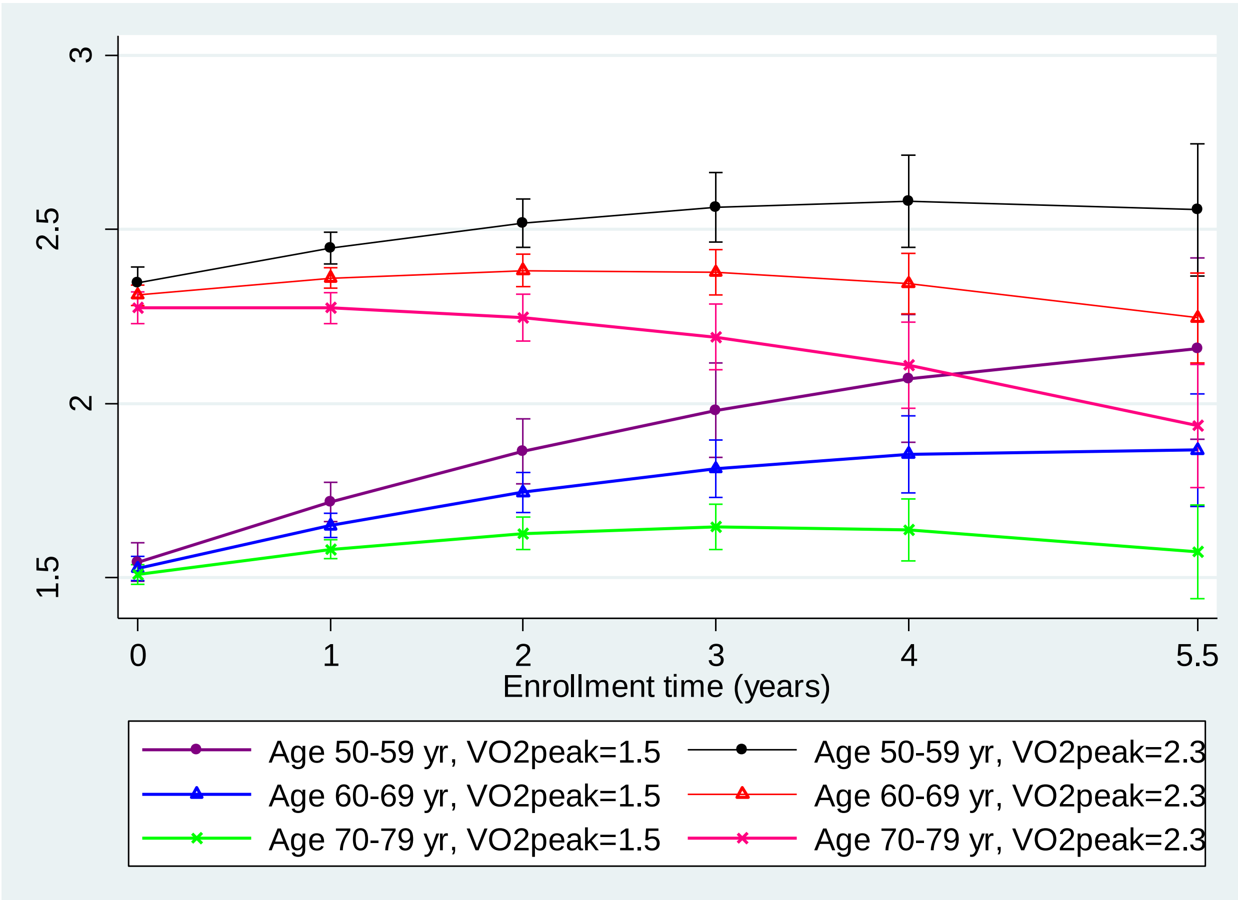


Table 2. Computed %/year changes in absolute VO_2peak by age and initial VO_2peak levels

	Low initial VO_2peak (1.5 l/min)			High initial VO_2peak (2.3 l/min)		
	50-59 yr	60-69 yr	70-79 yr	50-59 yr	60-69 yr	70-79 yr
0 to 1 yr	11.7	7.8	4.6	4.3	2.2	0.0
>1 to 2 yr	8.1	5.5	3.2	2.9	0.9	-1.2
>2 to 3 yr	6.5	4.0	1.2	1.6	-0.1	-2.4
>3 to 4 yr	4.5	2.3	-0.5	0.7	-1.3	-3.7
>4 to 5.5 yr	2.9	0.4	-2.6	-0.6	-2.8	-5.5

APPENDIX 9

Additional Analyses in Women from Chapter 3

Table 1. Calculation of VO_2peak literature comparison value in women

Age decade	N of women in our dataset	Literature Decline from Fleg et al. (2005)	Computing the weighted comparison value by using the number of women within each age decade
40s	1	-10.9%/decade	1/39 x -10.9%= -0.28%
50s	10	-13.5%/decade	10/39 x -13.5%= -3.46%
60s	14	-16.6%/decade	14/160 x -16.6% = -5.96%
70s +	14	-21.1%/decade	14/160 x -21.1%= -7.57%
Total	**39**		**= -17.3 %/decade or -1.73%/year**

Table 2. Calculation of 1RM skeletal muscle strength literature comparison value in women

Age decade	N of women in our dataset	Literature Decline From Keller & Engelhardt (2014) and von Haehling, Morley, & Ankler (2010)	Computing the comparison value by using the number of women within each age decade
40s	1	0%/decade	1/19 x 0%= 0%
50s	4	-15%/decade	4/19 x -15%= -3.16%
60s	8	-15%/decade	8/19 x -19.8% = -6.32%
70s +	6	-30%/decade	6/19 x -30%= -9.47%
Total	**19**		**= -19.0 %/decade or -1.90%/year**

Figure 1. Frequency of new members enrolled in CR program over 5-year intervals

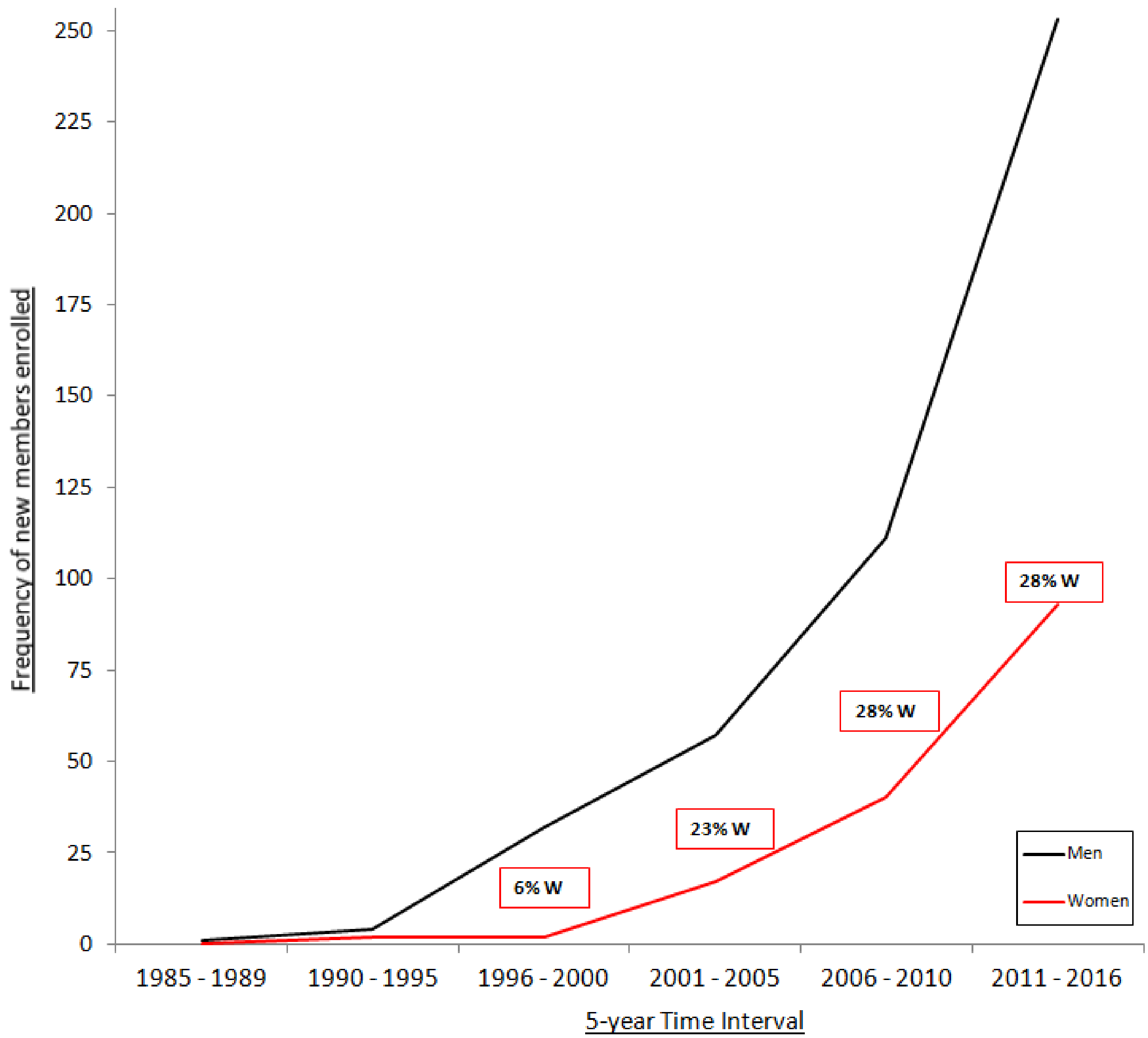


Figure 2. Trajectory of non-truncated VO_2peak data in women (n=39, 203 observations)

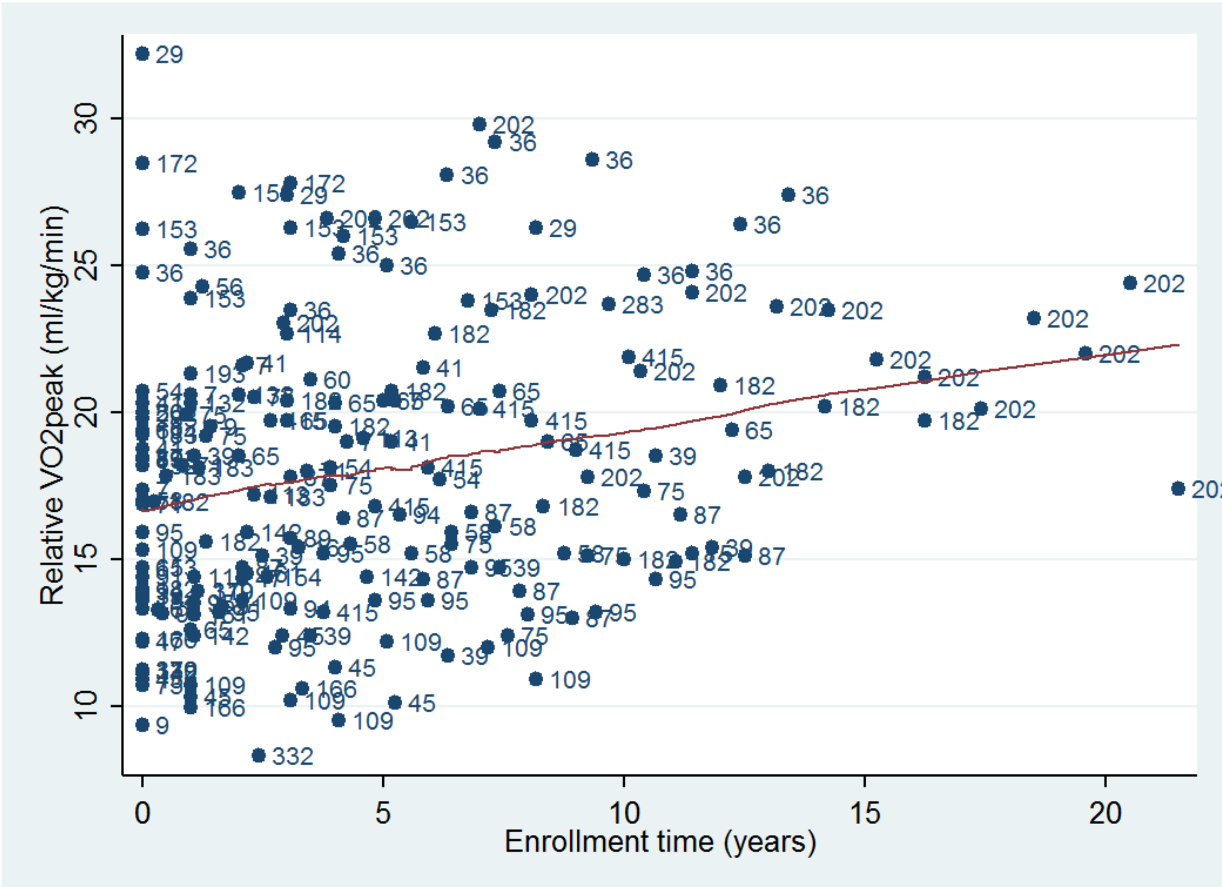


Figure 3A. Spaghetti plot of trajectory of non-truncated VO_2peak data in women (n=39, 203 observations)

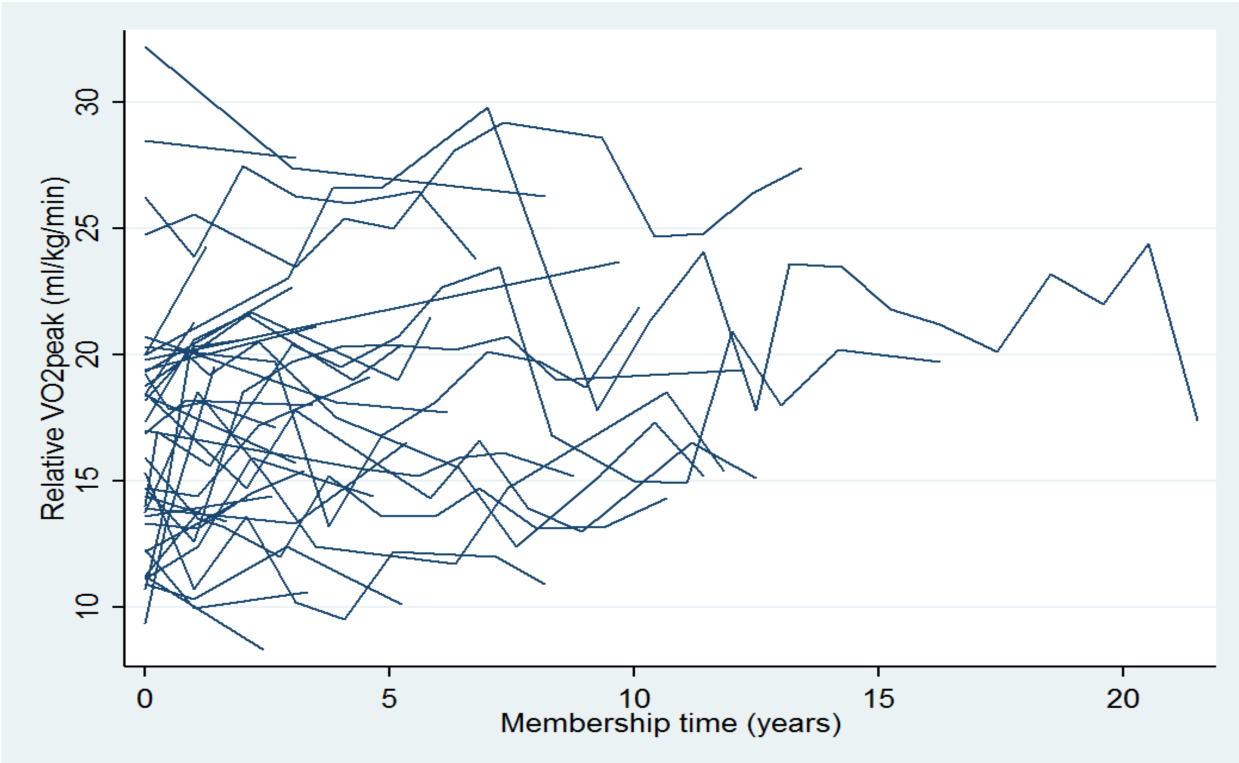


Figure 3B. Plot of fitted trajectory of non-truncated VO_2peak data in women (n=39, 203 observations)

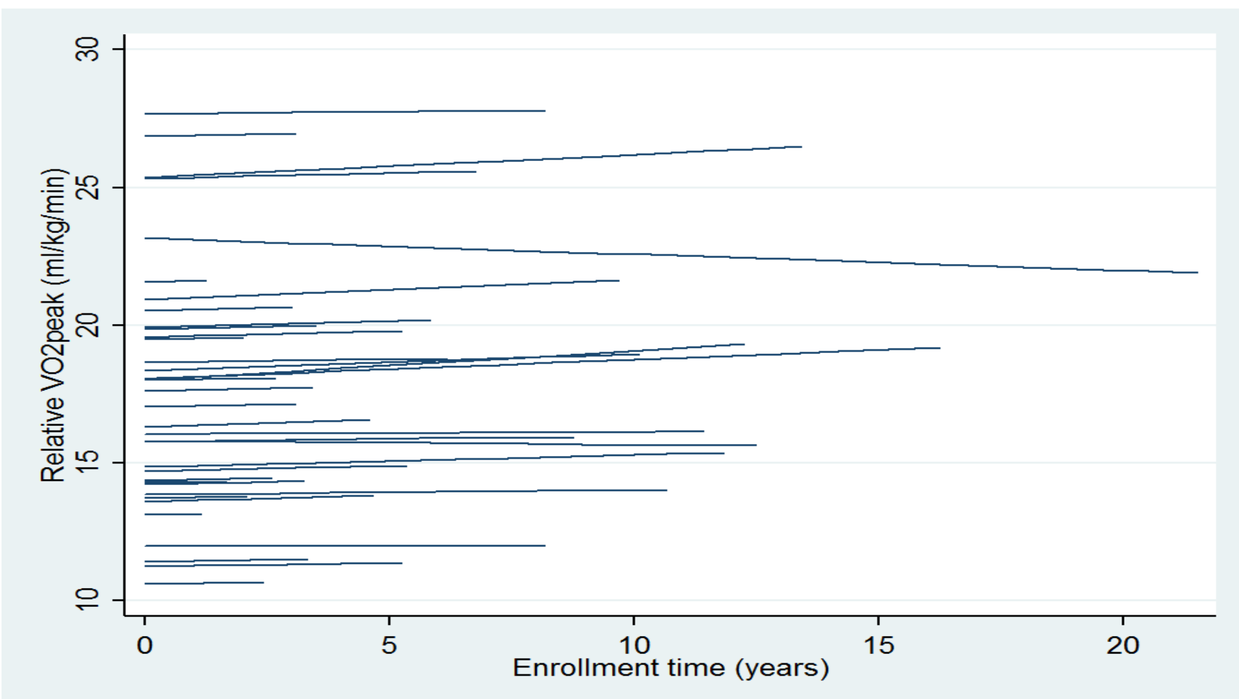


Figure 4A. Spaghetti plot of trajectory of truncated VO_2peak data in women (n=39, 123 observations)

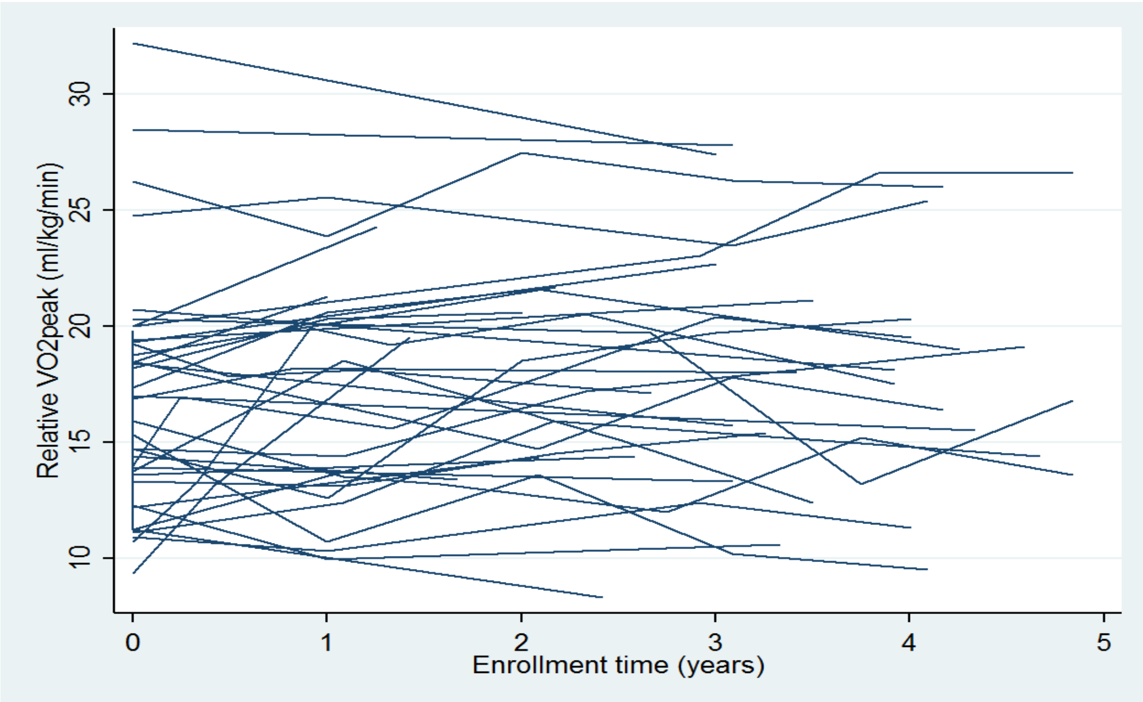


Figure 4B. Plot of fitted trajectory of truncated VO_2peak data in women (n=39, 123 observations)

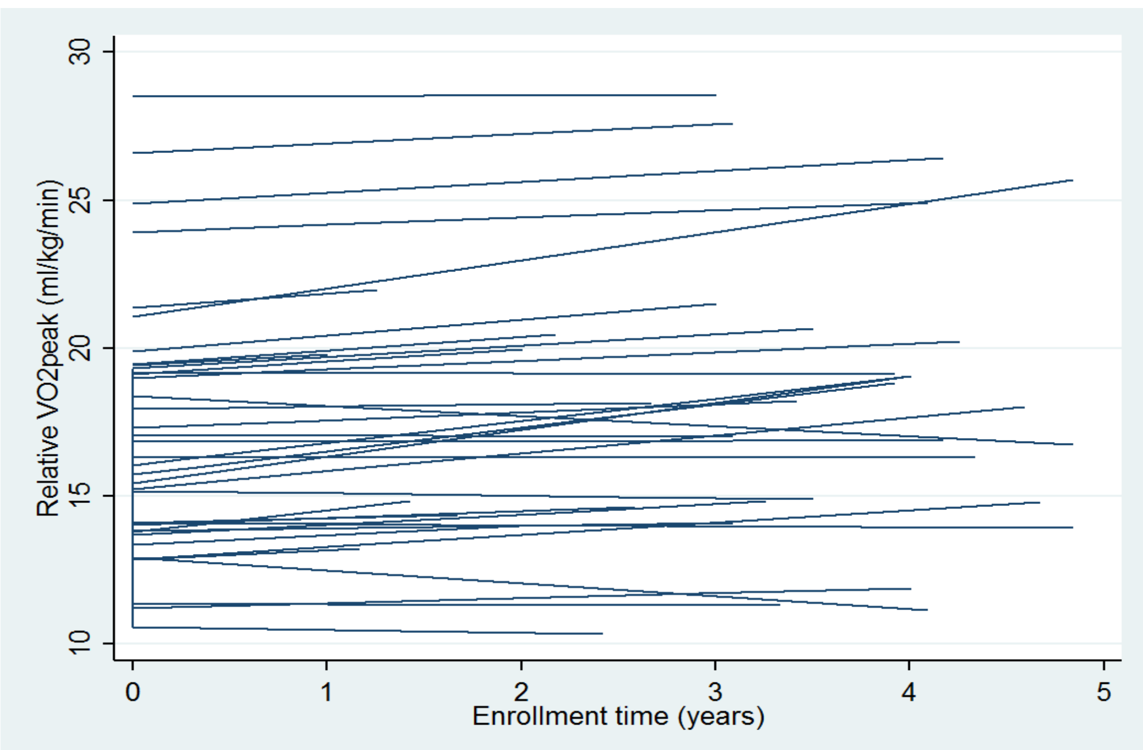


Figure 5. Trajectory of non-truncated 1RM chest press data in women (n=19, 108 observations)

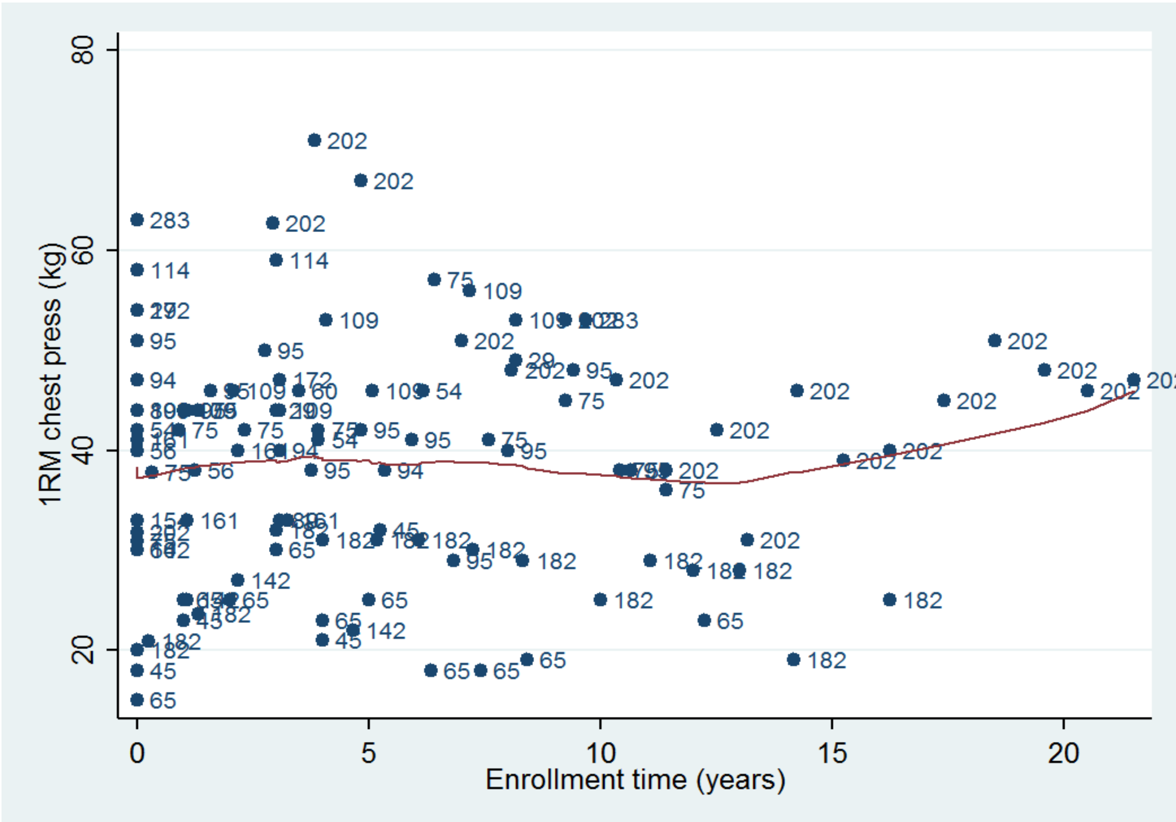


Figure 6. Trajectory of non-truncated 1RM seated back row data in women (n=19, 108 observations)

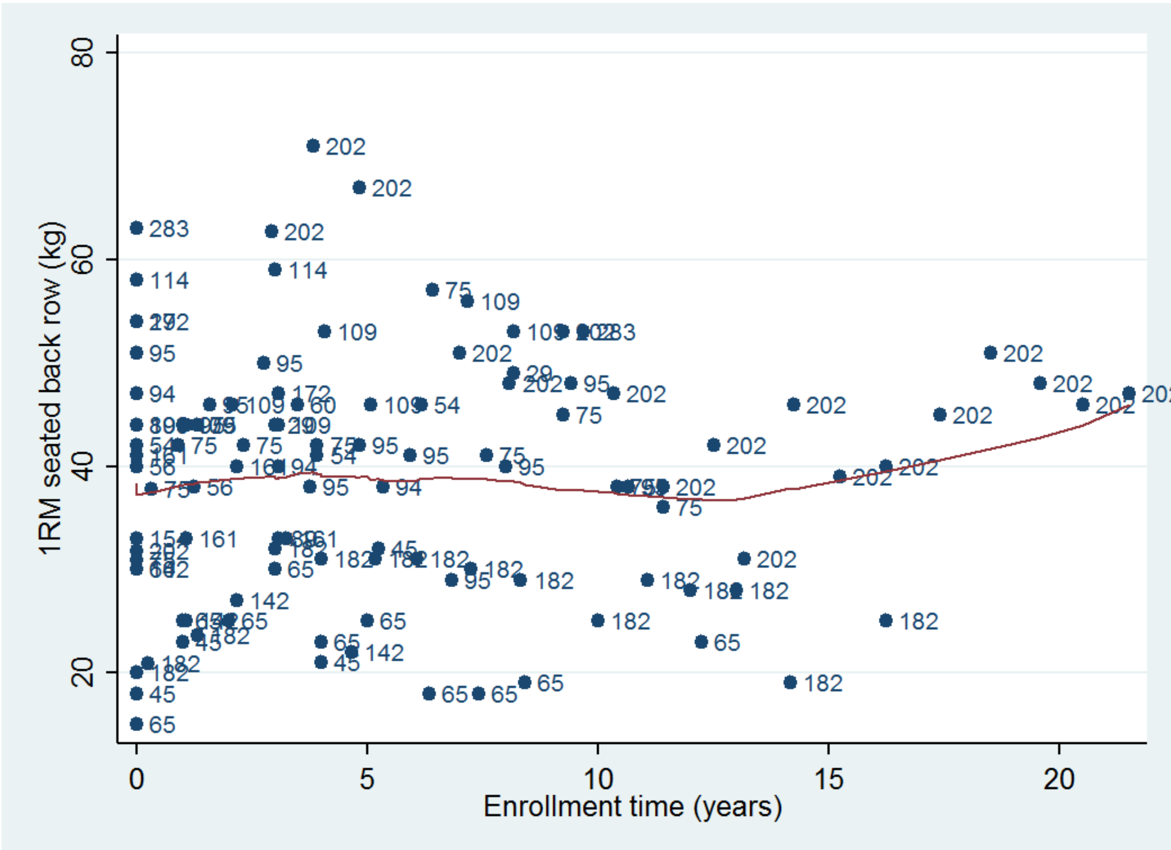


Figure 7. Trajectory of non-truncated 1RM knee extension data in women (n=19, 107 observations)

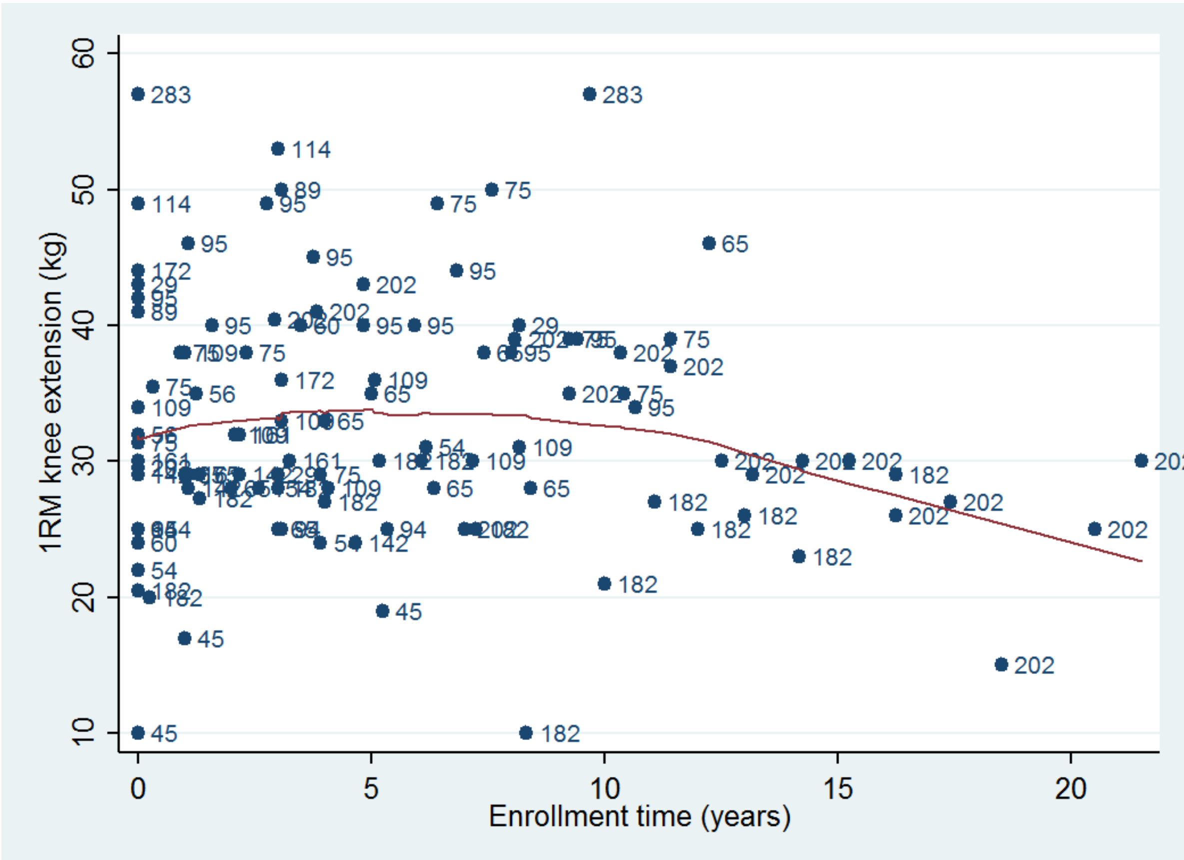


Figure 8A. Spaghetti plot of trajectory of non-truncated 1RM chest press data in women (n=19, 108 observations)

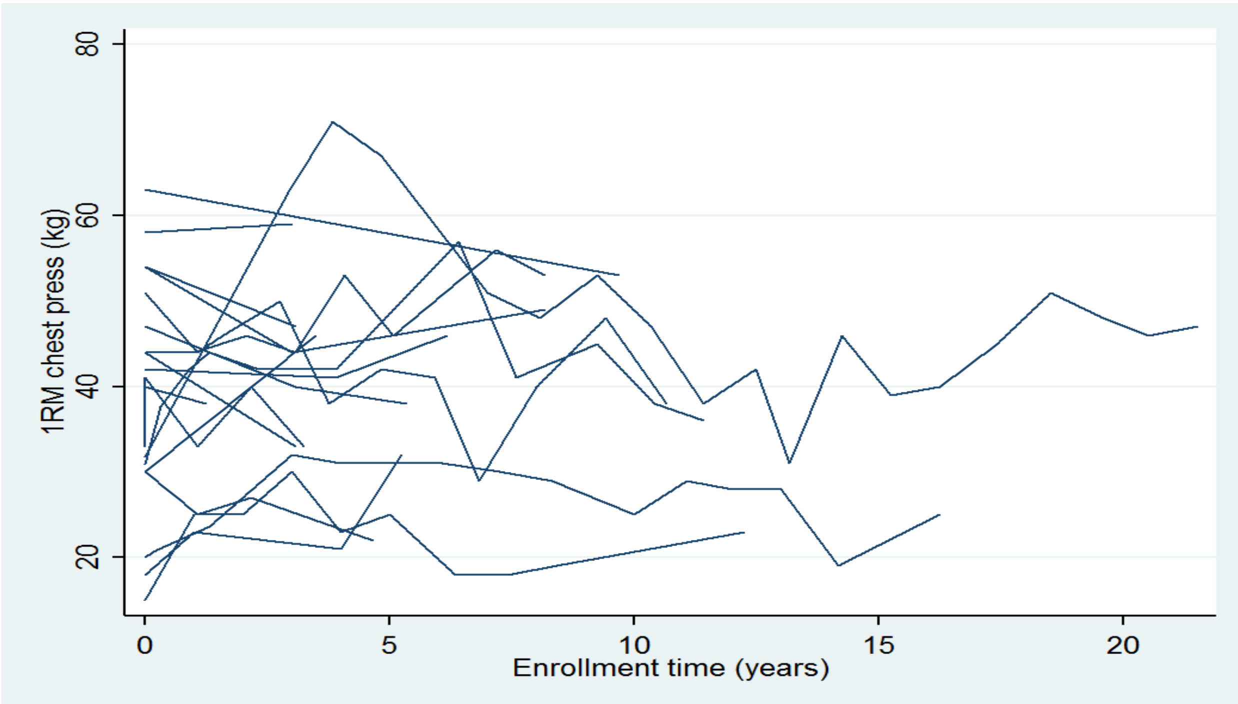


Figure 8B. Plot of fitted trajectory of non-truncated 1RM seated back row data in women (n=19, 108 observations)

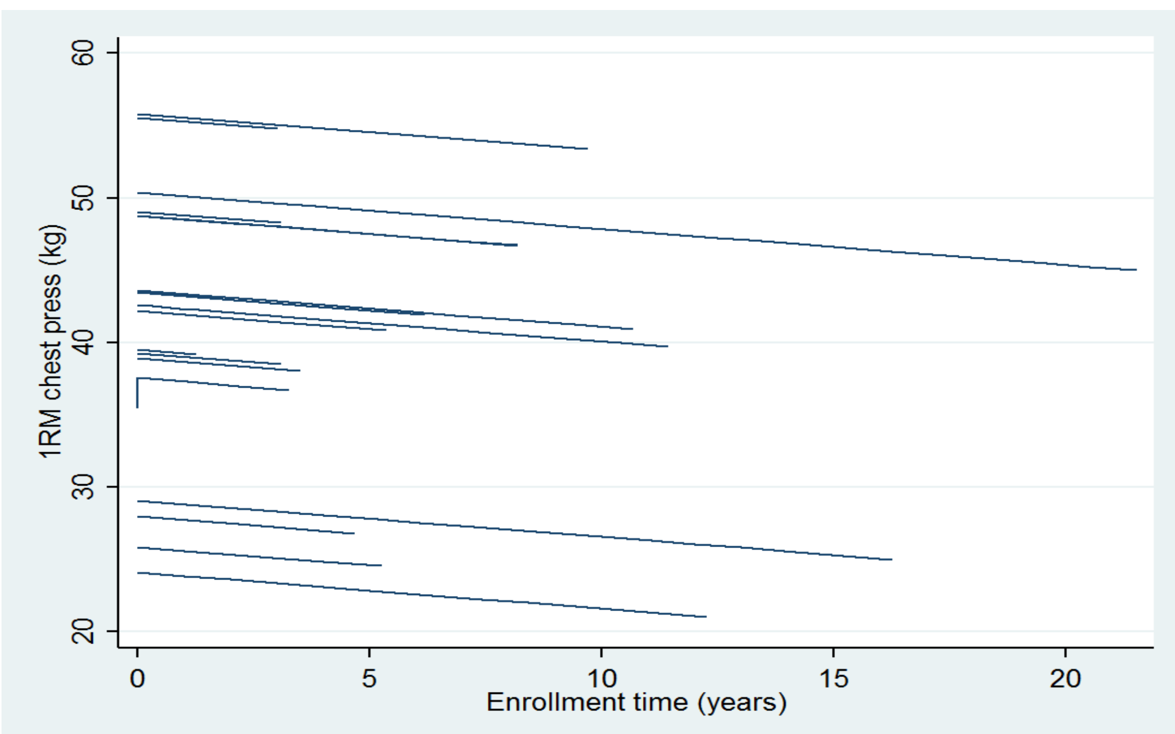


Figure 9A. Spaghetti plot of trajectory of non-truncated 1RM seated back row data in women (n=19, 108 observations)

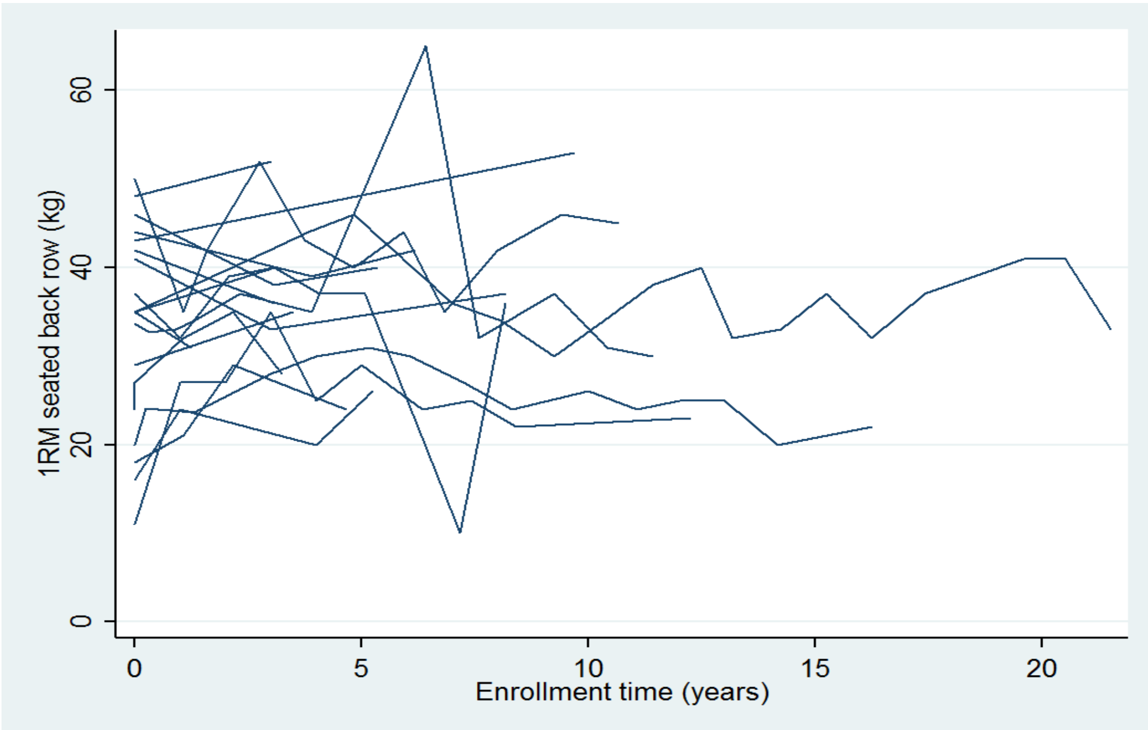


Figure 9B. Fitted plot of trajectory of non-truncated 1RM seated back row data in women (n=19, 108 observations)

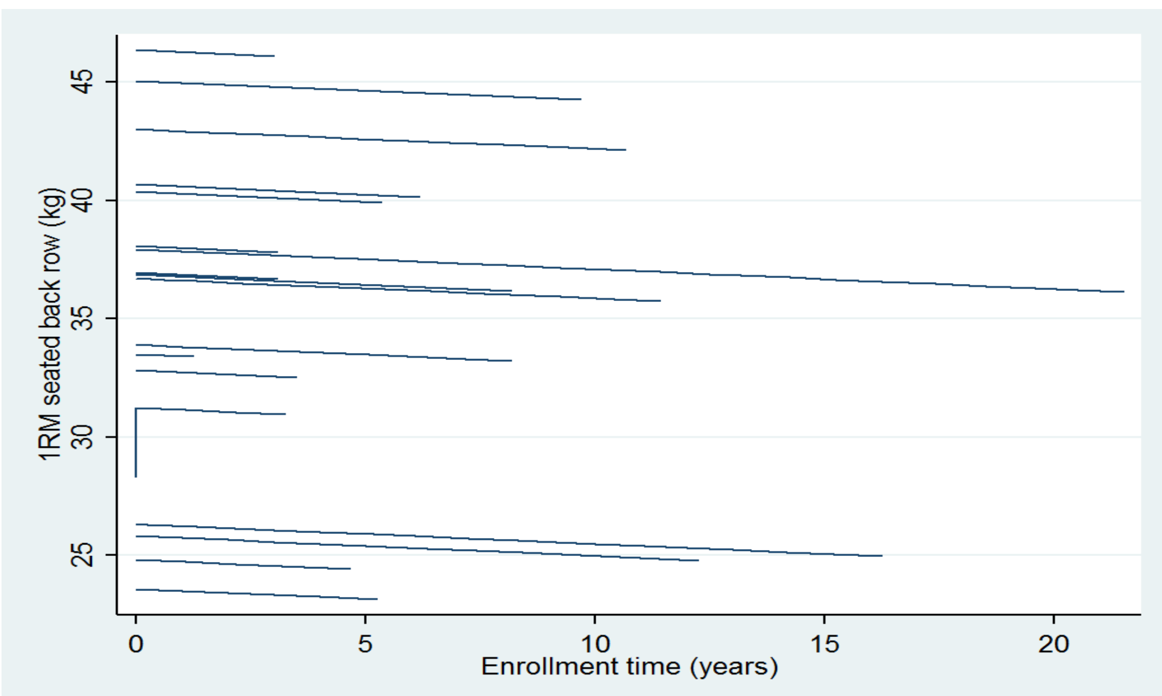


Figure 10A. Spaghetti plot of trajectory of non-truncated 1RM knee extension data in women (n=19, 107 observations)

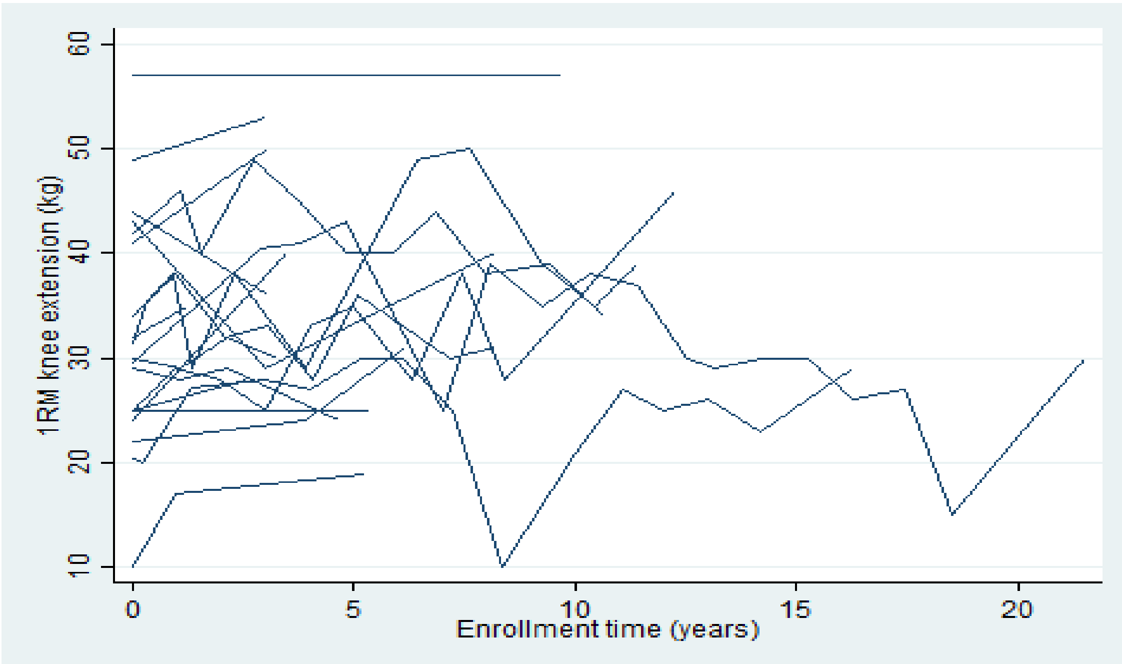


Figure 10B. Fitted plot of trajectory of non-truncated 1RM knee extension data over in women (n=19, 107 observations)

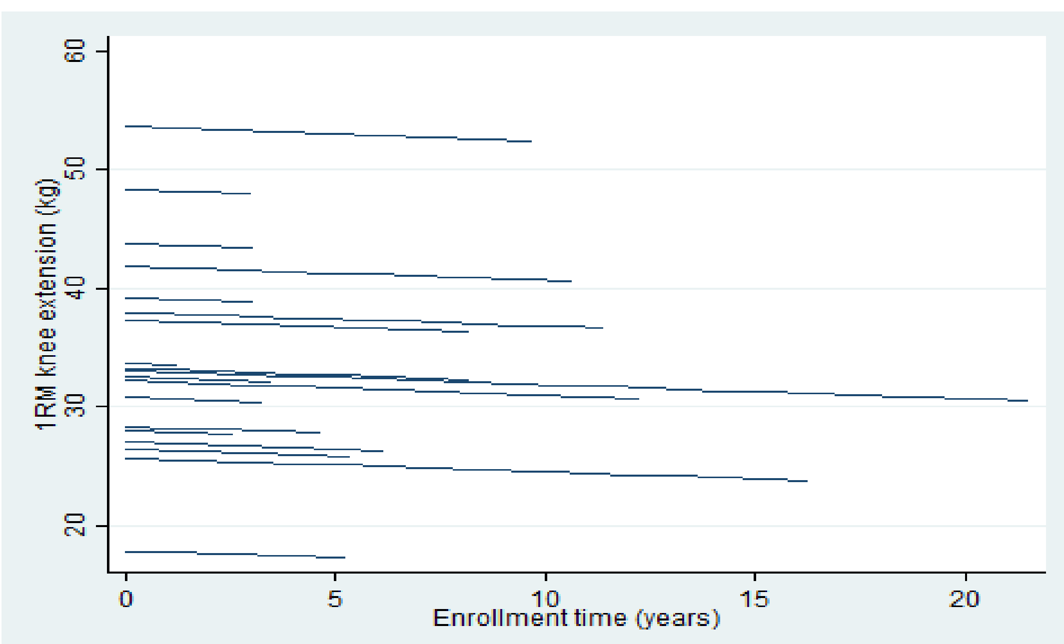


Figure 11A. Spaghetti plot of trajectory of truncated 1RM chest press data in women (n=19, 66 observations)

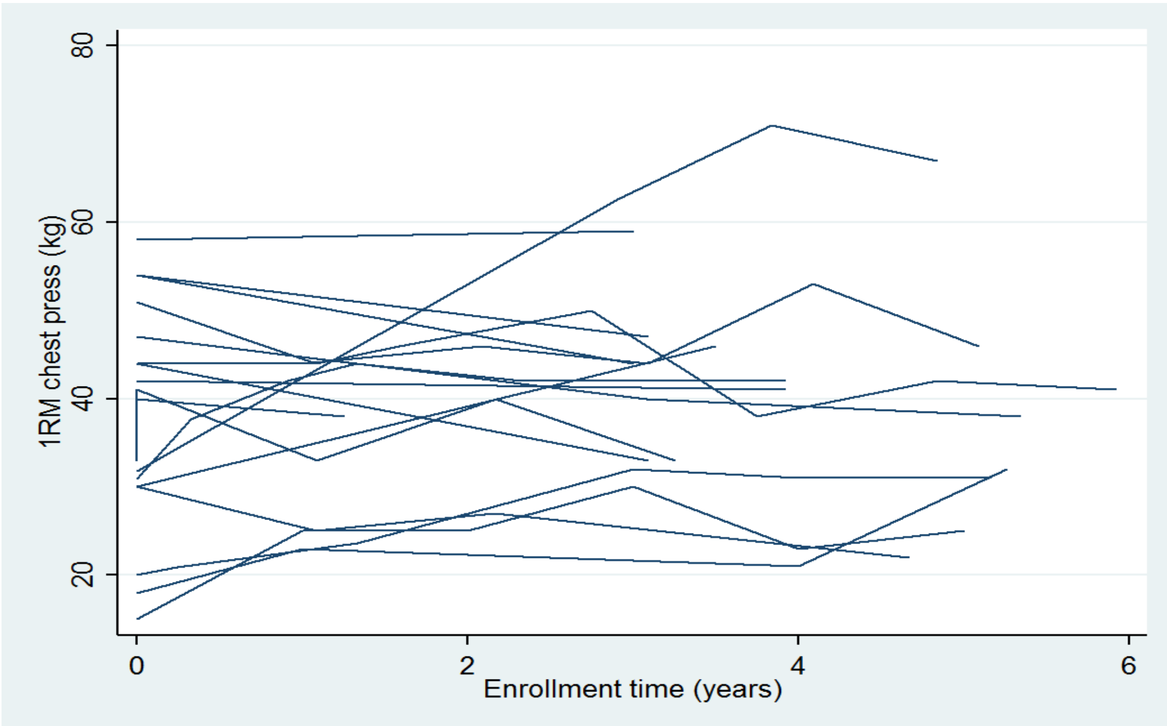


Figure 11B. Fitted plot of trajectory of truncated 1RM chest press data in women (n=19, 66 observations)

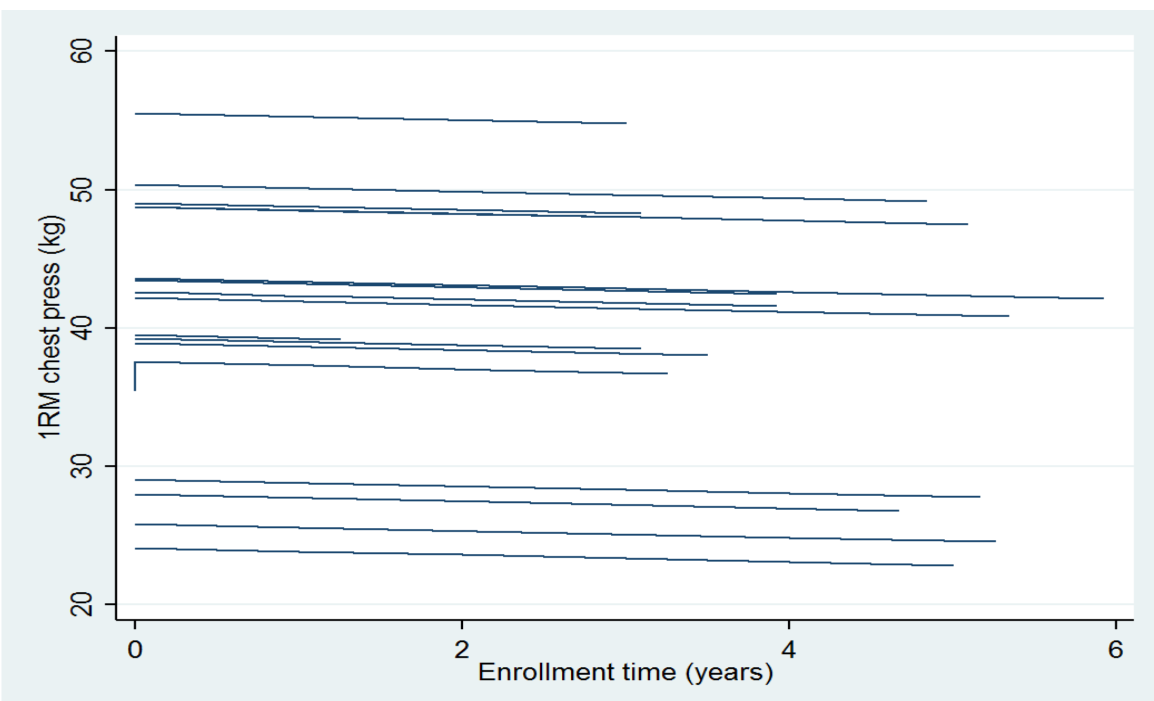


Figure 12A. Spaghetti plot of trajectory of truncated 1RM seated back row data in women (n=19, 66 observations)

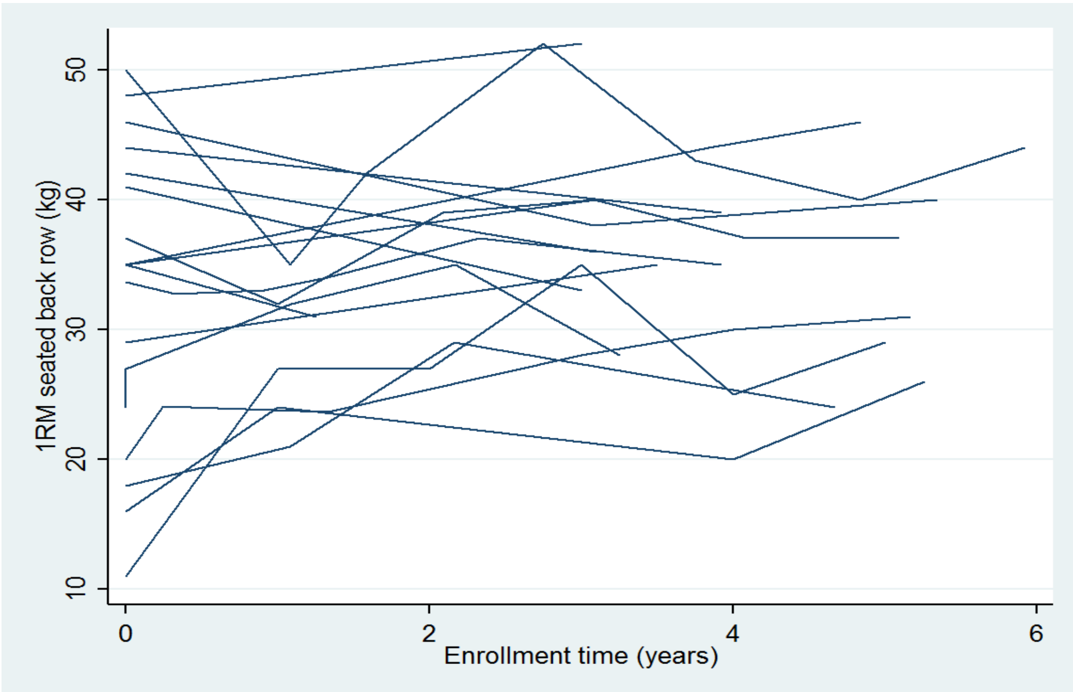


Figure 12B. Fitted plot of trajectory of truncated 1RM seated back row data in women (n=19, 66 observations)

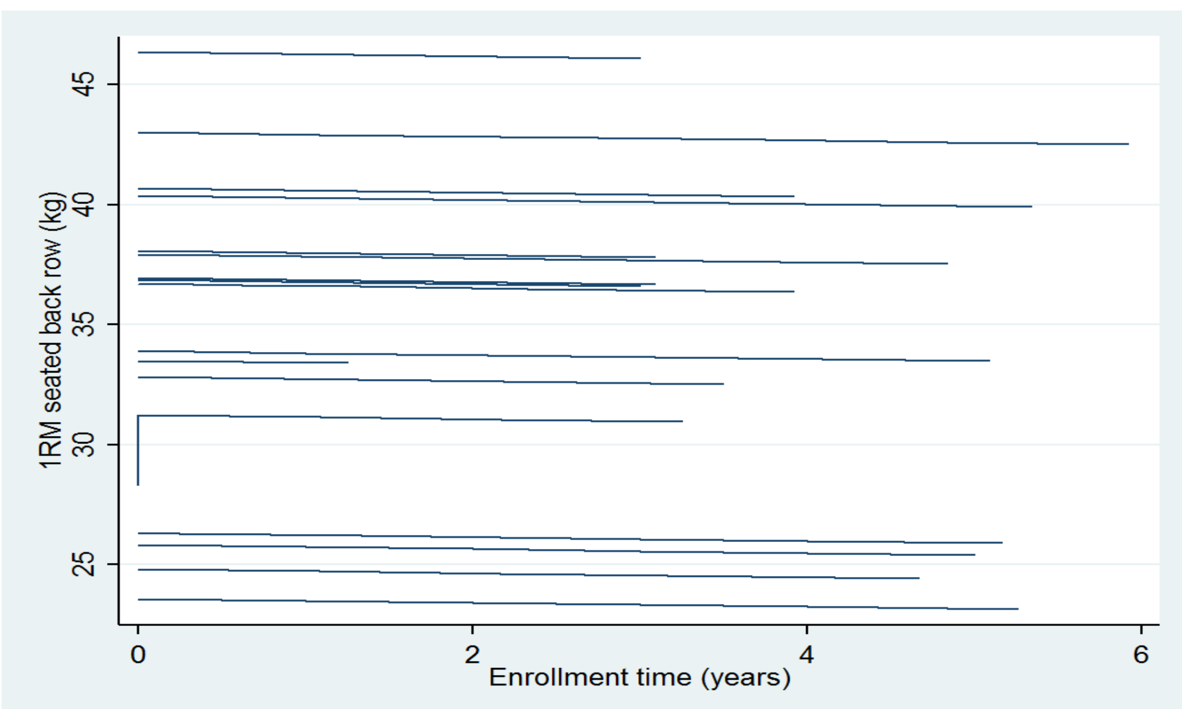


Figure 13A. Spaghetti plot of trajectory of truncated 1RM knee extension data in women (n=19, 66 observations)

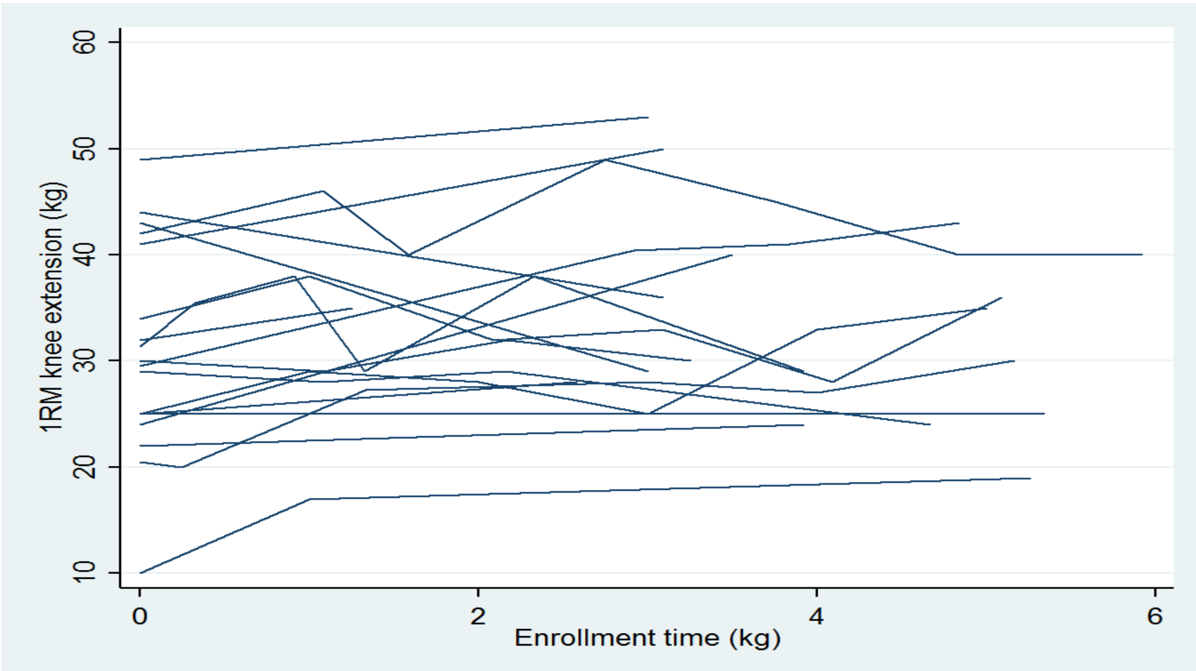


Figure 13B. Fitted plot of trajectory of truncated 1RM knee extension data over in women (n=19, 66 observations)

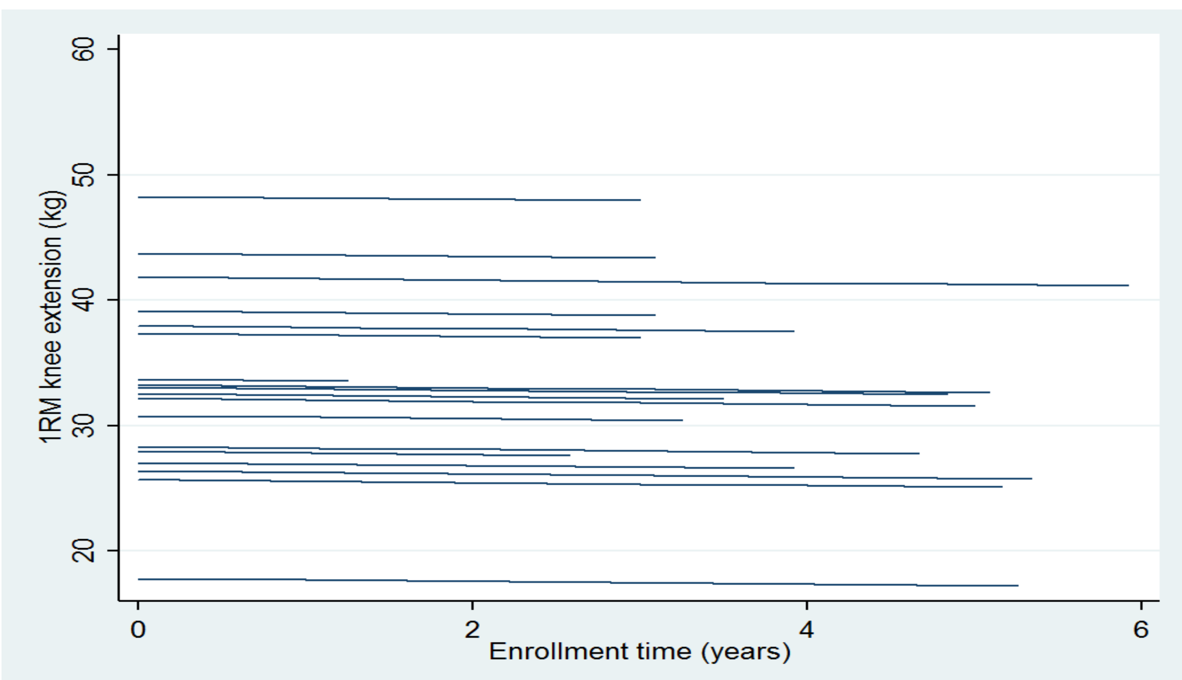


Table 3. Fixed effects of polynomial terms on changes in 1RM muscle strength over 6 years in female program members, after controlling for age (n=19, 66 observations)

Fixed Effects Polynomial terms	β (SE)	95% CI	p-value
1. 1RM chest press			
$Years^2$	0.466 (1.70)	(-2.86, 3.79)	0.784
$Years^3$	-0.085 (0.21)	(-0.50, 0.33)	0.686
2. 1RM seated back row			
$Years^2$	-0.176 (1.18)	(-2.48, 2.13)	0.881
$Years^3$	0.002 (0.15)	(-0.28, 0.29)	0.991
3. 1RM knee extension			
$Years^2$	-0.894 (1.13)	(-3.12, 1.33)	0.430
$Years^3$	0.089 (0.14)	(-0.19, 0.37)	0.528

Abbreviations: SE standard error; CI confidence interval

Figure 14. Trajectory of non-truncated absolute VO_2peak in women (n=39, 203 observations)

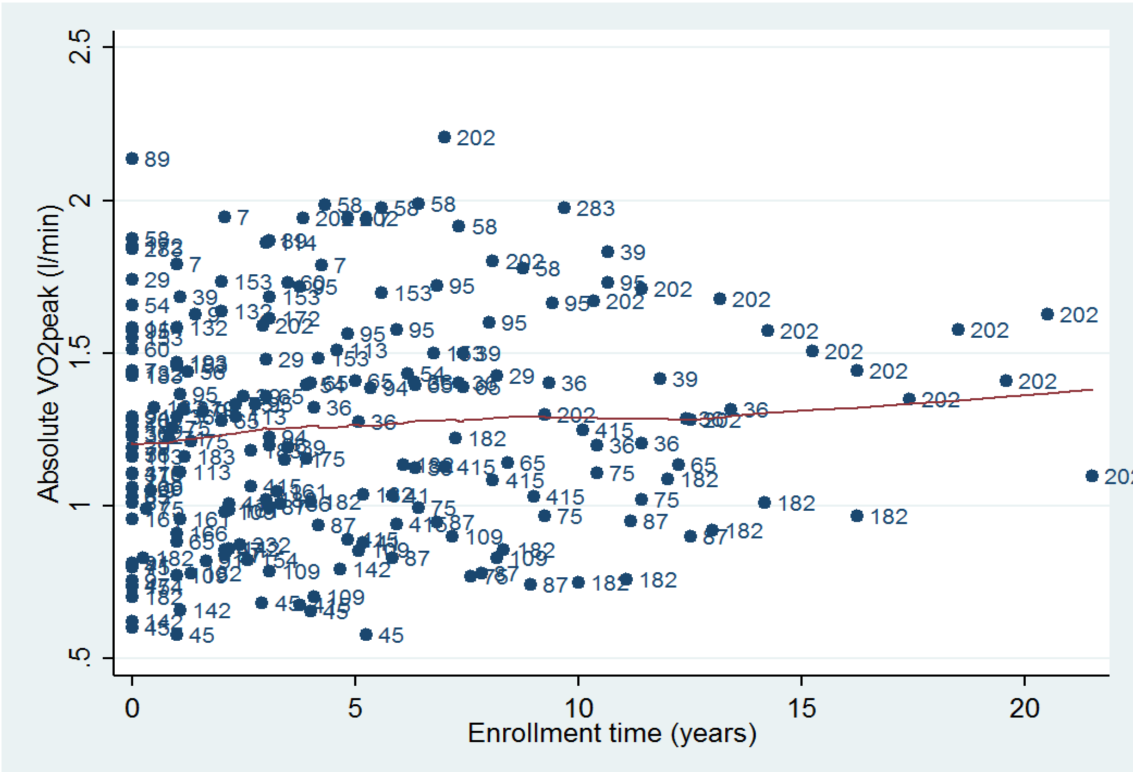


Figure 15. Trajectory of truncated absolute VO_2peak in women over 5 years of CR enrollment (n=39, 123 observations)

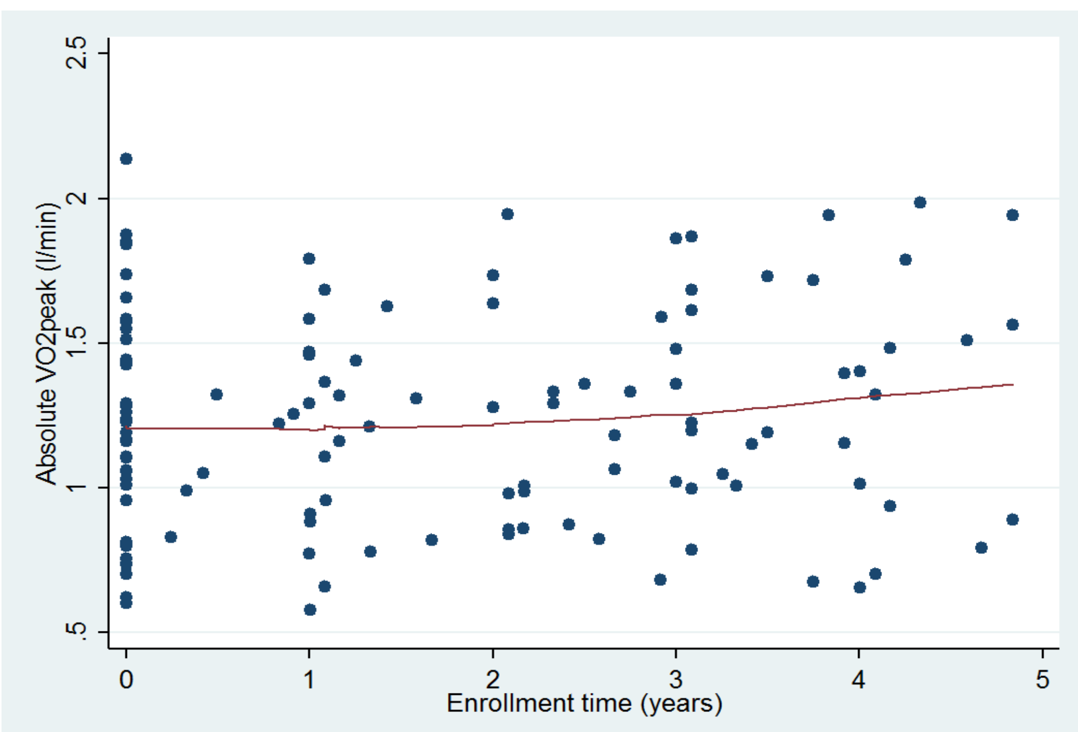


Table 4. Mixed model analysis on changes in absolute VO_2peak levels in women over 5 years of CR enrollment after controlling for age (n=39, 123 observations)

Fixed and random effects components from 0-5 years of enrollment			
Fixed Effects Variables	*β (SE)*	*95% CI*	*p-value*
IV1: Years	0.023 (0.01)	(0.003, 0.04)	0.027*
IV2: Age at enrollment	-0.025 (0.005)	(-0.03, -0.01)	0.001*
Random Effects Variance Components	*Estimate (SE)*	*95% CI*	
Intercept	0.07(0.02)	(0.04, 0.11)	
Residual	0.03 (0.004)	(0.02, 0.04)	
Model Fit Statistics	*Statistic*		
-2 log likelihood	3.74		
Bayesian Information Criteria	16.6		

Abbreviations: IV independent variable; SE standard error; CI confidence interval.

Figure 16. Comparison of change in predicted absolute VO_2peak in the 39 women over 5 years of enrollment compared to the literature value (Fleg et al., 2005)