Examining Frailty and Cardiovascular Disease Risk Profile in Middle-Aged and Older Women

By

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Abstract

Frailty assessment has been suggested to improve cardiovascular disease (CVD) risk management. Frailty is characterized as having a lack of reserve for tolerating health stressors. Few studies have tried standardizing frailty criteria to the population being assessed or examined the association of CVD risk profile before the onset of CVD. The purpose of my thesis is to: (1) determine if standardized frailty models better discriminate CVD risk compared to the traditional approach; and, (2) determine if there are differences in CVD risk profile based on frailty status in a sample of middle-aged and older women. The standardized model improved CVD risk discrimination by 39.4% ($p=0.016$) and 20.5% ($p = 0.017$) in the two composite CVD risk scores assessed. Comparison of CVD risk profiles between frailty groups identified variables indicating higher CVD risk as frailty status increased. Frailty assessment have the potential to identify women with elevated CVD risk.

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Chapter 1: Literature Review

This literature review will cover the basic pathophysiology commonly involved with cardiovascular disease (CVD) and the factors that can influence risk for these diseases. Methods of identifying individuals with CVD risk, new and old, will then be described. The review will shift toward frailty; its definition, prevalence, assessment, association with CVD. Finally, the review will identify the characterization of CVD risk profile in pre-frail populations as a knowledge gap that must be addressed in research.

1.1 CVD

CVD is a general term used to describe a variety of conditions that are caused by deficiencies in the structure and function of the heart and the body's vasculature. Damage to the endothelium, the inner lining of the artery, can be caused by both oxidation and inflammation of vascular structures, which, in turn, can lead to the development of lesions in the vessel, also known as atherosclerosis.[1] Atherosclerosis is the leading cause of CVD.[2] These plaques continue to develop and harden as cells, fats, cholesterol, calcium and other deposits all accumulate, eventually leading to restricted blood flow.[1] Eventually, plaque rupture can also lead to the development of a blood clot, or thrombus, which can block blood flow to parts of the body, such as the heart or brain.[3] These blockages lead to clinical outcomes such as stroke, coronary artery disease, which leads to angina and myocardial infarction (MI), and peripheral artery disease.[3]

Although the pathophysiology of these diseases are not through the same mechanisms, heart failure, rheumatic heart disease and congenital heart disease are all also considered

cardiovascular diseases.[4] Heart failure and rheumatic heart disease are acquired conditions caused by damage to the cardiac muscle and cardiac valves, respectively.[4] Damage to the heart muscle can result in the heart not filling with enough blood and the heart not pumping the blood out with enough force.[5] This inability to pump blood throughout the body properly due to cardiac muscle damage is called heart failure. Rheumatic fever causes damage to the heart's valves due to a streptococcal bacterial infection and often results in the valves requiring replacement.[6] Finally, congenital heart diseases are structural deficiencies in the heart that are present from birth.[7] These deficiencies can manifest in the walls of the heart, the valves of the heart or the vessels surrounding the heart.[7]

The global prevalence of CVD is widespread, as CVD accounted for three in every ten deaths worldwide in 2012.[8] Despite many research advances in the area in recent years, CVD remains the leading causes of death across the globe.[9] While the majority of cardiovascular disease cases are found in low and middle-income countries, Canada's population is still heavily influenced by the effects of heart disease and stroke.[9] Approximately 1.6 million Canadians are living with the effects of these conditions, and over 66,000 Canadians died due to these conditions in 2012.[10,11] That is the equivalent of a death every seven minutes being due to CVD.[10] These conditions also have a heavy economic impact in Canada. For example, CVD costs the Canadian economy over $20.9 billion due to hospitalizations, lost wages and productivity, and physician services.[12]

Research on CVD continues, but the burden of these conditions is likely to increase with Canada's aging population and increasing prevalence of obesity and diabetes, as these conditions all elevate CVD risk.[13] Despite improvements in CVD treatment and care, World Health Organization mortality projections for 2030 show that CVD issues are not anticipated to go away

as the percentage of deaths worldwide due to CVD will increase slightly from 31% to 32%.[14] Research will have to address this growing problem by finding means to reduce the impact that CVD conditions have on individuals, families and the healthcare system.

1.2 Risk Factors for CVD

Through longitudinal studies, such as the Framingham Heart Study,[15] research has led to an understanding of the risk factors involved with CVD. Risk factors are typically divided into those that are modifiable, either with pharmacological or lifestyle behavior change means, and those that are not (Table 1). Non-modifiable risk factors include age, ethnicity, gender, and genetics.[1,2] Modifiable or manageable risk factors often discussed in the literature are smoking, hypertension, diabetes, obesity, lack of exercise, dyslipidemia, poor diet, alcohol intake, and depression.[16–19] The presence of these risk factors can aggravate the inflammation, oxidation and atherosclerosis processes that contribute to adverse cardiovascular outcomes.[2]

Table 1: Risk Factors for CVD

Non-modifiable risk factors
• Age • Ethnicity • Gender • Genetics
Modifiable/Manageable risk factors
• Smoking • Obesity • Lack of exercise • Poor diet • Alcohol intake • Depression • Hypertension • Diabetes • Dyslipidemia

1.3 Early Detection of CVD Risk

The fight against CVD may seem like an uphill battle with its significant impact across the globe and in Canada, but there are means of mitigating CVD risk. Up to 80% of premature CVD events can be prevented by adopting healthier lifestyle behaviors and controlling risk factors like high blood pressure and diabetes.[12] Determining CVD risk and implementing interventions in advance of the development of CVD symptoms can delay or prevent morbid CVD events. Such an approach will allow for this asymptomatic population to lead healthier lives with normal life expectancy.[20] In order to direct interventions in a productive manner, the risk of developing CVD must be assessed in individuals and in populations to allow for efforts to

be focused on those at higher risk. Primary prevention, which is the prevention of disease onset, is a cost-effective means of preventing CVD and can increase years of life for those at risk.[21]

1.3.1 Framingham Disease Risk score

The current standard practice for CVD screening in Canada includes the Framingham Disease Risk (FRS) score approach.[22] A seminal project, the Framingham Heart Study[15] is a cohort study initially implemented in 1948 with the purpose of examining cardiovascular health and the risk factors involved as participants aged over time. This project has assisted with the identification of many of the traditional risk factors known to be associated with CVD today.[23] The data collected during that study has been used to create multiple clinical CVD risk calculators to identify individuals in need of preventative care throughout the years.[22] The most current form of the FRS, revised in 2008, is calculated based on age, gender, total cholesterol (mg/dL), HDL cholesterol (mg/dL), systolic blood pressure (mmHg), the presence of diabetes, smoking status, and if the patient is taking antihypertensive medication or not[24]. Values for these factors are entered into a mathematical model that calculates CVD risk for the individual based on data collected throughout the Framingham Heart Study.[15] The output of this calculation is a risk percentage of suffering from a CVD event in the next ten years. This tool has been shown to predict 10-year risk of myocardial infarction (MI) and good discrimination in Cox proportional-hazards regression (C statistic, 0.763 in men and 0.793 in women),[22] but it underestimates risk in older adults, specifically in women.[25] For example, a previous study found that the FRS underestimated the risk of experiencing CVD by 51% in older women and 8% in men, identifying a need for novel risk factors to be discovered and used to improve risk prediction.[25]

1.3.2 Alternative methods of assessing CVD risk

The traditional methods of assessing CVD have received some criticism as it is thought that risk screening should not be focused on indirect measures of CVD risk through the presence of risk factors.[26] Methods of assessing CVD risk in the population should focus on determining risk for impaired cardiovascular function in each individual, rather than based on risk factors associated with poor cardiovascular function, as risk factors do not determine how the target biological structures are being affected.[26] While the traditional methods predict adverse cardiovascular events at the population level, they are not sensitive enough to determine risk at an individual level.[27–29] Hence, risk management tools for the early detection of CVD risk must be enhanced further.

A number of alternative methods have been proposed for assessing CVD risk ranging from the addition of single risk factors to existing screening protocols, all the way to entirely new screening protocols. For example, cardiorespiratory fitness testing has been examined as a prognostic tool for CVD. A meta-analysis from 2009 found that poor results in cardiorespiratory fitness tests were associated with both all-cause mortality and CVD morbidity.[30] The value of performing these tests has also been recognized by the American Heart Association who recently published a scientific statement expressing the need to perform cardiorespiratory fitness tests in a clinical setting to assist with CVD prevention and treatment.[31] Cardiorespiratory fitness training has also been shown to improve reclassification of risk as determined by the FRS.[32] While the gold-standard for performing cardiorespiratory fitness testing is through measuring maximal oxygen consumption or determined through peak workload in maximal testing, these assessments are not as feasible in a clinical setting as they require specialized equipment and it is not realistic or safe for all populations to achieve this level of exertion.[33] The 6-minute walk

test[33] has been used as a simple aerobic exercise capacity assessment to assist with future CVD risk prediction in patients with a variety of different CVDs,[34–36] as the traditional risk factors for CVD do not fully explain the risk present in these populations.[34] This test involves having a participant cover as much distance as they can in six minutes while walking, making it inexpensive and easy to perform in a clinical setting. The testing is also performed at the participant's own pace, making it safer for populations who may be at risk for complications during maximal aerobic testing.[33] Beatty et al. found that this simple test had similar ability to treadmill cardiorespiratory fitness training for predicting CVD related morbidity over an eight-year follow-up period.[34]

Testing that includes an aerobic activity protocol has also been used to place a stress on the cardiovascular system so that the subject's blood pressure response to that stress can be assessed. Systolic blood pressure is expected to rise during exercise as the heart pumps increased volumes of blood to provide the muscles with oxygen, but some individuals have an abnormally large blood pressure response to exercise called hypertensive response to exercise (HRE).[37] There are multiple proposed mechanisms for these exaggerated systolic blood pressure increases, but the prevailing explanation in older adults is that of arterial stiffness.[37,38] Stiffer arteries are simply unable to buffer the blood pressure with increased cardiac output. Elevated blood pressure response to exercise in non-hypertensive and hypertensive, asymptomatic individuals has been shown to be associated with risk for future hypertension and CVD-related mortality.[39–41] A meta-analysis from 2013 concluded that HRE at moderate intensities was an independent risk factor for both cardiovascular morbidity and mortality.[42] These tests are typically performed in the literature using either the Bruce treadmill protocol[39,40] or a step test[41] at moderate intensities.

Another aspect of physical fitness other than cardiorespiratory fitness is muscular strength, which also has an important role in chronic disease prevention.[43] Handgrip strength tests are an easy-to-perform, validated surrogate method of assessing overall muscular strength.[44] These measures have been used in older populations as a prognostic tool and a predictor of mortality.[45–47] More specifically, handgrip assessment has also been used to assess cardiovascular morbidity and mortality.[47] In an analysis of 139,691 participants in 17 different countries by Leong et al., handgrip strength was found to be a stronger predictor of all-cause and cardiovascular mortality than systolic blood pressure.[47] Further research is needed to understand the mechanisms relating muscle strength and risk of death.[47]

Functional status and well-being are important factors to consider when assessing survival in geriatric populations.[48] Gait speed measures, often assessed over a distance of four to six meters,[49] have been shown to be a good indicator of this well-being and functional status.[48,49] These measures have also proven to be good predictors of cardiovascular morbidity and mortality in healthy older adults[49–51] as well as those awaiting cardiac surgery.[52] This association may be due to gait speed's value as a single-item assessment of frailty,[51,53] a complex physiological decline across multiple systems that can increase risk for a host of adverse health outcomes.[54] As with the 6-minute walking test, gait speed measures are easy to assess and inexpensive to perform.

As opposed to objective testing, subjective physical activity assessments and their relation to CVD risk have also been examined. For example, the capture of physical activity levels using the International Physical Activity Questionnaire[55] (IPAQ) has been used to improve CVD risk scores in previous research.[56] Higher levels of physical activity are known to reduce risk for CVD.[57] The IPAQ is a validated questionnaire used to characterize what intensities of

physical activity participants are performing, how often they perform them and what length of time they perform these activities for. The traditional methods of assessing CVD risk do not include lifestyle behavior aspects that are known to improve cardiovascular health, such as physical activity.[57] The inclusion of subjective physical activity measures is an inexpensive and easy to perform addition to CVD risk assessment.

Other prognostic risk factors for CVD discussed in the literature include the assessment of depressive symptoms.[58] Often described through the description of symptoms, such as loss of interest and pleasure in activities, poor sleep, and fatigue, depression has often been discussed in the care of those with previous CVD.[58] Depression is more common in those with CVD, and it has been shown to predict morbidity and mortality following CVD events.[58,59] Not only this, but depression is also an independent risk factor for a range of CVDs in those with no prior history.[60] A meta-analysis from 2006 found that, on average, those with depression were twice as likely to develop new CVD.[61]

Typically, assessment of blood pressure focuses on the peak systolic blood pressure and the end diastolic blood pressure. However, that approach does not consider the transient changes in blood that pulses, which is better characterized as a blood pressure curve. Emerging research indicates that the assessment of the blood pressure curve may provide useful information in the assessment of CVD.[62–64] Arterial stiffness and arterial elasticity (the opposite of arterial stiffness), are general terms that refer to the ability of a vessel to expand with increased blood flow, giving information on the structure and functionality of the vasculature.[65] In healthy individuals without endothelial damage, pulse pressure waves propagate throughout the body and the elastic nature of the vessels allows for this wave to be reflected back at the time of diastole, leading to increased blood pressure at diastole and a steadier more even outflow of blood

throughout the body[64]. Damage to the endothelium is a key progression to atherosclerosis and CVD[66] and the stiffening of the cardiovascular system's vessels is associated with risk of a host of adverse cardiovascular events.[67]Arterial stiffness is affected by age-related structural changes, but other factors that put people at risk for CVD, such as hypertension, diabetes and unhealthy lifestyle behaviours, can also play a role in this process[68]. Arterial stiffness has been assessed in many ways, and there is some confusion regarding the proper use of this terminology since it is actually more of an umbrella term.[69] Typically, studies assessing arterial stiffness have examined pulsewave velocity, which can be measured in a number of different methods and is known as the gold standard.[68] Cardio-ankle vascular index, augmentation index, and arterial compliance are also used to assess similar properties under the umbrella term arterial stiffness or elasticity, and each of these is assessed in numerous ways.[65] For the purposes of this specific thesis document, the focus will be on arterial compliance, which is the measure of the vasculature's ability to expand with increased blood flow during systole.[70] This method of arterial stiffness assessment has been shown to be a predictor of CVD events.[71]

New full screening protocols for assessing CVD risk in a clinical setting have also been proposed in the literature. For example, Cohn et al. have proposed the 10-test Rasmussen Cardiovascular Screening Program at the Center for Cardiovascular Disease Prevention, University of Minnesota.[72] This protocol assesses cardiac and vascular abnormalities and was designed in an attempt to improve the sensitivity of CVD risk assessment, allowing for interventions to be allocated to high-risk individuals earlier.[73] The majority of the ten different assessments (Appendix B) are non-invasive, including procedures like the elasticity of the arteries, blood pressure measures, a photograph of the vasculature in the back of the eye, ultrasound examinations of the different vasculature, an electrocardiogram, and a urine test to

detect microalbumin levels. A blood sample is also used to measure levels of brain natriuretic peptide, a marker of small artery disease. Each of these tests is scored from 0-2 (0=normal; 1=borderline; 2=abnormal), which results in a total Rasmussen Disease Score (RDS) from 0-20. Patients are then stratified based on risk categories (i.e. 0-2=low risk; 3-5=moderate risk; >6=high risk). A publication has shown that the RDS is a better predictor of adverse cardiovascular events than the FRS over a 2-5 year period after screening[72]. The areas under the curve for a receiver operating characteristics curve were compared to determine which model was a better predictor of cardiovascular events, and the RDS score surpassed the FRS in its predictive ability with an area under the curve of 0.74 as compared to 0.66. While the 10-screen RDS was shown to have good prognostic ability, it is quite labor intensive and expensive. This stimulated Cohn to develop a simpler 4-test screening protocol based on large and small artery elasticity measures, blood pressure at rest and in response to 3-min of moderate intensity exercise. These four assessments were chosen because of their high individual test contributions to the 10-screen RDS score in Spearman correlation coefficient calculations in a previous publication.[72] As with the 10-screen, each of the four components of the 4-test RDS are scored from 0-2 (0 = normal; 1 = borderline; 2 = abnormal) with a total RDS ranging from 0-8. Each participant is categorized based on risk (i.e. 0-2 = normal; 3-8 = abnormal). These non-invasive procedures aim to detect early stages of CVD for individual asymptomatic patients.

The Cardiovascular Health in Ambulatory Care Research Team (CANHEART) have also proposed their own health index to assess cardiovascular health risk behaviours and disease risk based on smoking status, fruit and vegetable consumption, body mass index, as well as the presence of diabetes and high blood pressure. [74] Maclagan et al. identified these six health parameters based on the definition of ideal cardiovascular health by the American Heart

Association[75] and the premise that meeting six of these parameters can reduce incidence of CVD by 89%.[76] Ideal criteria were determined in each of these six health factors by examining data from the Canadian Community Health Survey.[77] The presence of each health factor is assigned a value of one, for a total CANHEART score ranging from 0, poor, to 6, ideal. Adults with an ideal CANHEART score had 16 times lower prevalence of heart disease than those with the worst CANHEART score possible.[74]

1.4 CVD and Women

There is a common perception that CVD is a 'man's disease';[78] however, women tend to develop heart disease approximately 10-15 years later than men, with a prevalence rate similar between sexes after women turn 60 years of age or older.[79] This later onset of CVD in women is likely due to the protective effect of estrogen in pre-menopausal women.[78] Women are often underrepresented in cardiovascular clinical trials, which is an issue because their clinical presentation and prognosis of CVD differ from that of men.[80] In fact, women who suffer an acute MI are more likely to die, have a second MI, develop heart failure, or consequentially suffer sudden cardiac death, as compared to men.[81] Although improvements in CVD management have led to decreased mortality rates, more women than men have died from causes related to CVD since 1980.[81] In fact, heart disease is the leading cause of death in women worldwide.[82] Improvements in CVD knowledge is not providing the same benefit in women for diagnosis, treatment or prevention of heart disease as is being seen in men.[83]

It is important to highlight that traditional risk factors assessed by FRS score, the current clinical standard in Canada, underestimate the risk of experiencing an acute MI in women, as compared to men.[25,83] Thus, it appears that there is a need to refine existing tools or develop

innovative screening tools to better detect early stages of CVD risk amongst women. A previous study showed that as much as 80% of females identified as being at low risk according to the FRS, then went on to experience an acute MI.[29] In an eight year follow up study in older adults, the FRS poorly discriminated between those who had onset CVD and those who did not and this absolute risk was specifically underestimated in women (51%) versus men (8%).[25] While knowledge on CVD in women has come a long way recently, there is still a lot of work to be done to improve awareness and prognostic tools in this population.[84]

2.3 Frailty

A suggested method of improving CVD risk management is the addition of frailty assessments as vital signs.[85] While there is some disagreement on the exact definition of the term,[86] frailty can be characterized as having a lack of reserve for tolerating health stressors,[87] and has been shown to be an independent predictor of cardiovascular morbidity and mortality in the elderly.[88,89] Some literature suggests that this physiological age may, in fact, be more important than chronological age when assessing risk for CVD.[85]

The prevalence of frailty in the population is dependent on the tool used to assess frailty and the population being examined.[90] For example, an examination of Canadian Health Measures Survey data found the prevalence of frailty to be 7.8% with one method versus 20.2% with another in those 65 years of age or older.[91] The Cardiovascular Health Study[92] examined 5,317 community-dwelling men and women 65 years of age and older. In this cohort, 46% (n=2469) of the population was found to be pre-frail and 6.9% (n=368) of the population was considered frail. The prevalence rate of pre-frailty was similar between sexes, but increased for females when examining frailty; 46.5% (n=1431) of the female considered pre-frail, versus 46.8%%

(n=1049) of the males, and 8.2% (n=252) of the female contingent measuring as frail, versus 5.2% (n=116) in males. This prevalence also increased with age. A recent systematic review on frailty prevalence in older adults[90] found that pooled prevalence of frailty was 14% with increasing prevalence into older age. As with the Cardiovascular Health Study, this review established a higher prevalence of frailty in women than men. Prevalence of frailty has also been found to be increased in older adults living alone, implying that sociological factors may also play a role in this complex syndrome.[93,94]

2.3.1 Assessing frailty

Multiple methods of assessing frailty exist in the literature, and no model has proven itself to be a gold-standard for identifying frailty.[95] The method that has been the most widely used in research is the phenotype model proposed by Fried et al.,[96] partially because of its ease of use in a clinical setting.[85] The Fried Criteria (FC) assesses five specific domains: **(1)** muscle weakness; **(2)** slow walking speed; **(3)** low physical activity levels; **(4)** unintentional weight loss; and **(5)** self-reported exhaustion.[54] Total FC scores range from 0 to 5 depending on the number of variables present. The presence of these variables in Fried's cohort was determined by setting cutoffs based on the lowest quintile of the cohort's distribution.[54] Walking speed was assessed using a 15-foot walk test with two different lowest quintile cutoffs dependent on participant height. Muscle weakness was assessed with a grip strength measure. Cutoff values for grip strength testing were stratified based on the lowest quintile of each of four different body mass index quartiles. Unintentional weight loss was assessed with the use of a questionnaire asking "In the last year, have you lost more than 10 pounds unintentionally (i.e., not due to dieting or exercise)?" If yes, then the participant was considered frail for this criterion. Exhaustion was

assessed by the Center for Epidemiologic Studies – Depression Scale.[97] Finally, physical activity levels were assessed with the Paffenbarger Physical Activity Scale (PPAS).[98] The bottom quintile of physical activity levels were set as the criterion cutoff. These total scores were then used to stratify individuals into frailty groups (i.e. 0 = robust; 1-2 = pre-frail; ≥ 3 = frail). Participants that are pre-frail are at increased risk of becoming frail and the FC has been shown to independently predict disability, morbidity, and mortality.[54] This model was developed with the use of data collected as part of the Cardiovascular Health Study.[92]

2.3.2 Standardization of frailty

It has been suggested that using the same cutoff values across all populations, regardless of varying phenotypic diversity[99] or socioeconomic status,[100] may lead to the misclassification of frailty status, and in turn adverse outcome risk, in the population.[101] However, only one previous study, by Bouzon et al., has evaluated the improvement in risk prediction that might be seen with a standardized Fried Criteria (S-FC).[101] Briefly, creating an S-FC involves using the lowest quintile of the cohort being assessed to create criteria cutoffs in the same method Fried used in the original paper. All of the grip strength, gait speed, and physical activity level cutoffs are created in this method. The paper by Bouzon et al. reported that the S-FC was better at identifying pre-frail participants as an intermediate risk status between robust and frail. As well, they reported that hazard ratios for death, hospitalization, incident disability and falls were detected earlier in time with the S-FC, implying that it predicts shorter term adverse outcomes compared to the original FC model. Based on that novel data, there is a need to further confirm the predictive ability of the S-FC model across various populations. Bouzon et al. also did not examine CVD specific outcomes in their work.[101]

2.3.3 Pathophysiology of frailty

Frailty occurs when a reduction in physiological capacity prevents natural adaptation mechanisms to health stressors from occurring.[102] While it is understood that this homeostasis breakdown is associated with increased risk for a host of adverse health outcomes,[54,90] the causes of this physiological decline are less understood.[102] In an attempt to further understand this concept, biological factors have been assessed in term of their association with frailty. This research has demonstrated an association between both lipid levels and inflammation with frailty.[103–106] It is no surprise that the exact pathophysiology of frailty is not fully understood, as this is a complex aging process that covers a variety of physiological processes including metabolic disorders, inflammatory responses, and endocrine dysregulation.[107] Afilalo et al. discuss two different pathways leading to the development of the phenotype of frailty (Figure 1).[96] The first involves inflammation pathways, androgen deficiency and a resulting insult to the homeostatic balance between anabolism and catabolism. This response results in a decrease in muscle mass in the subject, also known as sarcopenia. This pathway is exacerbated in those with insulin resistance, metabolic syndrome, and with the confounding factors of bed rest and malnutrition that can be found in at-risk older adults. The second proposed pathway to the frailty phenotype is due to subclinical damage across a range of physiological systems that occurs over a lifetime and use, which can be aggravated through genetic predisposition and CVD. As with the previous pathway, these accumulated damages can lead to the decreased physiological reserve to health stressors seen in the frail, and the clinical presentation of slow walking speed, weakness, weight loss, physical inactivity and self-reported exhaustion.

Figure 1. Pathophysiology of the frailty phenotype

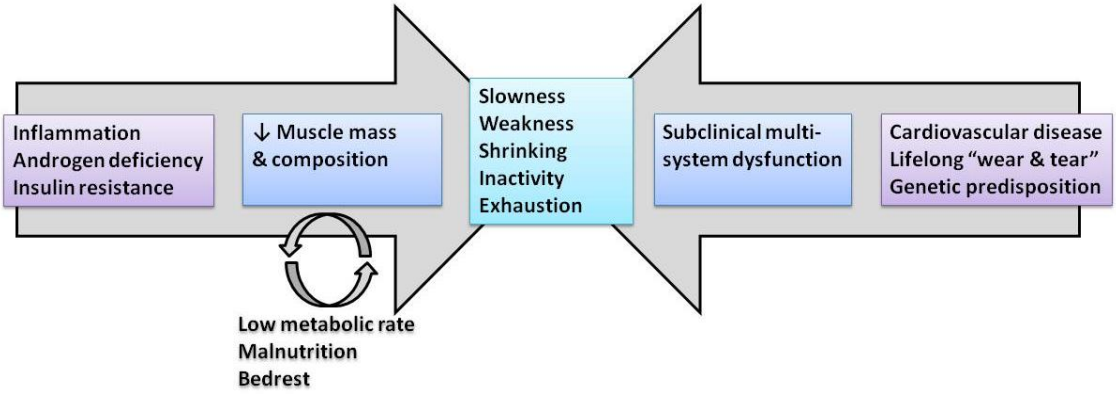


Figure 1 adapted from Afilalo et al.[96]

2.3.4 Frailty and CVD

As the population ages, the incidence of frailty and CVD will both rise as risk for both increases with age.[108] This makes the study of their coexistence increasingly important. The incidence of frailty in older adults ranges anywhere from 10% to 60%, dependent on the population and scales used for the assessment.[108] Frailty has been shown to be associated with increased risk for CVD in longitudinal studies,[54,109] but less is known about the mechanisms linking frailty and these adverse cardiovascular outcomes.[110] CVD and frailty share many of the same lifestyle behavior risk factors,[111] such as physical inactivity,[112] obesity,[113] smoking,[114] and poor diet.[115] A previous study showed that those with a higher FRS score at baseline were at increased risk of developing pre-frailty and frailty over the following 4-year period.[116] This relationship may, in fact, be bidirectional.[110] A study by Sergi et al. demonstrated that compared with those who did not develop frailty, those who developed pre-frailty had a significantly increased risk of developing CVD in the 4-year follow-up period, but there is little data assessing risk for CVD in this intermediate stage of frailty.[109] In fact, a recent meta-analysis was only able

to identify four longitudinal studies assessing CVD morbidity in pre-frail compared to non-frail participants.[89,109,117,118] Pooled risk estimates identified pre-frail participants with no previous history of CVD as being at increased risk for CVD morbidity (HR: 1.32) and CVD mortality (HR: 2.80) compared to non-frail.[119]

CVD health management is important for both pre-frail and frail older adults, specifically in females as they are at increased risk for frailty.[90,120] Assessing middle-aged and older adults for frailty can assist with the characterization of the patient, allowing for better care and more accurate prognoses.[96] If patients were identified in what is considered the more intervenable pre-frailty stage, interventions could be put in place to slow or reverse the frailty trajectory, potentially preventing the adverse events associated with frailty.[121,122] Pre-frailty is associated with a 4-fold higher risk to become frail over 4 years[54] and previous studies have already outlined the potential importance of assessing pre-frailty in apparently healthy older adults.[109] Despite the CVD risk associated with pre-frailty, many studies group study participants in this intermediary stage with either robust or frail groups in their cohort, meaning that few studies have specifically assessed the cross-sectional CVD risk profile associated with this at-risk population prior to CVD onset, although biomarkers and their association to pre-frailty have been assessed.[123]. It is important to separate pre-frailty in analyses such as these for the reasons stated above as well as for the reason that frailty should be viewed as a continuum as opposed to a dichotomous outcome. A meta-analysis by Veronese et al. identified ten cross-sectional studies comparing CVD risk variables between non-frail and pre-frail participants,[117,118,120,124–132] but of these only Ramsay et al.[120] compare data between these groups in a cohort with no previous history of CVD, and that cohort was entirely male. As well, the Veronese et al. meta-analysis[119] identified a longitudinal study by Sergi et al. that also included a cross-sectional comparison

CVD risk profile between non-frail and pre-frail participants before CVD onset in a prospective study.[109] That paper identified higher baseline CVD risk in pre-frail participants, compared to robust, across a range of measures, such as higher resting blood pressure, higher BMI, and higher LDL cholesterol levels. The longitudinal portion of that same paper reported that pre-frail participants have increased risk of developing CVD after 4.4 ± 1.2 years of follow up. As such, both Sergi et al. and Ramsay et al. identified the need for cohort studies to determine if pre-frailty and CVD risk factors are associated independent of established CVD.[109,120] Such knowledge could allow for better health screening of patients with early stages of frailty as a strategy to reduce risk for future adverse CVD health in an asymptomatic population.[96,108] Thus, there is a need to further examine cross-sectional CVD risk factors present in pre-frail and frail populations of varying populations in advance of clinical CVD.

Chapter 2: Statement of the Problem and Methods

2.1 Statement of the problem

The growth rate of Canada's population of persons aged 65 years and older is four times that of the total population, and by 2024 this age group will comprise 20% of the nation's total population.[133] As the population ages, a number of specific health concerns will come to the forefront, such as chronic diseases like CVD. Despite many research advances for CVD management in recent years, 25% of deaths in Canada were due to heart disease and stroke in 2012.[10] As the prevalence of chronic disease rises with the aging population, research will have to address this growing problem by finding means of reducing the impact these conditions have on individuals, families and the healthcare system. In order to direct interventions in a productive manner, the risk of developing CVD must be assessed to allow for efforts to be focused on those at higher risk.

As the population ages, the incidence of frailty and CVD will both rise as risk for both increases with age.[108] Frailty and pre-frailty are both known to increase the risk for CVD.[54,109] Identifying pre-frail and frail individuals earlier could allow for interventions to be put in place to reduce the risk of developing CVD.[121,122] Interventions aimed at the physiological decline inherent with frailty, and the concomitant CVD risk, should focus early in risk progression in those with subclinical CVD.[110] Knowledge of the CVD risk profile associated with pre-frailty and frailty before the onset of CVD will allow for better care and management of this at-risk population, but few studies have assessed these groups separately.[109,120] Furthermore, recent literature has suggested the improvement of frailty assessments by using cutoffs that have been standardized to the individual cohort they are assessing, but there is only a single paper that has

compared adverse outcome risk prediction between the FC and S-FC,[101] and it did not assess CVD specific outcomes. As well, there is a specific need to further our understanding of women's cardiovascular health and its relation to frailty as they have been underrepresented in CVD research and are at increased risk of frailty compared to males.[90,134] There is a need for further information on the CVD risk factors present in pre-frail and frail women before the onset of CVD.[120]

2.2 Thesis objective

The main objectives of my thesis research were to:

1) determine if standardized frailty measures are better able to discriminate CVD risk compared to the traditional approach proposed by Fried et al.[54]
2) determine if there are differences in CVD risk profile between robust, pre-frail and frail participants in a cohort of 985 women 55 years of age or older with no previous history of CVD.

As a secondary objective, this thesis project examined the odds ratios for different physiological and lifestyle behavior CVD risk factors in pre-frail and frail groups compared to robust.

2.2.1 Thesis hypotheses

In regard to my main objectives, I hypothesize that the S-FC model will better discriminate CVD risk compared to the FC model. This is based on previous literature that has reported that standardized models of frailty better predict adverse outcomes in populations that differ from the cohort used to create the original FC.[101] I also hypothesize that increasing levels of frailty will be associated with higher CVD risk according to the composite CVD risk scores

measured (FRS, RDS, and CANHEART), as well as the individual factors that would place an individual at increased risk for CVD. This hypothesis is based on a previous meta-analysis that has outlined the increased risk for adverse CVD outcomes for those who are pre-frail and frail.[119] Finally, for the same reason as just described, I hypothesize that those who are pre-frail and frail will have increased odds of the presence of physiological factors and lifestyle behaviors that are known to increase the risk for CVD.

2.3 Methods

2.3.1 Research design

The comparison of CVD risk profile was performed using a secondary, cross-sectional examination of baseline data collected during the Women's Advanced Risk-Assessment in Manitoba (WARM) Hearts cardiovascular screening project.[135] This prospective, observational study was designed to examine the ability of a series of non-invasive procedures to identify asymptomatic middle-aged and older women who are at an elevated risk of experiencing an adverse cardiovascular event in the five-year period after screening. The WARM Hearts study received clinical approval from the University of Manitoba Health Research Ethics Board (H2014:224) and the St. Boniface Hospital Research Review Committee (RRC/2014/1417) prior to its implementation. The WARM Hearts study was registered with ClinicalTrials.gov, a registry and results database of privately and publicly funded clinical studies (NCT02863211).

One-thousand female participants 55 years of age or older were recruited through a convenience sample method. We utilized radio interviews on popular local stations to discuss the study as well as presentations at community events related to cardiovascular health. Poster advertisements were also placed in community centers. Individuals interested in participating

were instructed to contact the research coordinator by email or telephone. Women were included in the study if they were 55 years or older and had a Manitoba Personal Health Information Number (PHIN). Previous hospitalization for CVD, as listed in Table 2, excluded participants from the study. Women with hypertension were invited to participate in the study if their hypertension was being medically managed. Due to their risk profile in regard to performing physical activity, we did not include participants with hypertension that was not being medically managed. If eligible, participants were invited to come to the I.H. Asper Clinical Research Institute where they were given both written and verbal information describing the nature of the study. Written informed consent was obtained before enrolment.

Table 2: Inclusion and exclusion criteria for the WARM Hearts study

Inclusion criteria
• Women aged 55 and older • Possess a Manitoba Personal Health Information Number
Exclusion criteria
Previous hospitalization for: • Ischemic heart disease • Acute myocardial infarction • Stroke • Percutaneous coronary intervention • Coronary artery bypass surgery • Congestive heart failure • Peripheral artery disease
Previous diagnosis of hypertension, which is not medically managed.

2.3.2 Measurements

Fried Frailty Phenotype

A phenotype of frailty was assessed using the FC as previously described by Fried et al.[54] Briefly, the FC assessed the following criteria: 1) unintentional weight loss; 2) self-reported exhaustion; 3) weakness; 4) slow walking speed; 5) low physical activity. Gait speed was assessed using a 5-meter gait speed test[51] and there were two different cutoffs dependent on participant height (i.e. height ≤159 cm → ≤0.76 meters/second (m/s); height >159 cm → ≤0.65 m/s). This is different than the original FC, which used a 15-foot walk test to assess walking speed, but previous studies have used the 5-meter gait speed test[96] and it has received attention as a single-item measure of frailty.[45] Grip strength was measured with both hands in kilograms with the use of a Jamaar hand dynamometer.[92] Cutoff values for grip strength testing were stratified based on body mass index (BMI) (i.e. BMI ≤23 → ≤17 Kg BMI 23.1-26 → ≤17.3 Kg BMI 26.1-29 → ≤18 Kg BMI >29 → ≤21 Kg). Unintentional weight loss was assessed with the use of a questionnaire asking "In the last year, have you lost more than 10 pounds unintentionally (i.e., not due to dieting or exercise)?" If yes, then the participant was considered frail for this criterion. Exhaustion was assessed by the Center for Epidemiologic Studies – Depression Scale.[97] Participants were asked to respond how often in the last week they felt either: a) everything was an effort, or; b) they could not get going. Participants who responded that they feel either of those a moderate amount of the time or most of the time were considered frail for this criterion. Finally, physical activity levels were assessed with the Paffenbarger Physical Activity Scale (PPAS).[98] Participants responses were converted into kilocalorie (Kcal) expenditure per week to compare to the original FC cutoff (i.e. <270 Kcals of physical activity per week). The original FC used the Minnesota Leisure Time Activity Questionnaire[136] to assess Kcal expenditure per week, but previous studies have replaced this with the PPAS.[96] The cutoffs

for gait speed, grip strength and low physical activity levels described above were determined by Fried et al. by looking at the lowest quintile of their original cohort's distribution.[54] Total FC scores ranged from 0 to 5 depending on the number of variables present in the individual. Total scores were then used to stratify individuals into groups (i.e. 0 = robust; 1-2 = pre-frail; ≥ 3 = frail).

Previous literature has suggested that using the same cutoff values across all populations may lead to the misclassification of frailty status, and in turn adverse outcome risk, in different cohorts.[101] Therefore, as recommended by Bouzon et al.,[101] new standardized cutoffs for grip strength, gait speed, and low physical activity levels were determined for the WARM Hearts cohort using the same methods as Fried et al. in their original paper.[54] Gait speed cutoffs, dependent on participant height, were adjusted based on the lowest quintile of this cohort and height (i.e. ≤161 cm → ≤1.10 m/s; >159 cm → ≤1.15 m/s). Cutoff values for grip strength testing were stratified based on the lowest quintile and body mass index quartiles (BMI) (i.e. BMI ≤23.3 → ≤21 Kg BMI 23.4-26.1 → ≤22 Kg BMI 26.2-29.6 → ≤22 Kg BMI >29.6 → ≤22 Kg). Physical activity levels, based on kilocalorie (Kcal) expenditure per week, cutoffs were adjusted based on the lowest quintile (i.e. for females: <640.1 Kcals of physical activity per week). Self-reported exhaustion and unintentional weight loss criteria did not change with the standardized method, as these cutoffs were not based on quintiles from the original cohort. Cutoffs for both the FC and S-FC are displayed in Appendix G.

4-test RDS

The WARM Hearts screening protocol involved the 4-test RDS protocol, which consisted of four measurements: 1) resting blood pressure; 2) systolic blood pressure response following 3-min of moderate intensity exercise; 3) large artery elasticity assessment, and; 4) small artery elasticity assessment. For these measurements, the HD/PulseWave™ CR-2000 Research CardioVascular Profiling System (CV profiler) was used. This device is indicated for use in determining both blood pressure and artery elasticity measures in human subjects for research purposes only. Measures from this instrument have been shown to be reproducible, with one study finding that intra-visit measurements five minutes apart only differed by 3% and inter-visit measures one to four weeks later only differed by 4%.[137] Research staff were trained in the use of the HD/PulseWave™ CR-2000 Research CardioVascular Profiling System and performed all of the testing. Each of the measures involved in the WARM Hearts protocol is described below.

Test 1: Resting blood pressure

A blood pressure cuff attached to the CV profiler was placed on the participant's arm while they were in a supine position. A resting blood pressure of less than 120/80 mmHg was considered normal (0 RDS points), 120-139/80-89 was considered pre-hypertensive (1 RDS point) with the potential for the development of high blood pressure (hypertension). Blood pressure greater than 140/90 was considered abnormal for adults (2 RDS points).[80]

Test 2: Systolic blood pressure response to exercise

The magnitude of the rise in blood pressure during exercise may be an indication of early risk for developing hypertension, even if the participant's resting blood pressure is normal.[138]

After the resting blood pressure was assessed, the participant was asked to perform 3 minutes of moderate exercise on a 2-step stool according to the Dundee Step Test,[139] or on a treadmill for those who were unable to perform the step test. Both of these exercise procedures were performed at a 5 metabolic equivalent (MET) workload. The participant then had their blood pressure measured once again in a supine position immediately following the exercise protocol (within 30 seconds). A rise in systolic blood pressure of under 30 mmHg and less than 169 mmHg absolute blood pressure was considered normal (0 RDS points), a rise of 30-39 mmHg and an absolute resting blood pressure of 170-179 was considered borderline (1 RDS point), and a rise of 40 mmHg or more and an absolute resting blood pressure of 180 mmHg or high was considered abnormal (2 RDS points).[80]

Test 3 and 4: Large and small artery elasticity

To measure artery elasticity a wrist stabilizer was placed on the participant's wrist while they were in a supine position. A piezoelectric transducer, or pulse wave sensor, was then placed on the location of strongest pulsation of the radial artery adjacent to the styloid process. The CV Profiler assessed the diastolic decay and waveform transmitted to it through the sensor. Based on the modified Windkessel model, the instrument then determined small artery and large artery elasticity. Scoring of normal, borderline and abnormal results for large and small arterial elasticity were based on age and sex cutoffs.[80] For females under 65, a large artery elasticity of 10 mL/mmHg x10 or greater was normal (0 RDS points), a value from 9-9.9 mL/mmHg x10 was considered borderline (1 RDS point) and any value below 9 mL/mmHg x10 was considered abnormal (2 RDS points). The small artery elasticity cutoffs for this age group were 4 mL/mmHg x100 and higher for normal (0 RDS points), 3.5-3.9 mL/mmHg x100 for borderline (1 RDS

point) and under 3.5 mL/mmHg x100 for abnormal (2 RDS points). Females over the age of 65 had lower cutoffs for both large and small artery elasticity. Normal large artery elasticity values were 9 mL/mmHg x10 or higher (0 RDS points), borderline values were 8-8.9 mL/mmHg x10 (1 RDS point) and abnormal values were under 8 mL/mmHg x10 (2 RDS points). Normal small artery elasticity values were 3 mL/mmHg x100 or higher (0 RDS points), borderline values were 2.5-2.9 mL/mmHg x100 (1 RDS point) and abnormal values were under 2.5 mL/mmHg x100 (2 RDS points).

Scoring the 4-test RDS protocol

Each of the tests in the 4-test RDS were scored as 0 for normal, 1 for borderline abnormal, and 2 for abnormal.[80] Total scores ranged from 0 to 8 and were used to stratify individuals into one of two risk groups: 0-2 = normal risk; $\geq$ 3 = moderate to high (abnormal) risk.

Assessment of the Framingham Risk Score

FRS was determined based on the calculations described by D'Agostino et al.[22] Information required for this calculation was acquired from a participant questionnaire, fasting blood sampling of high-density lipoprotein and total cholesterol, and the resting blood pressure reading from the CV Profiler. Participants were asked to fast for the 12 hours prior to the blood draw at their appointment. Approximately 10 mL of blood was collected by a phlebotomist. The samples were then centrifuged so that the plasma could be separated and analyzed for total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, and fasting glucose. These variables were analyzed using the cutoff values in the 2012 Canadian Cardiovascular

Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of CVD in the adult.[140]

Questionnaires

Participants were instructed to fill out a series of questionnaires. Approval was sought for the use of all intellectual property:

1) Baseline demographic information such as age, education and smoking status, were collected via questionnaire.
2) Physical activity behaviour was assessed using the International Physical Activity Questionnaire (IPAQ) short-version.[141] This questionnaire measured the amount and intensity of physical activity completed by an individual. The IPAQ has been used to improve CVD risk scores in previous literature .[56]
3) The Cardiovascular Health in Ambulatory Care Research Team (CANHEART) Health Index[74] was used to assess cardiovascular health behavior and disease risk based on self-reported physical activity (from the IPAQ short-version), smoking status, fruit and vegetable consumption, body mass index, as well as the presence of diabetes and high blood pressure;
4) Quality of life was assessed using the EuroQol Five Dimension Five Level questionnaire.[142] This quality of life questionnaire has been validated for use as an outcome measure in populations with CVD;[143]
5) Presence and severity of depressive symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9).[144]

6- Minute Walk Test

Participants were instructed to walk as many lengths of a 30-meter track as possible during the 6-minute duration. Distance covered during the test was recorded. A study by Beatty et al.[34] showed the prognostic value of the 6MWT for predicting cardiovascular events in patients with stable coronary heart disease.

2.3.3 Statistical Analyses

Statistical analyses were performed using the STATISTICA (version 13) and the Statistical Analysis System analytical platforms (version 9.4). Ability to discriminate CVD risk according to the FRS and RDS in the cohort were assessed between the FC and S-FC models with the use of receiver operating characteristic (ROC) curves by comparing the area under the curve (AUC) for both models. AUC for the ROC curves was calculated by the methods utilized in Statistical Analysis System version 9.4. Discrimination slope improvement and the reclassification of participants with the S-FC model, compared to the FC model, were assessed with integrated discrimination index (IDI) and net reclassification index (NRI). Comparison of biological and lifestyle behavior CVD risk profiles between robust, pre-frail and frail groups, as determined by the S-FC, were compared using one-way ANOVA tests to compare continuous variables and Chi-Square to compare categorical variables. When differences were detected by ANOVA, Tukey's Honest Significant Difference post-hoc analysis was used to identify differences between specific means. Multivariable logistic regressions were also performed to estimate both unadjusted and age-adjusted odds ratios (OR) of physiological and lifestyle behavior CVD risk factors between pre-frail and frail groups with the robust group as the

comparison, as assessed by the S-FC. A p value of ≤0.05 was determined to be statistically significant.

As the use of logistic regressions requires the outcome variable to be dichotomous, various clinical guidelines were used to create dichotomous outcomes from the variables collected in the WARM Hearts study. Abnormal BMI in the cohort was designated as any values that would classify a participant as Obese Class I in accordance with the World Health Organization report on global obesity.[145] Ex and current smokers were grouped together as both have been shown to have increased risk for coronary heart disease.[146] Cutoffs for abnormal bloodwork values across HDL cholesterol, LDL cholesterol, total cholesterol, triglycerides and fasting blood glucose were set based on the 2012 Canadian Cardiovascular Society/Canadian guidelines.[140] The cutoff of 150 minutes of moderate-to-vigorous physical activity has been previously established by the Canadian Society for Exercise Physiology as the minimum amount of physical activity to achieve Canada's Physical Activity Guidelines.[147] The CANHEART health index, created by Maclagan et al., has established cutoffs, with scores of ≤3 as being considered poor cardiovascular health.[74] This cutoff was used in the logistic regression models. FRS scores of 10% or higher 10-year CVD risk were considered abnormal based on the cutoffs developed by D'Agostino et al.[22] The RDS also has its own cutoffs, with scores of 3 or higher being considered abnormal.[72] Dichotomous cutoffs for the various factors comprising the RDS score (resting blood pressure, blood pressure response to exercise, large and small artery elasticity) were based on the "abnormal" cutoffs described in section 2.3.2. Due to all of the PHQ-9 scores in the cohort being relatively low, scores indicating mild depression, as determined by established cutoffs (≥5), were used as the dichotomous cutoff.[144] Cutoffs for the 6MWT have been pre-established by Beatty et al. in a cohort with stable coronary heart

disease.[34] The cutoff for moderate to high CVD risk, as established by Beatty et al. (<544 m), was used as the cutoff for this factor.

Chapter 3: Results

3.1 Baseline Characteristics

Mean age of the cohort was 65.5 (95% CI 65.1-65.9) with a mean BMI of 26.7 (26.4-27.1). Just over a quarter of the participants lived alone, and about 75% of the participants had received post-secondary education. Ex or current smokers composed 42% of the cohort. Prevalence of participants taking diabetes, lipid and blood pressure medications were 3.8%, 17.2%, and 23.6%, respectively. Baseline characteristics for the overall cohort are included in Table 3. Baseline CVD risk factors are outlined in Table 4 to describe the cohort. An in-depth analysis of the cohort characteristics will be performed based on frailty classification in a later section of the results.

Table 3: Baseline characteristics

Characteristic	**Cohort** (n = 985)
Age	65.47 (6.33)
BMI (kg/m^2)	26.74 (4.92)
Living alone	272 (27.6%)
PS education	736 (74.7%)
Ex/Current Smoker	420 (42.0%)
Diabetes med(s)	37 (3.8%)
Lipid med(s)	169 (17.2%)
BP med(s)	232 (23.6%)

Continuous variables expressed as Mean (standard deviation)Categorical variables expressed as N (%). ***BMI,*** *Body Mass Index;* ***PS,*** *Post-Secondary;* ***BP,*** *Blood Pressure.*

Table 4: Baseline CVD risk factors

Characteristic	Total Cohort *n = 985*
Frailty	
FC	0.33 (0.62)
S-FC	0.80 (0.95)
Bloodwork	
HDL cholesterol (mmol)	1.87 (0.53)
LDL cholesterol (mmol)	3.46 (0.94)
Total cholesterol (mmol)	5.48 (0.99)
Triglycerides (mmol)	1.14 (0.59)
Fasting blood glucose (mmol)	5.53 (0.99)
Subjective PA levels	
Total Vigorous min/week	123.15 (395.30)
Total Moderate min/week	162.56 (245.22)
Total Walking min/week	313.60 (403.08)
Total MVPA/week	298.93 (497.42)
Total PA min/week	638.03 (710.36)
Composite CVD risk scores	
CANHEART score	4.44 (1.08)
Framingham Risk Score (%)	9.73 (5.87)
RDS score	3.14 (2.20)
Cardiovascular parameters	
Large artery elasticity	12.05 (4.06)
Small artery elasticity	3.96 (2.40)
Systolic BP (mmHg)	131.11 (15.77)
Diastolic BP (mmHg)	72.22 (9.19)
Pulse pressure (mmHg)	58.88 (11.37)
ΔSystolic BP activity response	32.00 (17.06)
Other	
6MWT distance (m)	558.31 (71.87)
PHQ-9 score	2.88 (3.14)
Sedentary time hours/day	9.34 (22.18)

*Continuous variables expressed as Mean (standard deviation) compared using one-way ANOVA; * denotes statistical significance.* ***CVD,*** *Cardiovascular Disease;* ***FC,*** *Fried Criteria;* ***S-FC,*** *Standardized Fried Criteria;* ***HDL,*** *high-density lipoprotein;* ***LDL,*** *low-density lipoprotein;* ***PA,*** *Physical Activity;* ***MVPA,*** *Moderate-to-Vigorous Physical Activity;* ***RDS,*** *Rasmussen Disease Score;* ***BP,*** *Blood Pressure;* ***6MWT,*** *Six-minute Walk Test;* ***PHQ-9,*** *Personal Health Questionnaire-9.*

3.2 S-FC and FC Outcomes

The prevalence of robust, pre-frail and frail participants in the cohort differed between the S-FC and FC models. Reclassification of frailty status in the S-FC model reduced the number of participants considered robust by 278 participants, and increased the number of participants in the pre-frail and frail groups by 203 and 56, respectively. The prevalence of pre-frailty and frailty in the cohort was 47.1% and 6.4% for the S-FC, respectively, and 26.5% and 0.7% for the FC. Varying prevalence between the two models is displayed in Table 3. Looking at each frailty criteria, the S-FC model identified 26.4%, 20.1% and 20.1% of participants as having this frailty criterion for grip strength, gait speed and physical activity levels, respectively. These rates were higher than detected by the FC. The prevalence of grip strength flags in the S-FC model was 26.4% because of the large number of participants with the same whole number grip strength results. There was no difference in prevalence between the S-FC and the FC models for the presence of unintentional weight loss or self-reported exhaustion (Table 6).

Table 5: Comparison of participant classification based on scale used

	S-FC Classification		
FC Classification	Robust (n = 458)	Pre-frail (n = 464)	Frail (n = 63)
Robust (n = 725)	458	263	4
Pre-frail (n = 253)	0	201	52
Frail (n = 7)	0	0	7

Variables expressed as N. ***FC,*** *Fried Criteria;* ***S-FC,*** *Standardized Fried Criteria.*

Table 6: Frailty criteria prevalence

Characteristic (n = 985)	**FC**	**S-FC**
Weakness (grip strength)	87 (8.8%)	260 (26.4%)
Slowness (5-metre gait speed)	5 (0.5%)	198 (20.1%)
Low physical activity (Paffenbarger)	91 (9.2%)	198 (20.1%)
Unintentional weight loss	27 (2.7%)	27 (2.7%)
Self-reported exhaustion (CES-D)	130 (13.2%)	130 (13.2%)

*Variables expressed as N(%).**FC,** Fried Criteria; **S-FC,** Standardized Fried Criteria; **CES-D,** Center for Epidemiologic Studies Depression Scale.*

The S-FC showed superior ability to discriminate between CVD risk based on the RDS and FRS risk categories in the cohort in the ROC curve analyses (Figures 2 and 3). The AUC for the S-FC model discriminating risk according to the FRS was larger at 0.728 (95% CI 0.662-0.794) compared to 0.634 (95% CI 0.565-0.703) in the FC model ($p<0.001$). The change in AUC from the FC model to the S-FC model did not improve discrimination of risk for the RDS with AUCs of 0.552 (95% CI 0.512-0.593) compared to 0.594 (95% CI 0.548-0.641), respectively ($p=0.125$).

The discrimination slope improvement of the S-FC compared to the FC in the IDI analysis was 1.8% (95% CI, 0.4-3.3%, $p=0.014$) and 1.1% (95% CI, 0.2-2.0%, $p=0.016$) for the FRS and RDS risk scores, respectively. The reclassification of participants in the S-FC model improved FRS and RDS risk discrimination in the NRI analysis by 39.4% (95% CI 12.8-66.0%, $p=0.004$) and 20.5% (95% CI 4.0-36.9%, $p=0.017$), respectively. ROC, IDI and NRI results are outlined in Appendix H.

Figure 2: S-FC vs FC ROC discriminating FRS risk

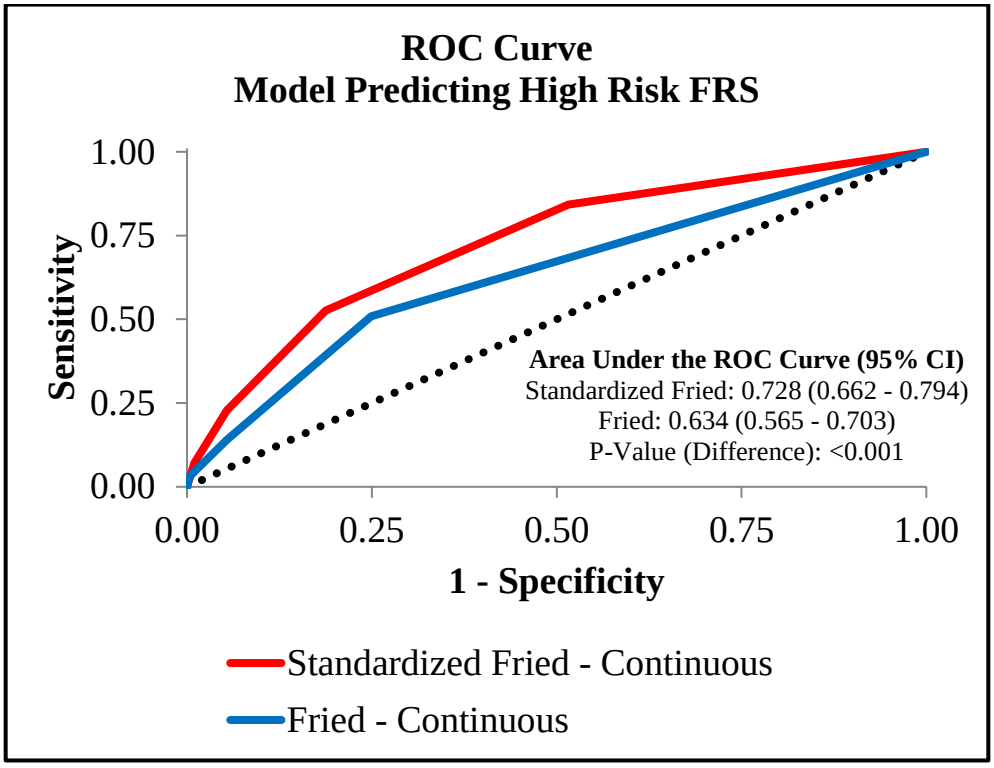
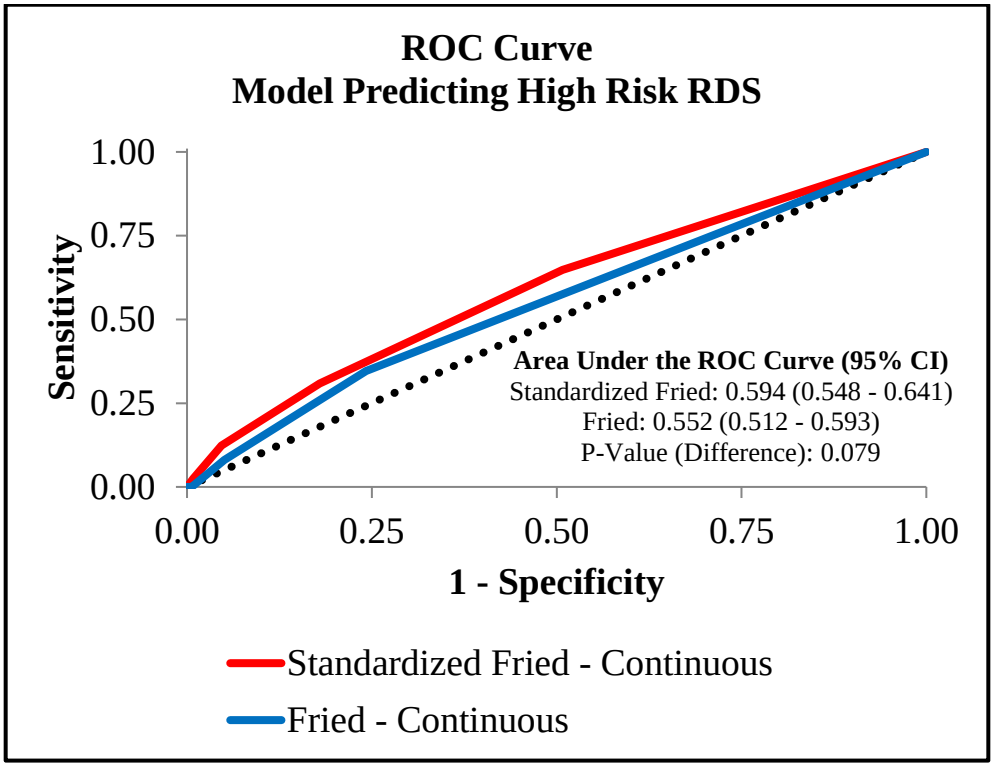


Figure 3: S-FC vs FC ROC discriminating RDS risk



3.3 Frailty Status Characteristics

In order to examine the differences in CVD risk profile between robust, pre-frail and frail participants, the S-FC was used to categorize the cohort into one of the three groups. The decision to categorize participants based on the S-FC was made because the S-FC exhibited superior ability to discriminate CVD risk compared to the FC. Baseline demographics and other cohort characteristics for robust, pre-frail and frail participants are displayed in Table 7. Participants in the robust group were approximately 3 and 5 years younger than the pre-frail and frail groups, respectively. A similar relationship was identified for BMI, where robust was less than pre-frail and frail. The prevalence of living alone was not different between groups, but there was a trend ($p=0.056$) that did not reach statistical significance. Prevalence of post-secondary education completion was also different between the three groups, where completion rates were higher for Robust, as compared to pre-frail and frail groups. Smoking status did not differ between the three groups. The prevalence of participants taking diabetes and blood pressure medications was higher in the pre-frail and frail participants, as compared to robust. Rates of lipid-controlling medications did not differ between groups.

Table 7: Characteristics comparing S-FC classification

Characteristic	Robust (n = 458)	Pre-frail (n = 464)	Frail (n = 63)	P-Value
Age	63.8 (0.29)	66.7 (0.28)a	68.9 (0.77)a,b	**<0.001***
BMI (kg/m^2)	25.8 (0.22)	27.2 (0.22)a	30.2 (0.60)a,b	**<0.001***
Living alone	110 (24.0%)	141 (30.4%)	21 (33.3%)	0.056
PS education	364 (79.5%)	337 (72.6%)a	35 (55.6%)a,b	**<0.001***
Ex/Current Smoker	189 (41.3%)	203 (43.8%)	28 (44.4%)	0.715
Diabetes med(s)	7 (1.5%)	23 (5.0%)a	7 (11.1%)a,b	**<0.001***
Lipid med(s)	68 (14.8%)	86 (18.5%)	15 (23.8%)	0.116
BP med(s)	68 (14.8%)	135 (29.0%)a	29 (46.0%)a,b	**<0.001***

*Continuous variables expressed as Mean (standard error) compared using one-way ANOVA; Categorical variables expressed as N (%) compared using Chi-square test; * denotes statistical significance, a = different from robust; b = different from pre-frail.* ***S-FC,*** *Standardized Fried Criteria;* ***BMI,*** *Body Mass Index;* ***PS,*** *Post-Secondary;* ***BP,*** *Blood Pressure.*

3.4 Primary Outcomes

ANOVA and post hoc tests identified a number of significant differences for CVD risk parameters between robust, pre-frail and frail participants (Table 8). Additional summary information for Table 8 is provided in Appendix I. While no differences were found for HDL cholesterol levels between pre-frail and robust, post-hoc analysis revealed lower levels of HDL cholesterol in the frail group [1.68 mmol (95% CI 1.58-1.79)] compared to both the robust and pre-frail groups. No differences for LDL or total cholesterol levels were identified between any of the three groups. Triglyceride levels were 0.15 mmol and 0.23 mmol higher in the pre-frail and frail groups, as compared to the robust. Fasting blood glucose levels were 0.18 mmol and 0.47 mmol higher in the pre-frail and frail groups, as compared to the robust.

Statistically significant differences in self-reported physical activity levels were identified for all categories assessed. Post-hoc analysis indicated that pre-frail participants performed 69 minutes of vigorous physical activity less than robust. No differences were found in vigorous

physical activity levels between frail and either robust or pre-frail despite a lower mean due to the wide range in the 95% CI. Similar between-group differences were observed for moderate physical activity and total moderate-to-vigorous physical activity minutes per week, where the pre-frail group had 52 minutes and 119 minutes less of moderate-intensity physical activity per week and moderate-to-vigorous physical activity (MVPA) compared to robust. Total time spent walking per week was 60 and 199 minutes lower in pre-frail and frail participants, respectively. Total time spent performing physical activity per week was 24% lower in the pre-frail and 49% lower in the frail groups compared to the robust group. There were no differences in self-reported sedentary hours per day in any of the groups.

Objective data from the 6MWT identified that walking distance was lower in the pre-frail and frail. In fact, robust individuals walked an average of 54 meters farther than pre-frail participants, whereas, the pre-frail group walked an average of 78 meters more than their frail peers.

Higher levels of frailty were associated with more symptoms of depression. PHQ-9 scores were higher for the pre-frail group than the robust group. Moreover, the frail group reported PhQ-9 scores that were 4 points higher than the robust group and 3 points higher than the pre-frail group.

All of the composite CVD screening tests (CANHEART, FRS, and RDS) included in the WARM Hearts protocol showed higher levels of risk with increasing levels of frailty. CANHEART scores were 0.5 lower in the pre-frail group compared to the robust group and 0.66 lower in the frail group compared to pre-frail. This data suggests a higher risk for CVD with greater levels of frailty. The FRS 10-year CVD risk percentage was 2.35% and 5.21% higher in the pre-frail and frail groups compared to the robust group, respectively. RDS scores were also

higher with increasing frailty levels (2.72 to 3.40 to 4.28 in the robust, pre-frail and frail, respectively).

Large artery elasticity, small artery elasticity, resting systolic blood pressure, and change in systolic blood pressure immediately following three minutes of moderate-intensity exercise were all lower in the pre-frail and frail groups, as compared to the robust group. No differences for these parameters were detected between pre-frail and frail groups. Resting diastolic blood pressure did not differ between any of the three groups. Pulse pressure was higher by about 3 mmHg in the robust group than in the pre-frail group, and about 4 mmHg higher in the pre-frail as compared to the frail.

Table 8: CVD risk profile by S-FC status

Characteristic	Robust *n = 465*	Pre-frail *n = 459*	Frail *n = 61*	P-Value
Bloodwork				
HDL cholesterol (mmol)	1.92 (0.02)	1.85 (0.02)	1.68 (0.07)a,b	**0.001***
LDL cholesterol (mmol)	3.49 (0.04)	3.45 (0.04)	3.39 (0.12)	0.652
Total cholesterol (mmol)	5.52 (0.05)	5.46 (0.05)	5.27 (0.13)	0.139
Triglycerides (mmol)	1.06 (0.03)	1.21 (0.03)a	1.29 (0.08)a	**<0.001***
Fasting blood glucose (mmol)	5.42 (0.05)	5.60 (0.05)a	5.89 (0.13)a	**<0.001***
Subjective PA levels				
Total Vigorous min/week	162 (18.95)	93 (19.24)a	53 (51.28)	**0.014***
Total Moderate min/week	190 (11.42)	138 (11.33)a	143 (30.75)	**0.004***
Total Walking min/week	359 (18.71)	290 (18.57)a	160 (50.40)a,b	**<0.001***
Total MVPA/week	364 (23.77)	245(24.14)a	205 (64.32)	**0.001***
Total PA min/week	744 (33.80)	566 (34.32)a	376 (91.46)a	**<0.001***
Composite CVD risk scores				
CANHEART score	4.75 (0.05)	4.25 (0.05)a	3.59 (0.13)a,b	**<0.001***
Framingham Risk Score (%)	8.30 (0.27)	10.65 (0.27)a	13.51 0.73)a,b	**<0.001***
RDS score	2.72 (0.10)	3.40 (0.10)a	4.28 (0.28)a,b	**<0.001***
Cardiovascular parameters				
Large artery elasticity	12.51 (0.19)	11.71 (0.19)a	11.22 (0.51)a	**0.003***
Small artery elasticity	4.29 (0.11)	3.71 (0.11)a	3.44 (0.30)a	**<0.001***
Systolic BP (mmHg)	129.21 (0.73)	132.28 (0.73)a	136.33 (1.97)a	**<0.001***
Diastolic BP (mmHg)	72.05 (0.43)	72.43 (0.43)	71.90 (1.16)	0.795
Pulse pressure (mmHg)	57.15 (0.52)	59.85 (0.52)a	64.43 (1.41)a,b	**<0.001***
ΔSystolic BP activity response	28.96 (0.79)	34.61 (0.79)a	35.38 (2.21)a	**<0.001***
Other				

6MWT distance (m)	591.81 (2.91)	538.28 (2.89)a	460.21 (7.96)a,b	**<0.001***
PHQ-9 score	2.24 (0.14)	3.12 (0.14)a	5.75 (0.38)a,b	**<0.001***
Sedentary time hours/day	9.27 (1.07)	9.32 (1.09)	9.94 (2.97)	0.978

*Continuous variables expressed as Mean (standard error) compared using one-way ANOVA; * denotes statistical significance. a = different from robust; b = different from pre-frail.* ***CVD,*** *Cardiovascular Disease;* ***S-FC,*** *Standardized Fried Criteria;* ***HDL,*** *high-density lipoprotein;* ***LDL,*** *low-density lipoprotein;* ***PA,*** *Physical Activity;* ***MVPA,*** *Moderate-to-Vigorous Physical Activity;* ***RDS,*** *Rasmussen Disease Score;* ***BP,*** *Blood Pressure;* ***6MWT,*** *Six-minute Walk Test;* ***PHQ-9,*** *Personal Health Questionnaire-9.*

3.5 Secondary Outcomes

Unadjusted and age-adjusted logistic regression models with robust participants as the reference identified odds ratios for CVD risk factors in the cohort (Table 9). Those who were prefrail were more likely to have not attended post-secondary education, but the statistical significance of this finding was lost in the age-adjust model. Both the unadjusted and age-adjusted models showed higher likelihood by 3.10 and 2.57 times, respectively, of not attending post-secondary education in the frail participants compared to robust. None of the logistic regression models detected statistically significant odds ratios for a history of smoking in the pre-frail and frail groups compared to the robust group. Pre-frail participants were more likely to have a BMI that would classify them as obese. The odds were higher after controlling for age. Frail participants were 5.19 times and 6.75 times more likely to be obese compared to robust participants in both the unadjusted and the age-adjusted models, respectively. Pre-frail and frail participants, as compared to the robust group, were significantly more likely to utilize diabetes and blood pressure-controlling medications, even after controlling for age. Pre-frail and frail participants were not more likely to be taking lipid-lowering medications, as compared to the robust group.

There were no frail participants with abnormal HDL levels; thus, the odds ratio for this assessment is listed as undefined. The examination of abnormal flags for LDL and total cholesterol did not identify any statistically significant odds ratios for pre-frail or frail participants compared to the robust group. Triglyceride levels were normal across all three groups based on the 2012 Canadian Cardiovascular Society/Canadian guidelines,[140] so they were not included in the logistic regression models. In the unadjusted and age-adjusted logistic

regression models, pre-frail participants were 2.41 times and 2.47 times, respectively, more likely to have abnormal blood glucose levels. These odds were even higher for abnormal blood glucose levels in the frail compared to the robust group in the unadjusted and age-adjusted models.

Pre-frail participants were almost twice as likely to not be meeting Canada's Physical Activity Guidelines compared to robust participants in both the unadjusted and age-adjusted models. These odds more than doubled in the frail participants compared to robust in both the unadjusted and adjusted logistic regression models. The odds of having a poor CANHEART risk score were over three times higher in the pre-frail group compared to the robust group for both the unadjusted and age-adjusted models. These odds were eight times higher in the frail group, as compared to the robust group, for both models.

Being pre-frail was associated with 2.11 higher odds for abnormal FRS flags in the unadjusted model and 1.52 higher odds in the age-adjusted model. These odds almost doubled for the frail group in both the unadjusted and age-adjusted models. Pre-frail participants had higher odds of having abnormal RDS scores in both the unadjusted and age-adjusted models. This was also true for frail participants in the unadjusted and age-adjusted logistic regressions.

Odds ratios for abnormal large artery elasticity were not significant in the pre-frail participants compared to the robust. However, the frail group had 3.10 higher odds of having abnormal large artery elasticity in the unadjusted model. The statistical significance was lost after controlling for age. This relationship was also observed for abnormal small artery elasticity, with only the unadjusted model in the frail participants being significant. Abnormal resting systolic blood pressure was 1.36 and 2.26 more likely to be present in pre-frail and frail participants in the unadjusted models, but this significance was not detected in the age-adjusted

models. Abnormal systolic blood pressure responses to moderate-intensity exercise were 2.37 and 3.50 more likely to occur in pre-frail and frail participants in the unadjusted model and 1.98 and 2.55 in the age-adjusted model.

The pre-frail group was more likely to have reported mild symptoms of depression in their PHQ-9 scores in both logistic regression models. The odds ratios were elevated substantially in the frail group with odds of 5.35 in the unadjusted model and odds of 7.14 in the age-adjusted model. Both pre-frail and frail participants had significantly higher odds of walking less than 544 m, which is classified as moderate to high risk based on the 6MWT. The pre-frail group was 7.53 times more likely in the unadjusted model and 5.74 times more likely in the age-adjusted model. These odds were significantly elevated in the frail group (70.11) in the unadjusted and the age-adjusted model (56.48).

Table 9: Logistic regression models with S-FC as exposure

Outcome	Model	Robust			Pre-Frail			Frail		
		OR	95% CI	P-Value	OR	95% CI	P-Value	OR	95% CI	P-Value
No PS education	Unadjusted	Reference			1.46	1.08 - 1.98	**0.015***	3.10	1.79 - 5.35	**<0.001***
	Age-Adjusted				1.31	0.95 - 1.79	0.096	2.57	1.47 - 4.51	**0.001***
Smoking History	Unadjusted	Reference			1.11	0.86 - 1.45	0.423	1.15	0.67 - 1.95	0.618
	Age-Adjusted				1.11	0.85 - 1.46	0.435	1.14	0.67 - 1.97	0.625
Abnormal BMI	Unadjusted	Reference			1.66	1.20 - 2.29	**0.002***	5.19	2.99 - 9.01	**<0.001***
	Age-Adjusted				1.90	1.36 - 2.65	**<0.001***	6.75	3.78 - 12.06	**<0.001***
Diabetes med	Unadjusted	Reference			3.36	1.43 - 7.91	**0.006***	8.05	2.73 - 23.81	**<0.001***
	Age-Adjusted				3.04	1.27 - 7.27	**0.012***	6.76	2.20 - 20.74	**<0.001***
BP med	Unadjusted	Reference			2.35	1.70 - 3.26	**<0.001***	4.89	2.80 - 8.55	**<0.001***
	Age-Adjusted				2.02	1.44 - 2.82	**<0.001***	3.79	2.13 - 6.75	**<0.001***
Lipid lowering med	Unadjusted	Reference			1.31	0.92 - 1.85	0.134	1.79	0.95 - 3.38	0.071
	Age-Adjusted				1.12	0.78 - 1.60	0.541	1.37	0.71 - 2.64	0.355
Abnormal HDL	Unadjusted	Reference			1.32	0.29 - 5.93	0.718		Undefined‡	
	Age-Adjusted				1.64	0.35 - 7.54	0.529		Undefined‡	
Abnormal LDL	Unadjusted	Reference			0.85	0.63 - 1.15	0.297	0.88	0.47 - 1.65	0.687
	Age-Adjusted				0.93	0.68 - 1.27	0.627	1.02	0.54 - 1.95	0.949
Abnormal TC	Unadjusted	Reference			0.96	0.70 - 1.31	0.791	0.69	0.34 - 1.42	0.316
	Age-Adjusted				1.03	0.75 - 1.43	0.843	0.79	0.38 - 1.64	0.530
Abnormal GLC	Unadjusted	Reference			2.41	1.18 - 4.94	**0.016***	3.60	1.21 - 10.73	**0.022***
	Age-Adjusted				2.47	1.19 - 5.13	**0.015***	3.75	1.22 - 11.52	**0.021***
Doesn't meet CPAG	Unadjusted	Reference			1.75	1.33 - 2.31	**<0.001***	4.47	2.46 - 8.13	**<0.001***
	Age-Adjusted				1.84	1.38 - 2.44	**<0.001***	4.89	2.65 - 9.00	**<0.001***
Poor CANHEART	Unadjusted	Reference			3.17	2.12 - 4.73	**<0.001***	8.75	4.75 - 16.11	**<0.001***
	Age-Adjusted				3.07	2.04 - 4.62	**<0.001***	8.27	4.42 - 15.47	**<0.001***
Abnormal FRS	Unadjusted	Reference			2.11	1.60 - 2.78	**<0.001***	4.55	2.60 - 7.94	**<0.001***
	Age-Adjusted				1.52	1.12 - 2.05	**0.007***	2.81	1.51 - 5.23	**0.001***
Abnormal RDS	Unadjusted	Reference			1.94	1.49 - 2.53	**<0.001***	2.84	1.57 - 5.14	**<0.001***

	Age-Adjusted		1.60	1.21 - 2.10	**<0.001***	2.05	1.10 - 3.82	**0.023***
Abnormal LAE	Unadjusted	Reference	1.12	0.77 - 1.63	0.541	2.60	1.42 - 4.79	**0.002***
	Age-Adjusted		0.83	0.56 - 1.24	0.362	1.61	0.84 - 3.10	0.156
Abnormal SAE	Unadjusted	Reference	1.18	0.91 - 1.54	0.208	1.73	1.02 - 2.94	**0.042***
	Age-Adjusted		1.12	0.86 - 1.46	0.411	1.57	0.92 - 2.70	0.100
Abnormal SBP	Unadjusted	Reference	1.36	1.02 - 1.82	**0.036***	2.26	1.32 - 3.89	**0.003***
	Age-Adjusted		1.14	0.85 - 1.55	0.381	1.69	0.96 - 2.98	0.068
Abnormal Ex BP	Unadjusted	Reference	2.37	1.79 - 3.14	**<0.001***	3.50	2.00 - 6.11	**<0.001***
	Age-Adjusted		1.98	1.48 - 2.64	**<0.001***	2.55	1.42 - 4.58	**0.002***
Mild PHQ9	Unadjusted	Reference	2.04	1.45 - 2.87	**<0.001***	5.35	3.05 - 9.38	**<0.001***
	Age-Adjusted		2.38	1.68 - 3.38	**<0.001***	7.14	3.95 - 12.91	**<0.001***
Moderate risk 6MWT	Unadjusted	Reference	7.53	4.21 - 13.44	**<0.001***	70.11	32.81 - 149.81	**<0.001***
	Age-Adjusted		5.74	3.18 - 10.37	**<0.001***	56.48	25.70 - 124.13	**<0.001***

** denotes statistical significance. ǂ sample size too small for analysis.* ***OR,*** *Odds Ratio;* ***PS,*** *Post Secondary;* ***BMI,*** *Body Mass Index:* ***BP,*** *Blood Pressure;* ***HDL,*** *High-density lipoprotein;* ***LDL,*** *Low-density lipoprotein;* ***TC,*** *Total Cholesterol;* ***GLC,*** *Blood Glucose;* ***CPAG,*** *Canada's Physical Activity Guidelines;* ***FRS,*** *Framingham Risk Score;* ***RDS,*** *Rasmussen Disease Score;* ***LAE,*** *Large Artery Elasticity;* ***SAE,*** *Small Artery Elasticity;* ***SBP,*** *Systolic Blood Pressure;* ***Ex BP,*** *Exercise Blood Pressure;* ***PHQ-9,*** *Personal Health Questionnaire-9;* ***6MWT,*** *Six-minute Walk Test. Cutoffs for dichotomous outcomes are described in the methods section.*

Chapter 4: Discussion

4.1 S-FC and FC Outcomes

The primary objectives of my thesis were to: (1) determine if the S-FC was better able to discriminate risk compared to the traditional FC approach; and, (2) determine if there are differences in CVD risk profile between robust, pre-frail and frail participants free of established CVD. The secondary objective was to establish odds ratios for different physiological and behavior CVD risk factors in pre-frail and frail groups, as compared to robust.

Established CVD is elevated in pre-frail and frail populations.[119] However, the underlying physiology to explain why CVD and frailty status are linked remains poorly understood.[110] Previous research has attempted to address this knowledge gap by conducting cross-sectional observational trials characterizing CVD risk profile characteristics in participants with frailty who were free of established CVD.[109,120] My data add to that body of knowledge by specifically examining the all-female WARM Hearts cohort. This approach was utilized because women are at increased risk for pre-frailty and frailty.[90] My data identified that CVD risk is elevated in older women with pre-frailty as well as those with frailty, which is novel because previous research in this area of CVD risk assessment has compared only the robust to the frail.

Objective 1 established that it is important to utilize a standardized approach to identify frailty. My data supports the work of Bouzon et al. who found that the use of the S-FC resulted in hazard ratios for adverse outcomes like falls, hospitalization and all-cause mortality reaching statistical significance over less time than the FC approach.[101] In fact, my data indicates that standardization of the Fried criteria specific for the WARM Hearts cohort resulted in the reclassification of many participants to higher levels of frailty status as the prevalence of pre-frailty in the cohort increased from 253 to 464 and the prevalence of frailty increased from 7 to

63. This was due to the large number of participants that were reclassified based on grip strength (i.e.an additional 173 participants were flagged for grip strength after standardization), gait speed (i.e.an additional 193 participants were flagged for gait speed standardization) and low physical activity level (i.e.an additional 107 participants were flagged for physical activity after standardization). The prevalence of unintentional weight loss and self-reported exhaustion did not change with the S-FC approach, as the cutoffs for these criteria are not affected by standardization of the FC.[101] The greater AUCs in the S-FC, as compared to the FC, further established that the standardization of cohort-specific critical cutoff values improved the discrimination of CVD risk for both the FRS and RDS. This finding is evident in the discrimination slope improvement reported in the IDI analysis and the improved risk discrimination identified by the NRI analysis for both the FRS and RDS by the S-FC model. Thus, the data reported in this thesis are unique because they establish for the first time that CVD risk profiles are progressively worse as frailty status worsens from robust, to pre-frail and to frail. Even so, it is important to acknowledge that the reported improvements in CVD risk prediction using the standardized model in my work aligns with the similar improvements for risk prediction for falls, hospitalization and all-cause mortality previously reported by Bouzon et al. [101] Collectively, it appears appropriate to recommend that future trials utilize the standardized frailty model to identify frailty as a modifier or mediator of CVD risk.

4.2 Pre-frailty, Frailty and CVD Risk Profile

Cardiovascular health management is important for pre-frail and frail older adults.[90,120] Veronese et al. reported that pre-frailty (HR 1.32, 95% CI 1.07-1.63) and frailty (HR 1.70, 95% CI 1.18-2.45) both increase the risk for CVD over a median of 4.4 years.[119] That data suggests

that the assessment of frailty could assist with the characterization of the patient, allowing for better care and more accurate prognoses.[96] However, there is a paucity of information about the prevalence of CVD risk factors in pre-frail and frail women free of established CVD.[120] My research addressed this knowledge gap and successfully detected differences in CVD risk profile between robust, pre-frail and frail participants in the WARM Hearts cohort. As expected, pre-frailty and frailty were associated with a number of CVD risk factors, where higher levels of frailty status were associated with higher CVD risk as well as higher odds ratios for the presence of CVD risk factors. These CVD risk factors included triglyceride levels, fasting blood glucose levels, physical activity levels, large artery elasticity, small artery elasticity, systolic blood pressure, blood pressure response to exercise, pulse pressure, symptoms of depression (PHQ-9 scores), 6MWT distance, and composite CVD risk scores (e.g. FRS, RDS, and CANHEART). Thus, it is evident that CVD risk is elevated in both the pre-frail and frail state. This observation supports the longitudinal meta-analysis by Veronese et al. that reported increased risk for CVD over a period of 4.4 years by 1.23 and 1.70 times in pre-frailty and frailty,[119] respectively. My data also supports the few cross-sectional studies that have reported that frail individuals have elevated CVD risk.[109,120,148] However, it is important to indicate that all previous works have only examined CVD risk profile and frailty in populations of either all males,[120] populations with past CVD onset,[148] or in only pre-frail but not frail individuals.[109] Furthermore, none of the previously published studies have attempted to control for age differences despite the fact that older age is associated with differences in CVD risk factors like artery elasticity[149] and resting blood pressure.[150] Additionally, it is important to control for age in such analyses because frailty is independent of age.[54] Therefore, my research is novel because CVD risk profiles are elevated in older women with either pre-frailty or frailty, independent of age. Controlling for age in these

data allows for the differences in CVD risk profile to be attributable to frailty per se, rather than due to higher chronological age per se. Moreover, my data clearly establish that pre-frailty is an intermediate step within the frailty continuum and is independently associated with elevated CVD risk.

My research generated data that differed from literature previously published. For example, my work reports that pre-frailty and frailty are associated with higher fasting blood glucose and triglyceride levels than the robust; whereas, Bastos-Barbosa et al. did not report such a finding.[148] The blood glucose data revealed that 42 participants had glucose levels higher than 7 mmol; whereas, triglycerides levels were not elevated high enough to be considered to be clinically high (i.e. greater than 5.6 mmol) [140]. Frailty and diabetes are thought to share a common pathophysiology.[151] My work supports that concept, as the pre-frail and frail groups had a higher number of participants who reported being treated for diabetes, as compared to the robust group. Future research should explore the etiology of frailty and diabetes to identify specific physiological processes that influence the development of both frailty and diabetes.

Previous literature has reported that low physical activity levels are a risk factor for frailty.[152] In fact, low physical activity levels are a flag in many frailty assessment tools, including the FC and S-FC.[54] Therefore, my discovery that frail participants were self-reporting that they accumulated similar levels of physical activity, as compared to pre-frail or robust individuals was unexpected. Self-reported physical activity tends to have large levels of variability,[141] which likely contributed to the lack of change in minutes spent doing physical activity at vigorous, moderate or walking (light) intensity, as well as total physical activity. Even so, it is important to acknowledge that total walking minutes per week and total physical activity minutes per week differed between the frail and robust groups. Further supporting this notion is

the fact that pre-frail and frail individuals were found to be significantly more likely to not be achieving Canada's Physical Activity Guidelines.[147] Exercise has been shown to be an effective means of preventing or delaying the onset of frailty as well as a means of managing frailty.[153]

Previously published literature has reported contradictory findings about the potential associations between artery elasticity and frailty. For example, Kannegieter et al. reported no reduction in artery elasticity across levels of frailty in 117 older adults;[154] whereas, Aurelian et al. reported that frailty was associated with reduced artery elasticity in 88 older adults.[155] In agreement with the findings of Aurelian et al., large artery elasticity and small artery elasticity were both lower in pre-frail and frail individuals in this thesis. However, this finding must be interpreted with caution. Pre-frail and frail individuals in the cohort were found to have lower mean artery elasticity values, but did not have increased odds of having clinically abnormal artery elasticity values after adjusting for age. It is important to adjust for age in such an analysis because artery elasticity declines with age.[67] Despite this, the lower artery elasticity values observed with frailty in this thesis likely contributed to the higher systolic blood pressure response following moderate-intensity exercise observed in pre-frail and frail individuals.[42] In fact, pre-frail and frail individuals were 1.98 and 2.55 times more likely to have a clinically abnormal systolic blood pressure response to moderate-intensity exercise after controlling for age. To our knowledge, this is the first time this outcome has been reported in a population of pre-frail and frail individuals. The resting systolic blood pressure difference observed in the pre-frail and frail participants, compared to robust, differs from that reported by Bastos-Barbosa et al.[148], who reported no difference in systolic blood pressures between robust, pre-frail or frail groups. This observation also differs from the systolic blood pressure response reported by Ramsay et al.[120], who found that systolic blood pressure was reduced in frailty. It is important to

identify that the highlighted studies by Bastos-Barbosa and Ramsay were in different populations (ie. populations with previous CVD or all males, respectively).

As expected, pre-frailty and frailty were associated with an increase in risk for CVD as identified by composite CVD risk scores included in the WARM Hearts protocol (FRS, RDS, and CANHEART). These composite scores are all known to be predictors of CVD,[22,74,80] as are pre-frailty and frailty.[119] Pre-frailty successfully identified an intermediate risk level for CVD between robust and frailty as was its intended definition as an intermediary risk stage in the original Fried et al. study.[54] This is a novel contribution to the literature and is clinically relevant because it suggests that frailty has the potential to act as an effective means of identifying elevated risk for CVD in asymptomatic individuals, allowing for the implementation of primary preventative approaches.[96,108] In order to more effectively direct interventions in the population, better identification of individuals at risk of developing CVD must be developed.[25] The identification of a wide range of CVD risk factors present in the profile of both pre-frail and frail individuals highlights the value of frailty screening for identifying early warning signs of CVD risk. The presence of these associations after controlling for age add further support for the notion that the connection between frailty and CVD is not just due to chronological age. These data indicate a need for careful management of CVD risk in pre-frail and frail individuals.

4.3 Limitations

There are some limitations in the current study design. The WARM Hearts study used a convenience sample method for recruiting participants, which creates a potential sample bias, as the participants were not representative of the overall population in Manitoba. It is likely that the participants of the WARM Hearts trial are health consumers, as they selected themselves for

participation in a cardiovascular screening project. This limits the external validity of the cohort study. It is also important to report that the study cohort was also comprised mostly of Caucasian females, which limits the generalisability of the findings to that population rather than to diverse ethnic groups. Furthermore, the convenience sample recruitment strategy likely reduced the prevalence of pre-frailty and frailty in the cohort, as those who were more frail or in worse health likely would not have participated in the study.

This research is a secondary analysis of original data captured by the WARM Hearts trial. As such, variables analyzed in this work are limited to the variables collected in the original trial. For example, the FC was used as this was the frailty measure used by the WARM Hearts study, but it is important to acknowledge that frailty is a biopsychosocial issue and the phenotype model developed by Fried et al.[54] does not necessarily fully capture this.[156] A modified Fried criteria (MFC) has been examined in the literature,[157] but the WARM Hearts project did not collect all of the variables necessary for this analysis. Frailty models based on clinical deficits, like the Frailty Index (FI),[158] have also been developed. While the creation of such a model was considered, the variables collected as part of the WARM Hearts study did not cover enough of a range of physiological systems to feasibly create an FI.[159] Finding a balance between efficacy and practicality of various frailty screening approaches in healthcare will have to be considered in future research in this area. On a related note, this thesis project also did not control for post-secondary education or other socioeconomic status measures in the logistic regression models. Future research should consider controlling for these factors. As well, the WARM Hearts research study did not collect information on family history of CVD, which can be an important predictor of risk.[160] This thesis successfully established that the S-FC is better able to discriminate CVD risk than the traditional FC approach, but it is important to acknowledge that

this work does not establish if the S-FC is able to detect future adverse CVD events. The WARM Hearts screening project collected some data by self-report, which reduced cost in collecting data. However, that decision limited the accuracy of the subjective data. For example, physical activity levels were self-reported, which is an issue because they have low-to-moderate correlation with direct measures of physical activity recorded by accelerometry.[161] It is also important to acknowledge that this secondary analysis of data utilized a cross-sectional design; therefore, the identified associations between levels of frailty and CVD risk factors cannot be interpreted as causal.

4.5 Future Research Directions

My thesis data has established that the S-FC model is better than the typical FC model for discriminating CVD risk in middle-aged and older women. This is an important finding that requires confirmation from additional research. The implementation of the typical FC approach has some value and could improve the healthcare management of those at risk for CVD.[85] However, the implementation of an S-FC model will lead to better CVD risk prediction than the traditional FC model. In fact, the use of the traditional FC frailty criteria cut-offs across all populations may lead to poorer risk prediction and, as a result, reduced the ability to risk for CVD in pre-frail and frail individuals. Further research is needed to support the use of S-FC models in longitudinal studies examining CVD risk and adverse CVD events as endpoints.[101]

My thesis data has identified a number of CVD risk factors associated with higher levels of frailty. This information may assist with the elucidation of the pathophysiology surrounding the frailty syndrome, specifically in relation to the increased CVD risk associated with the

syndrome.[120] The identification of such risk factors will guide the identification of effective interventions with the capacity to interrupt the pathophysiological decline that links frailty with CVD.[110] As suggested by Ramsay et al., an approach involving both primary prevention, to identify early frailty, and secondary prevention, to manage CVD risk, is needed to mitigate risk for CVD, especially in older adults.[120] Future research should examine the effectiveness of such an approach.

The overall WARM Hearts screening project was initiated because women tend to be underrepresented in CVD clinical research. Moreover, there is a less well-developed understanding of CVD risk and CVD health management strategies in women.[134] Women are a population that is at increased risk of developing frailty, as compared to males.[90] Therefore, understanding the physiological role of frailty in the CVD progression in women has the potential to improve the management of healthcare for this population. The WARM Hearts trial was originally designed to include a 5-year follow-up and will access health administrative data at that point to determine if the WARM Hearts screening program predicted CVD morbidities or mortality. Dr. Duhamel's future research (2022) will conduct that work and will allow for the comparison of CVD risk discrimination in the FC and S-FC models with adverse CVD outcomes, as opposed to the CVD risk scores explored in this thesis. That CVD outcomes data will further elucidate the potential benefits of the S-FC model.

There is an emerging recognition that biological biomarkers provide diagnostic information to detect age-related chronic conditions.[162] It has also been reported that frailty assessment tools that include blood-based biomarkers better predict poor health outcomes for individuals who were not flagged as frail based on clinical deficits (i.e. using a frailty index).[163] Those data suggest that current frailty models can be improved by including biomarkers of the

frailty phenotype. The WARM Hearts trial collected blood samples, which provides researchers with an opportunity to determine if blood-based biomarkers may improve frailty assessment techniques and, thereby, better predict poor CVD risk profiles in middle-aged and older women. That type of research should be conducted.

4.6 Conclusions

The novel observation that increased CVD risk is present in pre-frail and frail individuals – even after controlling for age - supports the link between frailty and CVD per se, rather than the relationship being attributed to older age. Furthermore, women are at an increased risk for developing frailty compared to men,[54] which make the study of the coexistence of frailty and CVD of particular importance in this population. The identification of specific factors placing pre-frail and frail individuals at increased risk for CVD could assist with the design of assessments and interventions to mitigate CVD risk in this population. My thesis also demonstrated the added value of standardizing FC criteria cutoffs based on the cohort it is being used on. In fact, the S-FC approach improved the discrimination of CVD risk in the WARM Hearts cohort. This is an important contribution because the misclassification of frailty status could lead to inaccurate predictions of CVD risk and the mismanagement of healthcare treatments. My thesis data also identify that a number of CVD risk factors are present in women free of established CVD who are classified as either pre-frail or frail. This finding highlights the potential for including frailty assessments into primary care settings. Such an approach will allow for the early detection of pre-frailty and frailty. By detecting the earliest stage of frailty (i.e. pre-frailty), clinicians may be able to recommend or prescribe lifestyle or clinical interventions with the capacity to alter the progression of CVD risk.[121,122]

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Appendix A - WARM Hearts Consent Forms

Participant ID:_____

UNIVERSITY OF MANITOBA

Hôpital St-Boniface Hospital

Research Participant Information and Consent Form

The Assessment of Large and Small Artery Elasticity For The Early Detection of Cardiovascular Disease.

Principal Investigator: Todd Duhamel, PhD
Faculty of Kinesiology and Recreation Management, University of Manitoba & Institute of Cardiovascular Sciences St. Boniface General Hospital Research Centre, R4012 - 351 Tache Ave, Winnipeg, MB, Canada, R2H 2A6

Co-investigators and their affiliations:

- Scott Kehler, Ivan Berkowitz, and Heather Blewett
  - St. Boniface Research Centre
- Randy Fransoo
  - Manitoba Centre for Health Policy
- Thang Nguyen and James Tam
  - St. Boniface General Hospital
- Danielle Bouchard and Shaelyn Strachan
  - Faculty of Kinesiology and Recreation Management, University of Manitoba
- Jay Cohn
  - University of Minnesota

You are being asked to participate in a research study. Please take your time to review this consent form and discuss any questions you may have with the research staff. You may take your time to make your decision about participating in this study and you may discuss it with your friends, family or (if applicable) your doctor before you make your decision. This consent form may contain words that you do not understand. Please ask the research staff to explain any words or information that you do not clearly understand.

Purpose of Study: Efforts to prevent disease of the heart and blood vessels (i.e. the cardiovascular system) focus on the traditional risk factors, such as age, gender, cholesterol and blood pressure. This method is shown to predict heart attacks; however, it is likely the method could be improved by adding new measurement approaches.

The purpose of this research study is to establish a cardiovascular health screening program in Winnipeg and will test how well a new cardiovascular screening program works for detecting cardiovascular events over a 5 year period. A total of 1000 women will be recruited to participate in this study.

Study procedures

If you choose to participate in the study, you will be asked to attend one meeting for approximately 90 minutes. During this meeting, you will be asked to provide your Personal Health Information Number (PHIN), which is needed so we can collect information about how you utilize the health care system over the next 5 year period after screening. Your PHIN will be given a coded number so that your personal health information is not compromised. This method of coding PHINs is in accordance with the Personal Health Information Act (PHIA) of Manitoba and is a step taken to protect the privacy of your health information.

You will also be asked to complete a series of 4 tests during this appointment. Other than taking a blood sample (10 ml or 2 teaspoons) to measure your cholesterol, blood sugar, and other markers of cardiovascular disease, the tests are non-invasive and include:

1. A measure of the stiffness in your blood vessels of the wrist;
2. A measure of your resting blood pressure;
3. A measure of your blood pressure in response to exercise on a treadmill during moderate intensity walking;
4. Your medical history from the Manitoba Centre for Health Policy Population Data Repository; and,
5. Height and weight measurements
6. Complete a series of questionnaires to characterize:
    a. Your physical activity level;
    b. Diet;
    c. Your health risk behaviours and readiness to change;
    d. Your general mood status;

e. Your quality of life, and;
f. Frailty
g. Your behaviour toward health information

7. A measurement of your physical fitness based on a 6 minute walking test. During this walking test, you will be asked to cover as much distance as you can over a 6 minute period. You are permitted to stop the test at any time during the procedure.
8. An assessment of grip strength using a hand dynamometer;
9. An assessment of your five meter gait speed;

Blood sampling collected as a part of this study will be kept in a lockable freezer on the 3rd floor of the Asper Clinical Research Institute. Your blood samples will not contain any personal information that could compromise confidentiality. Blood samples will be stored for approximately 10 years and then destroyed. For future research use, you will be asked to complete an additional consent form to retain blood samples.

Additional data for this project will be collected by linking your test data with your health information for a period of 5 years after the cardiovascular (CV) screening is completed. In order to monitor this information, we plan to utilize your PHIN and the Population Health Research Data Repository at the Manitoba Centre for Health Policy to collect information about how you interact with the health care system for a period of 5 years after the CV screening is completed. Research staff will review information in order to evaluate the effectiveness of the project for determining how well our cardiovascular health screening program assesses cardiovascular health for a period of 5 years after the CV screening is completed. Your health records may include information such as:

1. health service use;
2. information relating to cardiovascular health;
3. other health problems; and
4. demographic information including age and household income;

All data will be treated as confidential in accordance with the Personal Health Information Act of Manitoba. Any information that may reveal personal identifiers (such as name, address or telephone numbers) will be removed prior to data analysis in order to protect patient anonymity and confidentiality.

Risks

With respect to safety, other than blood sampling to assess cholesterol, blood sugar and other markers of cardiovascular disease, the tests you would be asked to complete are non-invasive. There is a very minor risk associated with walking on a treadmill. The risks associated with blood draws include pain, bruising, and a small risk of infection.

You are free to withdraw from participation in the study or withdraw your research data from the study at any time upon request. Withdrawal from the research study will not alter the standard of care you receive. Your participation in the study may also be discontinued upon the advice of the Asper Clinic medical staff for your safety.

Benefits

A benefit to participating in this study is that you will gain specific and detailed information regarding your cardiovascular health. We will provide you with detailed information regarding your physical activity behaviours, physical fitness, and blood pressure response to moderate intensity exercise, which is not currently available to participants in the health care setting. Although this information may help you to adopt a healthier lifestyle, your health status may or may not be influenced by your participation in the study.

Information from this study could help physicians and other health care providers to provide better care for their patients by preventing cardiovascular problems. Information from this study could also benefit health care providers by gaining new information describing the effectiveness of the project. This new information may be used to guide the development of future program initiatives.

Confidentiality

Information gathered in this research study may be published or presented in a program evaluation report to inform Manitoba Health and key stakeholders about the outcomes of the study. However, your name and other identifying information will not be used or revealed. Medical records that contain your identity will be treated as confidential in accordance with the Personal Health Information Act of Manitoba. All study documents related to you will bear only your assigned patient code. All records will be kept in a locked secure area and only those persons identified as Research Staff will have access to these records. Only persons

identified as Research Staff will have access to blood samples. Blood samples will be coded with your unique Participant ID and will not contain any other information that could identify you in any way. If any of your medical/research records need to be copied, information that may reveal personal identifiers will be removed. Blood samples will be kept in a lockable freezer and will be labeled with your participant ID number so they can be linked to other study documentation (e.g. questionnaires, test procedure outcomes). Only Research Staff will have access to linkable information and will be kept confidential by law. No information revealing any personal information such as your name, address or telephone number will leave the Asper Clinic nor will it be used for unauthorized purposes. Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. The University of Manitoba Health Research Ethics Board and the St. Boniface General Hospital may review research-related records for quality assurance purposes. After the completion of the study, research data will be kept for a maximum of 10 years and then destroyed. This information will be protected as confidential in accordance with the Personal Health Information Act of Manitoba.

Feedback

Participants in the study will be provided an opportunity to request specific feedback about their individual results as well as the overall results of the study. If you would like to receive feedback, please provide your contact information on the "Feedback Request Form" at the end of this consent form package. Research staff will provide individual feedback upon request.

Costs

All research-related procedures, which will be performed as part of this study, are provided at no cost to you.

Payment for participation

No compensation will be provided for participating in this study.

Alternatives

Instead of being in this study, you may request educational material about cardiovascular disease.

Voluntary Participation/Withdrawal From the Study

Your decision to take part in this study is voluntary. You may refuse to participate or you may withdraw from the study at any time. Your decision not to participate or to withdraw from the study will not affect your other medical care at this site. If medical staff determines that it is in your best interest to withdraw you from the study, the medical staff will inform the research team and will remove you from the study without your consent.

We will tell you about any new information that may affect your health, welfare, or willingness to stay in this study.

Medical Care for Injury Related to the Study

In the case of injury or illness resulting from this study, necessary medical treatment will be available at no additional cost to you. If the research team becomes aware of a condition that may affect your health, the research team will share this information with medical staff in order to enable the medical staff to provide you with appropriate care. You are not waiving any of your legal rights by signing this consent form, nor releasing the investigator(s) from their legal and professional responsibilities.

Questions

You are free to ask any questions that you may have about your treatment and your rights as a research participant. If any questions come up during or after the study or if you have a research-related injury, contact Dr. Todd Duhamel by phone at (204) 235-3589. For questions about your rights as a research participant, you may contact the University of Manitoba Health Research Ethics Board at (204) 789-3389.

A copy of this consent form has been given to you to keep for your records and reference.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

Statement of Consent

I have read this consent form. I have had the opportunity to discuss this research study with Dr. Todd Duhamel and/or his study staff. I have had my questions answered by them in language I understand. The risks and benefits have been explained to me. I believe that I have not been unduly influenced by any study team member to participate in the research study by any statement or implied statements. Any relationship (such as employee, student or family member) I may have with the study team has not affected my decision to participate. I understand that I will be given a copy of this consent form after signing it. I understand that my participation in this study is voluntary and that I may choose to withdraw at any time. I freely agree to participate in this research study.

I understand that any blood sampling collected will be kept in a lockable freezer for a 10 year period and will be labelled to only contain my participant ID to link to other study documentation (e.g. questionnaires, test procedure outcomes).

I understand that information regarding my personal identity will be kept confidential, but that confidentiality is not guaranteed. I authorize the inspection of my research study documents by the University of Manitoba Health Research Ethics Board, the St. Boniface General Hospital in the event that an audit is conducted.

By signing this consent form, I have not waived any of the legal rights that I have as a participant in a research study.

Do you agree to be contacted for a future research study?

Yes ☐ No ☐

Participant signature:_____ Date:_____

Participant printed name: _____ Time:_____ AM/PM

Research Staff

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given their consent

*Printed Name:*_____ *Date* _____

Signature: _____ *Time:*_____ *AM/PM*

Role in the study: _____ *Relationship to study team members:*_____

Participant ID:_____

Feedback Request Form

I would like to receive (check the box that applies):
_____ a specific feedback report detailing my individual results
_____ a summary report of the overall study findings.
_____ both reports.

Participant signature:_____ Date:_____

Participant printed name: _____Time:_____AM/PM

Please send me a copy of these reports by:

_____ email to the following email account:

_____

Appendix B - WARM Hearts Data Collection Form (45-64 years of age)

Participant ID	0
Age	0
BMI	0.0

Did participant report being diagnosed with high blood pressure?	0
Did participant report being diagnosed with diabetes?	0

4-TEST FINAL SCORES	
Total 4 test score	0
Eligible for 10-test screening?	0

Framingham Risk Score 10 year % risk	0.0%
Framingham Risk Score relative risk	0
Optimal FRS 10 year % risk	0.0%
Normal FRS 10 year % risk	0.0%
Heart/vascular age	0

4 Test results					
	Ordinal RDS score	Categorical score	Ordinal value	Do we need to provide follow up (e.g., with family doc, study MD, emergency department) for this participant?	No
Large artery elasticity category	2	0	0		
Small artery elasticity category	2	0	0		
Resting blood pressure category	2	0			
Exercise systolic blood pressure category	2	0	0		

Rasmussen Disease Score cut-offs for artery elasticity measurements						
	Large artery elasticity (mL/mmHg x 10)			Small artery elasticity (mL/mmHg x 10)		
	Normal	*Borderline*	*Abnormal*	*Normal*	*Borderline*	*Abnormal*
45-65 years old	>=10	9-9.9	<9	>=4	3.5-3.9	<3.5

Rasmussen Disease Score cut-offs for blood pressure measurements			
	Normal	*Borderline*	*Abnormal*
Resting blood pressure	SBP <130 AND DBP <85	SBP 130-139 OR DBP 85-89	SBP >=140 OR DBP >=90
Exercise blood pressure	SBP rise <30 AND SBP <=169	SBP rise 30-39 OR SBP 170-179	SBP rise >=40 OR SBP >=180

Blood pressure results			
	Value	Refer to family physician (>140 SBP OR >90 DBP)?	Hypertensive crisis (>180 SBP OR >110 DBP)?
Resting systolic blood pressure (mmHg)	0	No	No
Resting diastolic blood pressure (mmHg)	0		
On blood pressure medications?	No		

Blood Data results				
	Value (mmol/L)	Normal/Borderline/Abnormal	On medications for this factor?	Study MD to review if clinically relevant?
HDL cholesterol (normal >1.3 mmol/L; borderline 0.9-1.3; abnormal <0.9)	0	0	No	No
LDL cholesterol (normal <3.5; borderline 3.5-4.1; abnormal >4.1)	0	0	No	No
Total cholesterol (normal <5.2; borderline 5.2-6.2; abnormal >6.2)	0	0	No	No
Triglycerides (normal <1.7; borderline 1.7-5.6; abnormal >5.6)	0	0	No	No
Fasting glucose (normal 3.9-5.5; borderline 5.6-6.9; abnormal >=7.0)	0	0	No	No

PHQ-9 Scores		
	Value	Bring to emergency department (Severe category or thoughts of self harm)?
PHQ-9 Continuous score (0-27)	0	No
PHQ-9 Categorical score	0	
Thoughts of self- harm?	No	
On depression medications?	No	

6 minute walk test Score	
	Value
Distance walked (m)	0
Level of risk	0
Do they have a condition that would impair their walking ability?	0
Did they report any trouble in mobility on quality of life score?	FALSE

6 minute walk test score risk cut-offs (Beatty 2012)				
Level of risk	None	Low	Moderate	High
Cut offs (m)	>543	481-543	420-480	<420

Fried Frailty Score	
	Value
Continuous score (0-5)	0
Categorical score	0

Frailty score risk cut-offs (Fried 2001)			
Level of risk	Not frail	Pre-frail	Frail
Cut offs	0	1 to 2	3 to 5

CANHEART Health Index	
	Value
Continuous score (0-6)	0
Categorical score	Poor

CANHEART Health Index scoring			
Category	Ideal	Intermed	Poor
Cut offs	6	4 to 5	0 to 3

CANHEART Health Index Items	
1	Non-smoker (or former smoker who quit >1 year ago)
2	Physically active (>30 minutes walking/day)
3	>=5 fruits/vegetables per day
4	BMI <25
5	Non-diabetic
6	Non-hypertensive

IPAQ Scores	
Met PA guidelines?	0
MVPA per week	0
Total PA per week	0

Quality of life scores	
Mobility	0
Self-care	0
Usual activities	0
Pain or discomfort	0
Anxiety or depression	0

Appendix C - WARM Hearts Data Collection Form (65 and older years of age)

Participant ID	0
Age	66
BMI	0.0

Did participant report being diagnosed with high blood pressure?	0
Did participant report being diagnosed with diabetes?	0

4-TEST FINAL SCORES	
Total 4 test score	0
Eligible for 10-test screening?	0

Framingham Risk Score 10 year % risk	0.0%
Framingham Risk Score relative risk	0
Optimal FRS 10 year % risk	0.0%
Normal FRS 10 year % risk	0.0%
Heart/vascular age	0

4 Test results					
	Ordinal RDS score	Categorical score	Ordinal value	Do we need to provide follow up (e.g., with family doc, study MD, emergency department) for this participant?	No
Large artery elasticity category	2	0	0		
Small artery elasticity category	2	0	0		
Resting blood pressure category	2	0			
Exercise systolic blood pressure category	2	0	0		

Rasmussen Disease Score cut-offs for artery elasticity measurements						
	Large artery elasticity (mL/mmHg x 10)			Small artery elasticity (mL/mmHg x 10)		
	Normal	*Borderline*	*Abnormal*	*Normal*	*Borderline*	*Abnormal*
>=65 years old	>=9	8-8.9	<8	>=3	2.5-2.9	<2.5

Rasmussen Disease Score cut-offs for blood pressure measurements			
	Normal	*Borderline*	*Abnormal*
Resting blood pressure	SBP <130 AND DBP <85	SBP 130-139 OR DBP 85-89	SBP >=140 OR DBP >=90
Exercise blood pressure	SBP rise <30 AND SBP <=169	SBP rise 30-39 OR SBP 170-179	SBP rise >=40 OR SBP >=180

Blood pressure results			
	Value	Refer to family physician (>140 SBP OR >90 DBP)?	Hypertensive crisis (>180 SBP OR >110 DBP)?
Resting systolic blood pressure (mmHg)	0	No	No
Resting diastolic blood pressure (mmHg)	0		
On blood pressure medications?	No		

Blood Data results				
	Value (mmol/L)	Normal/Borderline/Abnormal	On medications for this factor?	Study MD to review if clinically relevant?
HDL cholesterol (normal >1.3 mmol/L; borderline 0.9-1.3; abnormal <0.9)	0	0	No	No
LDL cholesterol (normal <3.5; borderline 3.5-4.1; abnormal >4.1)	0	0	No	No
Total cholesterol (normal <5.2; borderline 5.2-6.2; abnormal >6.2)	0	0	No	No
Triglycerides (normal <1.7; borderline 1.7-5.6; abnormal >5.6)	0	0	No	No
Fasting glucose (normal 3.9-5.5; borderline 5.6-6.9; abnormal >=7.0)	0	0	No	No

PHQ-9 Scores		
	Value	Bring to emergency department (Severe category or thoughts of self harm)?
PHQ-9 Continuous score (0-27)	0	No
PHQ-9 Categorical score	0	
Thoughts of self- harm?	No	
On depression medications?	No	

6 minute walk test Score	
	Value
Distance walked (m)	0
Level of risk	0
Do they have a condition that would impair their walking ability?	0
Did they report any trouble in mobility on quality of life score?	FALSE

6 minute walk test score risk cut-offs (Beatty 2012)				
Level of risk	None	Low	Moderate	High
Cut offs (m)	>543	481-543	420-480	<420

Fried Frailty Score	
	Value
Continuous score (0-5)	0
Categorical score	0

Frailty score risk cut-offs (Fried 2001)			
Level of risk	Not frail	Pre-frail	Frail
Cut offs	0	1 to 2	3 to 5

CANHEART Health Index	
	Value
Continuous score (0-6)	0
Categorical score	Poor

CANHEART Health Index scoring			
Category	Ideal	Intermed	Poor
Cut offs	6	4 to 5	0 to 3

CANHEART Health Index Items	
1	Non-smoker (or former smoker who quit >1 year ago)
2	Physically active (>30 minutes walking/day)
3	>=5 fruits/vegetables per day
4	BMI <25
5	Non-diabetic
6	Non-hypertensive

IPAQ Scores	
Met PA guidelines?	0
MVPA per week	0
Total PA per week	0

Quality of life scores	
Mobility	0
Self-care	0
Usual activities	0
Pain or discomfort	0
Anxiety or depression	0

Appendix D – Rasmussen Disease Score 10-screen

Appendix B adapted from Duprez et al.[20]

Test	Normal	Borderline	Abnormal
RDS	0	1	2
Large artery elasticity	≥10*, ≥9**	9-9.9*, 8-8.9**	<9*, <8**
Small artery elasticity	≥4*, ≥3**	3.5-3.9*, 2.5-2.9**	<3.5*, <2.5**
Resting BP (mmHg)	SBP <130 and DBP <85	SBP 130-139 or DBP 85-89	SBP ≥140 or DBP ≥90
Exercise BP (mmHg)	SBP rise <30 and SBP ≤169	SBP rise 30-39 or SBP 170-179	SBP rise ≥40 or SBP ≥180
Retinal vasculature	A/V ratio >3:5	A/V ratio ≤3:5 or mild A/V crossing changes	A/V ratio ≤1.2 or A/V nicking
Carotid IMT	(age and gender dependent)		
Microalbuminaria (mg/mmol)	≤0.6	0.61-0.99	≥1.00
Electrocardiogram	No abnormalities	Nonspecific abnormality	Diagnostic abnormality
LV ultrasound LVMI (g/m^2)	<120	120-129	≥130
BNP (pg/dl)	≤50	51-99	≥100

A/V ratio = arteriole-to-venule ratio; BNP = B-type natriuretic peptide; BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; IMT = intima-media thickness; LV = left ventricular; LVMI = left ventricular mass index; RDS = Rasmussen Disease Score

**Values included are for women <65. Values for this measure are age and gender dependent*
***Values included are for women ≥65. Values for this measure are age and gender dependent*

Appendix E – Framingham Risk Score

Framingham Disease Risk Score
• **Sex** • **Age** • **Systolic blood pressure** • **Treatment for hypertension** • **Smoking status** • **Presence of diabetes** • **High density lipoprotein** • **Total cholesterol**
Classification (10 year risk %)
• **Low risk (<10%)** • **Intermediate risk (>=10% and <20%)** • **High risk (>=20%)**

Values for these factors are entered into a mathematical model that calculates CVD risk for the individual based on data collected throughout the Framingham Heart Study.[15]

Appendix F – Personal Health Questionnaire-9

1. Over the last 2 weeks, how often have you been bothered by the following problems?

	Not at all (0)	Several days (1)	More than half the days (2)	Nearly every day (3)
a. Little interest or pleasure in doing things	☐	☐	☐	☐
b. Feeling down, depressed, or hopeless.	☐	☐	☐	☐
c. Trouble falling/staying asleep, sleeping too much	☐	☐	☐	☐
d. Feeling tired or having little energy	☐	☐	☐	☐
e. Poor appetite or overeating.	☐	☐	☐	☐
f. Feeling bad about yourself, or that you are a failure, or have let yourself of your family down.	☐	☐	☐	☐
g. Trouble concentrating on things, such as reading the newspaper or watching TV.	☐	☐	☐	☐
h. Moving or speaking so slowly that others could have noticed. Or the opposite; being so fidgety or restless that you have been moving around more than usual	☐	☐	☐	☐
i. Thoughts that you would be better off dead or of hurting yourself in some way.	☐	☐	☐	☐

2. If you checked off any problem on this questionnaire so far, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

☐ Not difficult at all ☐ Somewhat difficult ☐ Very difficult ☐ Extremely difficult

TOTAL SCORE _____

Appendix G – Fried and Standardized Fried Frailty Phenotype

Total Fried scores range from 0 to 5 depending on the number of variables present. These total scores are then used to stratify individuals into frailty groups (i.e. 0 = robust; 1-2 = pre-frail; ≥ 3 = frail).

	FPC	S-FPC
Weight loss	*In the last year, have you lost more than 10 pounds (4.54 kg) unintentionally?* *If answer is yes, this criterion is positive.*	
Exhaustion	*Using the CES-D, the following two statements are read asking how often in the last week did you feel this way?* - I felt that everything I did was an effort - I could not get going 0 = rarely or none of the time (<1 day) 1 = some or a little of the time (1-2 days) 2 = a moderate amount of time (3-4 days) 3 = most of the time *Persons answering "2" or "3" to either of these questions are categorized as positive.*	
Slowness	*Gait speed stratified by height* Height ≤ 159cm… ≤ 0.76 m/s Height > 159cm… ≤ 0.65 m/s	Height ≤ 161cm… ≤ 1.10 m/s Height > 161cm… ≤ 1.15 m/s
	If gait speed is lower than these cut-offs, the criterion is positive	
Weakness	*Grip strength stratified by gender and BMI quartiles*	
	BMI ≤ 23… ≤17 kg BMI 23.1-26… ≤17.3 kg BMI 26.1-29… ≤ 18 kg BMI >29… ≤ 21 kg	BMI ≤ 23.3… ≤21 kg BMI 23.4-26.1… ≤22 kg BMI 26.2-29.6… ≤ 22 kg BMI >29.6… ≤ 22 kg
	If grip strength is lower than these cut-offs, the criterion is positive	
Low activity	*Kcal of leisure physical activity stratified by gender:* <270 Kcal	<640.1 Kcal
	If Kcal of leisure physical activity are under these cut-offs, the criterion is positive	

Appendix H – S-FC vs FC ROC, NRI and IDI Results

Results of receiver operating curve areas under the curve for the FC and S-FC for discriminating between low/medium and high risk based on the RDS and FRS. Corresponding integrated discrimination index and net reclassification index for the two models are also listed.

ROC		AUC	95% CI	P-Value	IDI (%)	95% CI	P-Value	NRI (%)	95% CI	P-Value
FRS AUC	FC	0.634	0.565 - 0.703	**<0.001**	3.0%	1.4% - 4.7%	**<0.001**	67.9%	43.8% - 92.1%	**<0.001**
	S-FC	0.728	0.662 - 0.794							
RDS AUC	FC	0.552	0.512 - 0.593	0.079	1.5%	0.8% - 2.3%	**<0.001**	26.0%	9.2% - 42.7%	**0.003**
	S-FC	0.594	0.548 - 0.641							

ROC, *Receiver Operating Characteristic;* ***AUC,*** *Area Under the Curve;* ***IDI,*** *Integrated Discrimination Index;* ***NRI,*** *Net Reclassification Index;* ***FRS,*** *Framingham Risk Score;* ***FC,*** *Fried Criteria;* ***S-FC,*** *Standardized Fried Criteria;* ***RDS,*** *Rasmussen Disease Score.*

Appendix I – Summary of Table 8 ANOVAs

Characteristic	Sum of squares	*df*	Mean square	*F*	P-Value
Bloodwork					
HDL cholesterol (mmol)	3.684	2	1.842	6.749	**0.001***
LDL cholesterol (mmol)	0.761	2	0.381	0.428	0.652
Total cholesterol (mmol)	3.883	2	1.941	1.977	0.139
Triglycerides (mmol)	6.412	2	3.206	9.311	**<0.001***
Fasting blood glucose (mmol)	15.19	2	7.594	7.922	**<0.001***
Subjective PA levels					
Total Vigorous min/week	134E4	2	671E3	4.325	**0.014***
Total Moderate min/week	665E3	2	332E3	5.578	**0.004***
Total Walking min/week	270E4	2	135E4	8.445	**<0.001***
Total MVPA/week	353E4	2	177E4	7.241	**0.001***
Total PA min/week	110E5	2	552E4	11.18	**<0.001***
Composite CVD risk scores					
CANHEART score	98.58	2	49.29	46.92	**<0.001***
Framingham Risk Score (%)	0.219	2	0.110	33.98	**<0.001***
RDS score	186.4	2	93.19	20.06	**<0.001***
Cardiovascular parameters					
Large artery elasticity	192.3	2	96.17	5.904	**0.003***
Small artery elasticity	96.18	2	48.09	8.462	**<0.001***
Systolic BP (mmHg)	4015	2	2008	8.196	**<0.001***
Diastolic BP (mmHg)	38.76	2	19.38	0.229	0.795
Pulse pressure (mmHg)	3748	2	1874	14.90	**<0.001***
ΔSystolic BP activity response	8012	2	4006	14.14	**<0.001***
Other					
6MWT distance (m)	128E4	2	642E3	166.3	**<0.001***
PHQ-9 score	729.2	2	364.6	39.98	**<0.001***
Sedentary time hours/day	22.35	2	11.17	0.023	0.978

Appendix J – CANHEART Health Index

Participants are given 1 point for reaching the minimum cut-off in each of the following criteria:

1) **Smoking –** non-smoker or former smoker who quit more than 12 months prior
2) **Overweight/obesity** – body mass index <25
3) **Leisure physical activity** – walking >30 min per day or equivalent based on moderate to vigorous aerobic physical activity
4) **Fruit and vegetable consumption** – fruit and vegetables consumed ≥5 times per day
5) **Hypertension** – self-reported hypertension diagnosed by a health care professional
6) **Diabetes** – self-reported diabetes diagnosed by a health care professional

Total CANHEART Health Index scores range from 0 to 6 (0-3 = poor; 4-5 = intermediate; 6 = ideal)

Appendix K – International Physical Activity Questionnaire

Participant ID:_____

International Physical Activity Questionnaire

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____ **days per week**

   ☐ No vigorous physical activities → ***Skip to question 3***

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

   _____ **hours per day**

   _____ **minutes per day**

   ☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

   _____ **days per week**

   ☐ No moderate physical activities → ***Skip to question 5***

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

☐ No walking → ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

Appendix L - EQ-5D-L

Participant ID:_____

EuroQol Five Dimension Five Level (EQ-5D-5L)

Under each heading, please tick the ONE box that best describes your health TODAY

1. MOBILITY	☐ I have no problems in walking about. ☐ I have slight problems in walking about. ☐ I have moderate problems in walking about. ☐ I am unable to walk about.
2. SELF-CARE	☐ I have no problems washing or dressing myself. ☐ I have slight problems washing or dressing myself. ☐ I have moderate problems washing or dressing myself. ☐ I am unable to do my usual activities.
3. USUAL ACTIVITIES (e.g., work, study, housework, family or leisure activities)	☐ I have no problems doing my usual activities. ☐ I have slight problems doing my usual activities. ☐ I have moderate problems doing my usual activities. ☐ I am unable to do my usual activities.
4. PAIN/DISCOMFORT	☐ I have no pain or discomfort. ☐ I have slight pain or discomfort. ☐ I have moderate pain or discomfort. ☐ I have severe pain or discomfort. ☐ I have extreme pain or discomfort.
5. ANXIETY/DEPRESSION	☐ I am not anxious or depressed. ☐ I am slightly anxious or depressed. ☐ I am moderately anxious or depressed. ☐ I am severely anxious or depressed. ☐ I am extremely anxious or depressed.

Appendix K – WARM Hearts Fictitious Report for Participant at High CVD Risk

Hello,

Thank you very much for your recent participation in the Happy Hearts Research Study. You are receiving this letter because you requested to receive a specific report detailing your individual results in the Feedback Request Form at your appointment.

Heart disease is the number one killer of women, including the number one cause of death for women over the age of 55. Yet, there has been limited attention focused on how heart disease presents in women and how to improve health outcomes in women.

Compared to a man, a woman runs a greater risk of dying following a heart attack or stroke. Women are less likely to be treated by a specialist and are less likely to be transferred to a specialized facility for treatment. We know that even when age and other health conditions are taken into consideration, a woman's risk of dying within the first thirty days after a heart attack is 16% higher than for a man. For stroke it is 11% higher. The reasons for this are unclear.

Currently, there are more questions than answers. The time has come to focus on women's heart health. Following wide consultation, review of available research and the completion of an independent needs assessment, the decision was made to establish a long-term initiative to address the critical issues in women's heart health: the Women's Heart Health Initiative. St. Boniface Hospital Foundation is committed to raise $10 million to create a Women's Cardiac Treatment and Research Centre at St-Boniface Hospital, housed in the I H Asper Cardiac Research Institute.

While the women's cardiovascular research and treatment centre will be implemented incrementally as funds are raised, research is underway to begin to improve women's health. The Happy Hearts Research study is conducting research to test a new approach for identifying people who are at risk for developing cardiovascular diseases before they develop major clinical complications. The cardiovascular health screening protocol we are now testing in Manitoba was initially developed in Minnesota. The original research on 5,000 participants at three sites in the U.S.A. demonstrated this cardiovascular health screening protocol to be a better approach for identifying individuals who have early stages of cardiovascular disease, when compared to traditional cardiovascular health screening methods. The Happy Hearts cardiovascular health screening protocol needs further assessment before it can be implemented in Canada because it is not known if the approach will have similar predictive value within the context of the Canadian health care system.

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Information from this study could benefit health care providers by gaining new information describing the effectiveness of the Happy Hearts cardiovascular screening approach. This new information may be used to guide the development of future cardiovascular screening initiatives.

The following report card will outline some of the cardiovascular measures that were collected during your Happy Hearts appointment, and what the scores mean in terms of your cardiovascular health risk. Please note that measures collected in the Happy Hearts study are for research and are not diagnostic values, but this information can help you to make an informed decision about whether or not you would like to seek medical advice from a primary care provider (e.g. a physician or nurse practitioner).

If you do not currently have a primary care provider, the Government of Manitoba provides a service called Family Doctor Finder that can help connect you to a primary care provider. To register for this service by phone, call 204-786-7111 between 8:30am and 4:30pm Monday to Friday to reach the Family Doctor Finder call centre. Additional information can be found at this website: http://www.gov.mb.ca/health/familydoctorfinder/.

Cholesterol and triglycerides

Lower levels of high density lipoprotein (HDL or "good" cholesterol) have been associated with increased cardiovascular risk. During your Happy Hearts appointment, one of the blood samples collected was analyzed for this measure. Typical measures for HDL cholesterol should be greater than 1.3 mmol/L.

Your HDL was measured at **1.0 mmol/L**. This value is considered in the **abnormal** range. We recommend that you have your cholesterol checked by a primary care provider. Research indicates that people can increase their HDL by: (1) maintaining a healthy body weight; (2) exercising regularly; and (3) stopping smoking if they are a smoker.

Higher levels of low density lipoprotein (LDL or "bad" cholesterol), total cholesterol and triglycerides are associated with increased cardiovascular risk. These measures were also analyzed using one of the blood samples collected during your Happy Hearts appointment. Typical measures for LDL cholesterol should be below 3.4 mmol/L, while typical measures for total cholesterol and triglycerides are below 5.2 mmol/L and 1.7 mmol/L respectively.

Your LDL was measured at **5.0 mmol/L**. This value is considered in the **abnormal** range. We recommend that you have your cholesterol checked by a primary care provider.

Your total cholesterol was determined to be **7.0 mmol/L**. This value is considered in the **abnormal** range. We recommend that you have your cholesterol checked by a primary care provider.

Your triglycerides were measured at **6.0 mmol/L**. This value is considered in the **abnormal** range and it is recommended that you discuss this value with your physician. To lower your level of triglycerides, limit alcohol, limit foods high in sugar, follow a low fat high fibre diet, and get regular exercise and lose weight if you are overweight.

Blood glucose

Your fasting blood sample was analyzed for glucose (sugar) concentration. Higher levels of glucose in the blood can increase the risk for developing diabetes. Typical measures for fasting glucose rest between 3.9 and 5.5 mmol/L. Your fasting glucose was measured at **7.0 mmol/L**. This value is considered in the **abnormal** range. We recommend that you have your blood glucose checked by a primary care provider.

Framingham Risk Score

The Framingham Risk Score is a calculation based on age, gender, cholesterol levels, blood pressure and lifestyle behaviours that is used to estimate 10 year risk of developing coronary heart disease. This is the traditional risk assessment measure that we are comparing our new measure against.

Based on the measures we collected during your Happy Hearts appointment, your Framingham Risk Score was **27**. This indicates a **high level** of risk for coronary heart disease and a **x%** chance of developing heart disease in the next 10 years. Based on this Framingham Risk Score calculation, your heart/vascular age is >85. We recommend that you bring this score to your health care provider's attention so that they can provide guidance on how to manage the different factors (systolic blood pressure, diabetes, HDL cholesterol levels and total cholesterol levels) involved in this calculation.

6 minute walking test

People who walk a longer distance during a six minute walking test have fewer adverse cardiovascular events than people who walk shorter distances. Therefore, we believe there is value in including the six minute walking test to the Happy Hearts protocol.

Walking a distance of over 543m during the six minute walking test indicates no increased relative risk for a cardiovascular event. During the six minute walking test at your appointment, you walked **120 meters**. This score relates to a **high** level of risk for a cardiovascular event.

Performing more physical activity can help to achieve longer distances in the six minute walking test. Canada's physical activity guidelines state that adults should be doing at least 150 minutes of moderate to vigorous intensity aerobic physical activity per week in bouts of at least 10 minutes. They also recommend muscle and bone strengthening activities at least twice per week.

Fried questionnaire

Frailty has been found to be associated with higher risk for adverse health outcomes. Fried et al. (2001) define frailty as having at least three of the following: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed and low physical activity levels. All of these measures were assessed during your Happy Hearts appointment.

Your accumulated Fried frailty score was **5**, meaning that you fit all of the frailty characteristics listed above. This puts you in the **frail** category, which suggests you are at **higher risk** for adverse health outcomes.

CANHEART

The CANHEART health index scoring is scored based on the following factors: non-smoker (or former who quit > 1 year ago), physically active (>30 mins/day), >=5 fruits/veggies per day, BMI <25, non-diabetic, and non-hypertensive. An ideal score would have a participant fitting into all six of these criteria, giving them a score of 6. Health index scoring decreases as less of these criteria are met.

Your CANHEART health index score was measured by using information you entered in the questionnaire at your Happy Hearts appointment. Your health index score was **0**, meaning that you did not meet any of the criteria above. This score would be considered in the **poor** range, meaning that you are **not meeting** most of ideal criteria for the different cardiovascular health factors outlined in the index.

International Physical Activity Questionnaire (IPAQ)

The International Physical Activity Questionnaire was created as a means of assessing physical activity and inactivity. During your appointment you filled out an abbreviated IPAQ as an assessment of whether or not you were meeting Canada's Physical Activity Guidelines. Canada's physical activity guidelines state that adults should be doing at least 150 minutes of moderate to vigorous intensity aerobic physical activity per week in bouts of at least 10 minutes.

According to your questionnaire that you filled out at your appointment, you **are not meeting** Canada's physical activity guidelines. This means that you are not performing enough physical activity to attain health benefits and improved functional ability as outlined by Canada's Physical Activity Guidelines.

(If no data available) You responded that you were unsure of some of your physical activity levels on the questionnaire at the time of your visit. Therefore, we were not able to provide you a value for your physical activity accumulation for that period of time. Please note that accumulating over 150 minutes of moderate to vigorous intensity aerobic physical activity every week may contribute to health benefits and improved functional ability as outlined by Canada's Physical Activity Guidelines.

Patient Health Questionnaire 9

During your Happy Hearts appointment you completed the Patient Health Questionnaire 9. The PHQ-9 is a multiple choice self-report measure used for screening and diagnosing depression. The questionnaire consists of 9 different questions, each scored from 0-3 with a score of 27 being the highest.

Your total PHQ-9 score was 27, indicating **severe** depression. Based on this, we recommend that you seek the advice of a healthcare provider. Health care providers are trained to assist those with depressive symptoms.

Arterial elasticity

The arteries, which are blood vessels that supply oxygen rich blood from your heart to your body, change in size to allow a constant flow of blood. Arteries need to be elastic to change in size. Arterial elasticity decreases with age, but is more prominently reduced with blood vessel abnormalities that place individuals at risk for heart attacks or strokes. As a result, our heart needs to work harder to provide oxygen rich blood to our body. Premature loss of elasticity may help predict risk of developing cardiovascular disease and may indicate a need for more specific diagnostic evaluation by a physician.

During your Happy Hearts appointment, your arterial elasticity was measured using computer analysis of the arterial pressure recorded from your wrist. This measure provided information on elasticity of both your large and small arteries. *Please note that the cut offs used in this report are based on research-informed cut offs, whereas, the ones that you were previously provided at your appointment were based on values given by the company that produced the instrument.*

As an example, a typical large arterial elasticity measure for a female 65 years of age or older would be a value greater than 9 mL/mmHg, while the value for someone under 65 tends to be a value greater than 10 mL/mmHg. Your large arterial elasticity value was **7 mL/mmHg**. This measure is in the **abnormal** range for large artery elasticity, and would put you at increased risk of cardiovascular disease.

A typical small arterial elasticity measure for a female 65 years of age or older would be a value greater than 3 mL/mmHg, while the value for someone under 65 is a value greater than 4 mL/mmHg. Your small arterial elasticity value was **2 mL/mmHg**. This measure is in the **abnormal** range for small artery elasticity, and would put you at increased risk of cardiovascular disease.

Arterial elasticity can be improved by adopting healthy lifestyle behaviour changes like a low-fat diet, increasing exercise, quitting smoking, decreasing alcohol consumption and losing weight.

Blood pressure at rest

Two numbers are recorded when measuring your blood pressure. The higher (systolic) number represents the pressure while the heart is beating; whereas, the lower (diastolic) number represents the pressure when the heart is resting between beats. For adults, a blood pressure of less than 120/80 is considered to be typical; whereas, 120-139/80-89 is considered the pre-hypertensive with the potential for the future development of high blood pressure (hypertension). Blood pressure of greater than 140/90 is considered to be hypertension for adults and is considered harmful. Your blood pressure can change from minute to minute, morning or night, with changes in posture, exercise or sleeping. Elevated blood pressure causes the heart to work harder than normal. That means both the heart and arteries are more prone to injury. High blood pressure increases the risk of heart attacks, strokes, kidney failure, damage to the eyes, congestive heart failure and atherosclerosis.

As part of your appointment, we measured your resting blood pressure. Your resting blood pressure reading was **180/100 mm Hg**. This value is in the **abnormal** range for blood pressure readings, and would put you at increased risk of cardiovascular disease. We recommend that you have your blood pressure checked by a primary care provider.

Blood pressure in response to exercise

As part of your appointment, we measured your systolic blood pressure response to exercise. The magnitude of rise in blood pressure during exercise may be an indication of early stiffening of the arteries even if the resting blood pressure is normal. In response to moderate intensity exercise, your systolic blood pressure went up to **250 mm Hg**, which is a change of **70 mm Hg** from your resting systolic blood pressure measure. This is a **higher** increase in blood pressure than would typically be seen in response to this intensity of exercise. We recommend that you discuss this value with your primary health care provider.

Rasmussen Disease Score

Developed at the Center for Cardiovascular Disease Prevention at the University of Minnesota, the Rasmussen Disease Score (RDS) consists of a series of non-invasive procedures designed to detect early stages of cardiovascular disease for individual patients. The tests included in this measure are the resting blood pressure, blood pressure response to exercise, large artery elasticity, and small artery elasticity. Each of these tests are scored from 0-2 (0 = normal, 1 = borderline, 2 = abnormal) with a total RDS ranging from 0-8. Each individual is categorized based on risk (ie 0-2 = normal, 3-8 = abnormal). Please note that this scoring system is still only in the research stages and is not recognized as a diagnostic tool.

Based on the measures collected at your Happy Hearts appointment, your total Rasmussen Disease Score is 8, putting you in the **abnormal** risk category. This score can be improved by lowering blood pressure and increasing arterial elasticity. Recommendations on how to improve these measures have been provided in each of their respective sections.

Healthy Living and Older Adults in Manitoba

Manitoba has a large number of resources available for those who wish to lead more active and healthier lives. Fitness centres in Winnipeg, such as the Reh-Fit Centre and the Wellness Institute, provide fitness and education programs geared specifically toward older adults. Many community centres and businesses also offer a variety of recreation and leisure programs to support healthy living. The Government of Manitoba department of Healthy Living and Seniors also provides valuable information on healthy living, including different programs that are available in the province. Further information from this department can be found at this link: www.gov.mb.ca/healthyliving/.

It is important to note that risk for cardiovascular disease does not mean that you will have a cardiovascular event, rather, it is an assessment of the likelihood of you developing a cardiovascular disease. Please also note that this data is for research purposes only and is not diagnostic. If you have any questions about the information provided in this report, you can contact us by phone at 204-235-3589 or by email at happyhearts@sbrc.ca. If you have any concerns about your health, we recommend that you seek the advice of a primary care provider.

Thank you very much for your participation in the Happy Hearts Research Study. Your participation in the study will help to guide the development of future cardiovascular health screening initiatives. We greatly appreciate that you have taken the time to participate in the Happy Hearts Research Study.

Sincerely,

[redacted]

Appendix M - WARM Hearts Fictitious Report for Participant at Low CVD Risk

Hello,

Thank you very much for your recent participation in the Happy Hearts Research Study. You are receiving this letter because you requested to receive a specific report detailing your individual results in the Feedback Request Form at your appointment.

Heart disease is the number one killer of women, including the number one cause of death for women over the age of 55. Yet, there has been limited attention focused on how heart disease presents in women and how to improve health outcomes in women.

Compared to a man, a woman runs a greater risk of dying following a heart attack or stroke. Women are less likely to be treated by a specialist and are less likely to be transferred to a specialized facility for treatment. We know that even when age and other health conditions are taken into consideration, a woman's risk of dying within the first thirty days after a heart attack is 16% higher than for a man. For stroke it is 11% higher. The reasons for this are unclear.

Currently, there are more questions than answers. The time has come to focus on women's heart health. Following wide consultation, review of available research and the completion of an independent needs assessment, the decision was made to establish a long-term initiative to address the critical issues in women's heart health: the Women's Heart Health Initiative. St. Boniface Hospital Foundation is committed to raise $10 million to create a Women's Cardiac Treatment and Research Centre at St-Boniface Hospital, housed in the I H Asper Cardiac Research Institute.

While the women's cardiovascular research and treatment centre will be implemented incrementally as funds are raised, research is underway to begin to improve women's health. The Happy Hearts Research study is conducting research to test a new approach for identifying people who are at risk for developing cardiovascular diseases before they develop major clinical complications. The cardiovascular health screening protocol we are now testing in Manitoba was initially developed in Minnesota. The original research on 5,000 participants at three sites in the U.S.A. demonstrated this cardiovascular health screening protocol to be a better approach for identifying individuals who have early stages of cardiovascular disease, when compared to traditional cardiovascular health screening methods. The Happy Hearts cardiovascular health screening protocol needs further assessment before it can be implemented in Canada because it is not known if the approach will have similar predictive value within the context of the Canadian health care system.

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If you do not currently have a primary care provider, the Government of Manitoba provides a service called Family Doctor Finder that can help connect you to a primary care provider. To register for this service by phone, call 204-786-7111 between 8:30am and 4:30pm Monday to Friday to reach the Family Doctor Finder call centre. Additional information can be found at this website: http://www.gov.mb.ca/health/familydoctorfinder/.

Cholesterol and triglycerides

Lower levels of high density lipoprotein (HDL or "good" cholesterol) have been associated with increased cardiovascular risk. During your Happy Hearts appointment, one of the blood samples collected was analyzed for this measure. Typical measures for HDL cholesterol should be greater than 1.3 mmol/L.

Your HDL was measured at **x mmol/L**. This value is considered in the **normal** range. Research indicates that people can increase their HDL by: (1) maintaining a healthy body weight; (2) exercising regularly; and (3) stopping smoking if they are a smoker.

Higher levels of low density lipoprotein (LDL or "bad" cholesterol), total cholesterol and triglycerides are associated with increased cardiovascular risk. These measures were also analyzed using one of the blood samples collected during your Happy Hearts appointment. Typical measures for LDL cholesterol should be below 3.4 mmol/L, while typical measures for total cholesterol and triglycerides are below 5.2 mmol/L and 1.7 mmol/L respectively.

Your LDL was measured at **x mmol/L**. This value is considered in the **normal** range.

Your total cholesterol was determined to be **x mmol/L**. This value is considered in the **normal** range.

Your triglycerides were measured at **x mmol/L**. This value is considered in the **normal** range. To lower your level of triglycerides, limit alcohol, limit foods high in sugar, follow a low fat high fibre diet, and get regular exercise and lose weight if you are overweight.

Blood glucose

Your fasting blood sample was analyzed for glucose (sugar) concentration. Higher levels of glucose in the blood can increase the risk for developing diabetes. Typical measures for fasting glucose rest between 3.9 and 5.5 mmol/L. Your fasting glucose was measured at **x mmol/L**. This value is considered in the **normal** range.

Framingham Risk Score

The Framingham Risk Score is a calculation based on age, gender, cholesterol levels, blood pressure and lifestyle behaviours that is used to estimate 10 year risk of developing coronary heart disease. This is the traditional risk assessment measure that we are comparing our new measure against. Results are represented as a percent chance of developing heart disease in the next 10 years.

Based on the measures we collected during your Happy Hearts appointment, your Framingham Risk Score 10 year risk score was **x%.** This indicates a **low relative risk** for developing coronary heart disease in the next 10 years. Based on this Framingham Risk Score calculation, your heart/vascular age is **x**.If you wish to receive guidance on how to manage the different factors (systolic blood pressure, diabetes, HDL cholesterol levels and total cholesterol levels) involved in this calculation, we recommend that you discuss this with your health care provider.

6 minute walking test

People who walk a longer distance during a six minute walking test have fewer adverse cardiovascular events than people who walk shorter distances. Therefore, we believe there is value in including the six minute walking test to the Happy Hearts protocol.

Walking a distance of over 543m during the six minute walking test indicates no increased relative risk for a cardiovascular event. During the six minute walking test at your appointment, you walked **x meters**. This score relates to a **low level** of risk for a cardiovascular event.

Performing more physical activity can help to achieve longer distances in the six minute walking test. Canada's physical activity guidelines state that adults should be doing at least 150 minutes of moderate to vigorous intensity aerobic physical activity per week in bouts of at least 10 minutes. They also recommend muscle and bone strengthening activities at least twice per week.

Fried questionnaire

Frailty has been found to be associated with higher risk for adverse health outcomes. Fried et al. (2001) define frailty as having at least three of the following: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed and low physical activity levels. All of these measures were assessed during your Happy Hearts appointment.

Your accumulated Fried frailty score was **x.** This does not put you in the frail category, which suggests you are at a **lower risk** for adverse health outcomes.

CANHEART

The CANHEART health index scoring is scored based on the following factors: non-smoker (or former who quit > 1 year ago), physically active (>30 mins/day), >=5 fruits/veggies per day, BMI <25, non-diabetic, and non-hypertensive. An ideal score would have a participant fitting into all six of these criteria, giving them a score of 6. Health index scoring decreases as less of these criteria are met.

Your CANHEART health index score was measured by using information you entered in the questionnaire at your Happy Hearts appointment. Your health index score was **x**. This score would be considered in the **ideal** range, meaning that you are meeting **most** of ideal criteria for the different cardiovascular health factors outlined in the index.

International Physical Activity Questionnaire (IPAQ)

The International Physical Activity Questionnaire was created as a means of assessing physical activity and inactivity. During your appointment you filled out an abbreviated IPAQ as an assessment of whether or not you were meeting Canada's Physical Activity Guidelines. Canada's physical activity guidelines state that adults should be doing at least 150 minutes of moderate to vigorous intensity aerobic physical activity per week in bouts of at least 10 minutes.

According to your questionnaire that you filled out at your appointment, you **are** meeting Canada's physical activity guidelines. This means that you are performing enough physical activity to attain health benefits and improved functional ability as outlined by Canada's Physical Activity Guidelines.

Patient Health Questionnaire 9

During your Happy Hearts appointment you completed the Patient Health Questionnaire 9. The PHQ-9 is a multiple choice self-report measure used for screening and diagnosing depression. The questionnaire consists of 9 different questions, each scored from 0-3 with a score of 27 being the highest.

Your total PHQ-9 score was **x,** indicating **none or minimal** depression.

Arterial elasticity

The arteries, which are blood vessels that supply oxygen rich blood from your heart to your body, change in size to allow a constant flow of blood. Arteries need to be elastic to change in size. Arterial elasticity decreases with age, but is more prominently reduced with blood vessel abnormalities that place individuals at risk for heart attacks or strokes. As a result, our heart needs to work harder to provide oxygen rich blood to our body. Premature loss of elasticity may help predict risk of developing cardiovascular disease and may indicate a need for more specific diagnostic evaluation by a physician.

During your Happy Hearts appointment, your arterial elasticity was measured using computer analysis of the arterial pressure recorded from your wrist. This measure provided information on elasticity of both your large and small arteries. *Please note that the cut offs used in this report are based on research-informed cut offs, whereas, the ones that you were previously provided at your appointment were based on values given by the company that produced the instrument.*

As an example, a typical large arterial elasticity measure for a female 65 years of age or older would be a value greater than 9 mL/mmHg, while the value for someone under 65 tends to be a value greater than 10 mL/mmHg. Your large arterial elasticity value was **x mL/mmHg**. This measure is in the **normal** range for large artery elasticity.

A typical small arterial elasticity measure for a female 65 years of age or older would be a value greater than 3 mL/mmHg, while the value for someone under 65 is a value greater than 4 mL/mmHg. Your small arterial elasticity value was **x mL/mmHg**. This measure is in the **normal** range for small artery elasticity.

Arterial elasticity can be improved by adopting healthy lifestyle behaviour changes like a low-fat diet, increasing exercise, quitting smoking, decreasing alcohol consumption and losing weight.

Blood pressure at rest

Two numbers are recorded when measuring your blood pressure. The higher (systolic) number represents the pressure while the heart is beating; whereas, the lower (diastolic) number represents the pressure when the heart is resting between beats. For adults, a blood pressure of less than 120/80 is considered to be typical; whereas, 120-139/80-89 is considered the pre-hypertensive with the potential for the future development of high blood pressure (hypertension). Blood pressure of greater than 140/90 is considered to be hypertension for adults and is considered harmful. Your blood pressure can change from minute to minute, morning or night, with changes in posture, exercise or sleeping. Elevated blood pressure causes the heart to work harder than normal. That means both the heart and arteries are more prone to injury. High blood pressure increases the risk of heart attacks, strokes, kidney failure, damage to the eyes, congestive heart failure and atherosclerosis.

As part of your appointment, we measured your resting blood pressure. Your resting blood pressure reading was **x/x mm Hg**. This value is in the **normal** range for blood pressure readings.

Blood pressure in response to exercise

As part of your appointment, we measured your systolic blood pressure response to exercise. The magnitude of rise in blood pressure during exercise may be an indication of early stiffening of the arteries even if the resting blood pressure is normal. In response to moderate intensity exercise, your systolic blood pressure went up to **x mm Hg**, which is a change of **x mm Hg** from your resting systolic blood pressure measure. This is a typical increase in blood pressure given the intensity of exercise performed.

Rasmussen Disease Score

Developed at the Center for Cardiovascular Disease Prevention at the University of Minnesota, the Rasmussen Disease Score (RDS) consists of a series of non-invasive procedures designed to detect early stages of cardiovascular disease for individual patients. The tests included in this measure are the resting blood pressure, blood pressure response to exercise, large artery elasticity, and small artery elasticity. Each of these tests are scored from 0-2 (0 = normal, 1 = borderline, 2 = abnormal) with a total RDS ranging from 0-8. Each individual is categorized based on risk (ie 0-2 = normal, 3-8 = abnormal). Please note that this scoring system is still only in the research stages and is not recognized as a diagnostic tool.

Based on the measures collected at your Happy Hearts appointment, your total Rasmussen Disease Score was **x**, putting you in the **normal** risk category. This score can be improved by lowering blood pressure and increasing arterial elasticity. Recommendations on how to improve these measures have been provided in each of their respective sections.

Healthy Living and Older Adults in Manitoba

Manitoba has a large number of resources available for those who wish to lead more active and healthier lives. Fitness centres in Winnipeg, such as the Reh-Fit Centre and the Wellness Institute, both provide fitness and education programs geared specifically toward older adults. Many community centres and businesses also offer a variety of recreation and leisure programs to support healthy living. The Government of Manitoba department of Healthy Living and Seniors also provides valuable information on healthy living, including different programs that are available in the province. Further information from this department can be found at this link: www.gov.mb.ca/healthyliving/.

It is important to note that risk for cardiovascular disease does not mean that you will have a cardiovascular event, rather, it is an assessment of the likelihood of you developing a cardiovascular disease. Please also note that this data is for research purposes only and is not diagnostic. If you have any questions about the information provided in this report, you can contact us by phone at 204-235-3589 or by email at happyhearts@sbrc.ca. If you have any concerns about your health, we recommend that you seek the advice of a primary care provider.

Thank you very much for your participation in the Happy Hearts Research Study. Your participation in the study will help to guide the development of future cardiovascular health screening initiatives. We greatly appreciate that you have taken the time to participate in the Happy Hearts Research Study.

Sincerely,

[redacted]