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PREDICTION OF CORONARY HEART DISEASE WITHIN THE AEROBICS CENTER LONGITUDINAL STUDY POPULATION

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DEDICATION

I Dedicate this Accomplishment to my Friends, Family, and Mentors.

It was Your Love and Support

That Gave Me the Strength and Perseverance

To Never Give Up

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This dissertation would not have been possible without the support of my wonderful mentors of my dissertation committee. I want to, first and foremost, thank my dissertation chair Dr. Steven N. Blair and my co-chair Dr. Xuemei Sui. Your patience throughout this process is unmeasurable. I also want to extend my sincere appreciation to the remaining members of my dissertation committee: Dr. Linda Hazlett, Dr. Bo Cai, and Dr. James Hébert. Your guidance and insight taught me not to be afraid to ask questions and always answer with a stiffened back. Thank you to my friends and colleagues Dr. Shae Sutton, Ms. Alysa S Perrin, Ms. Drew Westmoreland, Ms. Meredith Ray, Dr. Rachel Patzer, Ms. Mohua Basu, and Mr. Christopher Miller for your critical feedback, statistical support, and overall encouragement. Lastly, I would like to thank my parents for their unwavering support and steadfast love.

My mentors, my friends, and my family have enabled me to remain focused and strong throughout this process. This and future accomplishments would not be possible without you.

ABSTRACT

This dissertation is a compilation of three studies that were conducted to better 1) Further validate a thoroughly tested Framingham Risk Score (FRS) on a unique cohort with comprehensive measures available, 2) Update and improve the predictability of the FRS through the addition of cardiorespiratory fitness (CRF) while resolving limitations in previous studies, and 3) Assess the predictability of non-exercise estimated CRF (e-CRF) and FRS on CHD. A manuscript was generated for each study utilizing data from the Aerobics Center Longitudinal Study.

To validate the FRS, a multivariable Cox Proportional Hazard Model was used to determine the association between FRS component and CHD. The Area Under the Curve (c-statistic) from the receiver operating characteristic (ROC) curve was used to determine predictability of the FRS model on ACLS. The FRS' components were significantly associated with CHD and the c-statistic was statistically significant.

The second study's goal was to update the FRS by adding CRF. This study included 29,854 men from ACLS that completed a baseline examination from 1979-2002. FRS was defined as a composite score and modeled as a continuous and categorical variable. CRF was defined as a continuous variable through maximally achieved metabolic equivalent of task (METs) and categorical: low, moderate, or high CRF. Multivariable survival analysis showed a significant association between CRF, FRS and

CHD. Although the second study found there was a significant relationship with CRF, FRS, and CHD, traditionally measured CRF is not a clinically viable tool.

The third study aim was to use a non-exercise estimated CRF (e-CRF) to determine the relationship between e-CRF, FRS, and CHD. Estimated CRF was defined through a 5-item questionnaire and the same data from study #2 was utilized for the multivariable Cox Proportional Hazard modeling. The relationship between e-CRF and CHD was investigated in subset populations based on age, smoking, hypertension, and diabetes diagnosis. Our study found that among men with 'moderate or high' risk for CHD, men with moderate or high fitness had a decreased risk for CHD compared to men with low fitness.

CHD is one of the leading causes of death in the U.S. and early establishment of CHD risk is important for primary and secondary prevention. The series of papers presented in this dissertation provide the evidence needed to begin establishing a more comprehensive and clinically feasible risk prediction tool. Clinicians may want to consider capturing their patients' medical history, CHD risk factors, and their e-CRF so they can take advantage of CRF's improved prediction of CHD. This comprehensive approach can help physicians predict adverse events for their patients while also counseling them on how to improve their overall health through improvement of CRF.

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CHAPTER I

INTRODUCTION

Statement of the Problem

Cardiovascular diseases (CVDs), including coronary heart disease (CHD) and stroke, represent the leading cause of death in the United States. [1] CVDs account for approximately 17% of the overall national health care expenditures. [1-3] The American Heart Association (AHA) stated in 2004 that their goal for 2010 is to "…reduce coronary heart disease (CHD), stroke, and risk by 25%" utilizing the following indicators: reduce death rate due to CHD and stroke 25%, reduce prevalence of associated risk factors (smoking, physical inactivity, high cholesterol, and high blood pressure), and eliminate the progression of obesity and diabetes. [4] The AHA recognized the need to expand their 2010 goals for their 2020 proposal. AHA decided to broaden its scope beyond CHD to include all of cardiovascular disease (CVD) mortality and CVD health. The 2020 goal of the American Heart Association is to reduce the deaths caused by CVD and stroke by 20% [5] and to improve the cardiovascular health of Americans by 20%.

The AHA estimates that more than one in three adults have one or more types of CVD with approximately 50% of this population over the age of 59 years. [5] Within the 45 million adults reporting having a functional disability, heart disease is among the 15

leading conditions that caused those disabilities. Disability was defined as difficulty with daily activities and limitation in ability to do work around the house or on the job. [5]

CHD is the accrual of plaque in the arteries of the heart [6] that supply the heart with blood to maintain normal cardiac function. The accumulation of plaque narrows the heart's arteries forcing the heart muscle to work harder. The formation of CHD depends on the extent of plaque build-up, reduced blood flow, and damage caused to the heart muscle. The deprivation of oxygen to the heart muscle may cause dead muscle cells or scar tissue to form, decreasing the pump efficiency of the heart and often the accumulation of blood on the right side. Another main cause of CHD is the deposition of fat beneath the endothelium reducing the elasticity of arteries. Decreased elasticity, coupled with high blood pressure, could lead to the artery hemorrhaging, also called an aneurysm. CHD has substantially decreased worldwide in the past 30 years [7,8] primarily due to the improvements of modifiable lifestyle characteristics. [9,10] The modifiable lifestyle characteristics include smoking, high blood pressure, and high cholesterol.

An American Cancer Society Cancer Prevention Study compared two different groups derived at different time points with a 20-year gap between them: group one was surveyed between 1959-1965 while group two was surveyed between 1982-1988. [11] The survey of these volunteers in both groups showed that there was a noticeable decline in deaths related to CHD between the two sampling periods. Although both lifelong nonsmokers and smokers at enrollment experienced a decline in CHD mortality, the smokers at enrollment still had a higher mortality ratio. [11] These results show that although smoking cessation decreases an individual's risk for mortality compared to

current smokers, past smokers are still at a higher risk of CHD mortality than lifelong nonsmokers.

High blood pressure can subject an individual's arteries to increased force that creates microscopic tears in the walls that may develop in to scar tissue. [6] This scar tissue creates a lattice for plaque to accumulate within the artery and may eventually lead to a partial or full blockage. [6] Cholesterol is a substance that contributes to plaque formation. [12] High cholesterol coupled with high blood pressure and scar tissue formation within arteries may increase an individual's risk for CHD. [6,13] Most deaths related to high blood pressure or high cholesterol are attributed to CHD. [13] It is important to note that the decrease of CHD mortality in recent years can be attributed to the improvement of blood pressure and cholesterol management. [14]

The body breaks down the food we consume into sugars, which it utilizes as an energy source. [15] The pancreas produces insulin that enables the cells within the body to utilize these sugars. [6] Diabetes is diagnosed when the body cannot adequately utilize these synthesized sugars. [16] Diabetes can cause impairment in the cardiac muscle that may lead to cardiomyopathy, congestive heart failure, or ischemic heart disease and can increase the 5-year mortality rate after a myocardial infarction. [16,17] Research shows that individuals with diabetes and hypertension have a higher incidence of heart disease compared to people with diabetes or hypertension alone. [18,19] [16]

Investigators from across the world have taken these and other covariates into consideration as they have developed risk factor scores to help model and predict an individual's risk for CHD in a given time period. The Prospective Cardiovascular Münster Study (PROCAM) cohort of middle-aged men was utilized to develop a risk

factor score encompassing age, low density lipoprotein, high density lipoprotein, triglycerides, smoking status, diabetes diagnosis, family history of myocardial infarction, and systolic blood pressure. [20] The Second Joint Task Force instigated the development of a risk score that was based on European cohorts in 12 different countries. [21] The result was a sex- and age-stratified risk chart that assessed the individual's smoking history and cholesterol profile. This risk chart is aimed to estimate the total risk of CVD rather than just CHD. [21]

The Framingham Heart Study developed a risk score aimed at simplifying the dynamic and potentially convoluted task of estimating a person's CHD risk. [22] The Framingham Risk Score (FRS) utilized the Framingham Heart Study cohort that dates back to 1948. [23] The original risk score was derived more than forty years ago and, when updated in 1991, the risk factors considered remained the same: age, systolic blood pressure, diastolic blood pressure, cholesterol (total cholesterol and high density lipoproteins), smoking status, diagnosis of diabetes, and electrocardiogram to determine CHD risk. [22] The result from the FRS regression model was translated into a worksheet that clinicians can employ for the approximation of the five and ten year risk for CHD. [22] In a recent publication from Sposito et al, 48% of surveyed physicians across the globe self-reported utilizing the FRS more often than other scores, [24] which was higher than any other risk score.

An initial limitation of the FRS was the homogeneous demographic that comprised the Framingham Heart Study. The population recruited for the Framingham Heart Study is derived from a suburb west of Boston and is comprised primarily of Non-

Hispanic White men and women. [25] However, since its origination, FRS or similar scores have been applied to various racial and ethnic populations.

The Honolulu Heart Study was initiated in 1965with the overall concept of standardizing cardiovascular examination. [26] The cohort was comprised of Japanese men born between 1900 and 1919 and updated their World War II Selective Service Files; the final population with a baseline examination was approximately 8,000 individuals. [26] The majority of this population consisted of first generation immigrants, 50% never attended high school and only 15% had any technical or university training. [26]

Validation of the FRS also occurred in the Physician's Health Study. Male physicians in the United States between 40-84 years of age (n=22,071) were randomized in a double-blinded, placebo-controlled study. [27] Coronary risk factors were collected through questionnaires prior to randomization and surveys were mailed to the participants every 6 months. Individuals would self-report nonfatal CHD incidence, and the non-responders were followed up with a telephone-based survey. [27] Stampfer et al also found similar effects of the FRS covariates , with the exception of smoking. The Physician's Health Study also reported the significant joint effect HDL and total cholesterol has on CHD's relative risk. [27,28]

There are various risk factors that have a significant relationship with CHD and other cardiovascular events. However, it is not enough for these risk factors to have independent predictive power, the risk factor has to improve the predictability traits that the traditional risk score, FRS, encompasses. Pischon et al investigated the predictive power of C-reactive protein (CRP) and the feasibility to substitute this for low-density lipoprotein cholesterol measure [29]. CRP was measured through highly sensitive assays

and then applied to the FRS. [29] Cox regression indicated that the FRS plus CRP was a significant prediction model for myocardial infarction and stroke; although the inclusion of CRP did not improve the predictive accuracy of the original FRS. [29]

Instead of attempting to modify the FRS with biological factors, Gallo et al evaluated augmentation of the FRS with social factors that may increase the risk of CHD. [30] Gallo et al. explored the effect involuntary job loss after the age of 50 years may have on 10-year risk on myocardial infarction and stroke. They used a Cox regression model to analyze the first ten years of data in the US Health and Retirement Survey with the outcome as self-reported myocardial infarction or stroke. Job loss was the main independent variable and was treated as a time dependent variable. [30] Gallo and his associates found that individuals who lost their job involuntarily had a 2.48 times higher risk (95% CI 1.49-4.14) for myocardial infarction and a 2.43 higher risk of stroke compared to individuals who did not experience involuntary job loss. [30] Like many studies that attempted to improve or modify the FRS, Gallo et al did not perform goodness-of-fit tests to determine if this model was truly a better predictor of 10-year cardiovascular disease risk than the original FRS.

During Wilson et al's augmentation of the 1991 FRS model, the analysis tested the addition of other risk factors [25] and considered the inclusion of physical activity or CRF. Unfortunately, the Framingham Heart Study did not capture this information at the baseline examination prohibiting its inclusion in the model. [25]

Physical activity could improve an individual's blood pressure, cholesterol levels, and glucose tolerance through various mechanisms. [31] Regular physical activity promotes higher levels of high-density lipoproteins that help countervail the effect of low-density

lipoprotein cholesterol, improve the efficiency of pumping in the heart, and retard clotting formation within arteries. [6,32] From a research standpoint, measuring physical activity is not entirely standardized. Physical activity has been categorized differently across studies, which has produced variable results, thus making comparability to previous findings difficult. [33] In addition to this, the primary components that calculate the volume of physical activity (duration, intensity, and frequency) performed cannot be captured accurately. [33] Cardiorespiratory fitness (CRF) resolves the limitation of physical activity measures not being able to capture energy expenditure consistently.

Usual physical activity habits are the primary determinant of fitness [34] in addition to CRF's genetic component. [35-37] Cardiorespiratory fitness (CRF) is defined as the ability of the circulatory system to supply and utilize oxygen during sustained physical activity. [38] Cardiorespiratory fitness is typically measured in epidemiological studies through maximal or submaximal exercise tests to measure exercise capacity. [39] CRF has been shown to have a significant protective relationship for various outcomes that range from a diabetes diagnosis, [34,40] cancer morbidity, [41] obesity, CHD diagnosis, [42] all-cause mortality, [43] diabetes mortality, [40,44] and CHD mortality. [45,46]

A large prospective cohort focused on determining the independent and joint associations CRF and obesity may have on the incidence of type 2 diabetes in American women. [34]. More than 140 women developed diabetes in a 17-year follow-up period. [34] Age-adjusted incidence rates were calculated for increments of CRF and the results show that women with a low exercise capacity (<7 METs) had a three times higher risk of developing type 2 diabetes compared to women with a higher exercise capacity (≥10 METs). [34] When the combined effects of CRF and BMI were analyzed, normal-weight

(BMI <25 kg/m^2) unfit women (lowest CRF tertile) did not present an increased risk for diabetes incidence while overweight/obese (BMI≥25 kg/m^2) unfit women had twice the risk for diabetes incidence; both groups were compared to the referent group comprised of normal weight fit women. [34]

CRF is also protective against all-cause mortality. More than 13,000 participants from the Aerobic Center Longitudinal Study (ACLS) were divided into quintiles of fitness and then analyzed for various joint effects of fitness and various comorbidities on all-cause mortality. [43] In men with cardiovascular disease, there was a significant protective linear trend relationship between CRF and all-cause mortality. [43]

An early study portrayed the significant effect CRF has on CHD risk factors in women. [42] Women ages 18-65 years who completed a comprehensive medical exam between 1971 and 1980 were included in the regression analysis to determine the relationship between CRF and CHD, a relationship already found to be significant in men. [47-49] The CHD risk factors employed in the analysis were based on the Framingham Risk Score. [23] CRF was shown to have significant impact on the CHD risk factors, including current smoking, total cholesterol, HDL cholesterol, and blood pressure. [42]

To better assess the risk factors for CHD mortality and the impact CRF may have, Lee et al (1999) conducted an analysis to examine the relationship between body composition, CRF, and CHD mortality. Approximately 22,000 men completed a medical examination between 1971 and 1989. [46] Body composition of these men was measured either through hydrostatic weighing, skinfold-thickness measurements, or both; body composition was defined as a three-level variable: lean (<25th percentile), normal (25th to <75th percentile), or obese (≥75th percentile). Unfit lean men had a significantly three

times higher risk for CHD mortality compared to fit lean men[46]. Although there were significantly higher risks of CHD mortality across the body composition groups, this significant relationship was attenuated in fit men. Fit men with a normal body composition had a 1.43 (95% CI 0.77, 2.67) higher risk of CHD mortality compared to fit lean men while fit obese men had a 1.35(95% CI 0.66, 2.76) times higher risk compared to referent group [46] although neither association were statistically significant.

Gupta et al sought to determine CRF's contribution to traditional CHD risk factors [50] and utilized the ACLS cohort with data collected from 1970 through 2006. CRF was defined as quintiles and the results showed that all variables included in the traditional risk factor score and all quintiles of CRF were significant with CHD mortality. [50] When comparing the traditional versus CRF-augmented model in men, the CRF-augmented CHD risk factor model correctly reclassified participants with CHD death based on their 10-year risk. [50] However, a potential limitation of this study was the use of a very basic model to represent the traditional CHD risk factor model which included only age, systolic blood pressure, diabetes, total cholesterol, and smoking status. The FRS includes the covariates mentioned in Gupta et al's report, adjusts for sex similarly to Gupta et al, but also includes diastolic blood pressure and high density lipoproteins in their risk calculation. [22]

Purpose and Study Aims

CHD is one of the leading causes of death in the United States. A diagnosis of CHD can cost an individual tens of thousands of dollars and shorten his or her lifespan. FRS provides clinicians a tool to accurately predict their patients' 10-year risk for CHD that can be used to prevent disease. CRF has been consistently shown to provide a

protective effect on CHD as well as other comorbidities associated with CHD. The purpose of this study is to further validate a thoroughly tested FRS on a unique cohort with comprehensive measures available; update and improve the predictability of the FRS through the addition of CRF while resolving limitations in previous studies; and asses the predictability of non-exercise estimated CRF (e-CRF) and FRS on CHD.

PAPER 1: Framingham Risk Score (FRS) applied to the Aerobic Center Longitudinal Study (ACLS)

Hypothesis: The Framingham Risk Score will significantly predict CHD events for men within the ACLS population

PAPER 2: Augment the Framingham Risk Score (FRS) applied to the Aerobic Center Longitudinal Study (ACLS) with the addition of Cardiorespiratory Fitness (CRF)

Hypothesis: The CRF variable will improve the Framingham Risk Score predictive ability of CHD events for men within the ACLS population

PAPER 3: Determine the association between non-exercise estimated CRF (e-CRF) and CHD. Utilize e-CRF and FRS to predict the risk of CHD.

Hypothesis: Estimated CRF (e-CRF) will be significantly protective against CHD. We also hypothesized that e-CRF and FRS will have a significant association with CHD.

Study Outline

Chapter I of this dissertation has served as an introduction to the problems associated with CHD, the purpose of this research, and the study's hypothesizes. Chapter

II is a review of the relevant literature. This review provides detailed insight on CHD and how CHD prevalence and CHD mortality incidence has changed over time. This chapter continues to discuss the clinical tools generated by researchers and implemented by physicians to help detect this problem in hopes of preventing CHD. Chapter II focuses on the FRS and its ability to predict a 10-year CHD risk. The chapter also points out the limitations of FRS and proceeds to state how this publication will correct for these limitations. Chapter III states the methodology employed to test the hypothesis in each of the three manuscripts. Chapter IV represents Paper 1 'Framingham Risk Score applied to the Aerobic Center Longitudinal Study (ACLS)' including background, results, and discussion in manuscript layout. Chapter V focuses on Paper 2 'Augment the Framingham Risk Score (FRS) applied to the Aerobic Center Longitudinal Study (ACLS) with the addition of Cardiorespiratory Fitness (CRF)' and reporting the results of the analysis aimed at augmenting FRS; this chapter is formatted similar to Chapter IV. The subsequent chapter, Chapter VI, captures the results from Paper 3 'Determine the association between estimated CRF (e-CRF) and CHD. Utilize e-CRF and FRS to predict the risk of CHD'. Chapter VII concludes the dissertation through the summation of each of the three presented papers and their specific hypotheses. Chapter VII also includes how the conclusions from each paper relate to one another, the strengths and limitations to the research, possible directions for future research, overall conclusions, and the lessons learned throughout the dissertation process.

CHAPTER II

LITERATURE REVIEW

The following literature review will reiterate findings from several studies on the severity of coronary heart disease, encompassing characteristics of the Framingham Risk Score, the positive health effects of cardiorespiratory fitness, Framingham Risk Score's 10-year risk predictability of CHD events, and the potential augmentation of this risk score with the addition of cardiorespiratory fitness.

Overview of Coronary Heart Disease

Brief History

The American Heart Association (AHA) stated in 2004 that their goal for 2010 is to "…reduce coronary heart disease (CHD), stroke, and risk by 25%" utilizing the following indicators: reduce death rate due to CHD and stroke 25%, reduce prevalence of associated risk factors (smoking, physical inactivity, high cholesterol, and high blood pressure), and eliminate the progression of obesity and diabetes. [4]

Lloyd-Jones reported the progress of the reduction of CHD, stroke, high blood pressure, and high cholesterol depicted in Figure 2.1. [4] The achievement of these goals is partially attributed to the work practitioners and scientists conducted to improve medical prevention and treatment of heart disease and public health's initiative to eliminate smoking and increase individuals' physical activity while controlling their blood pressure and cholesterol. [4]

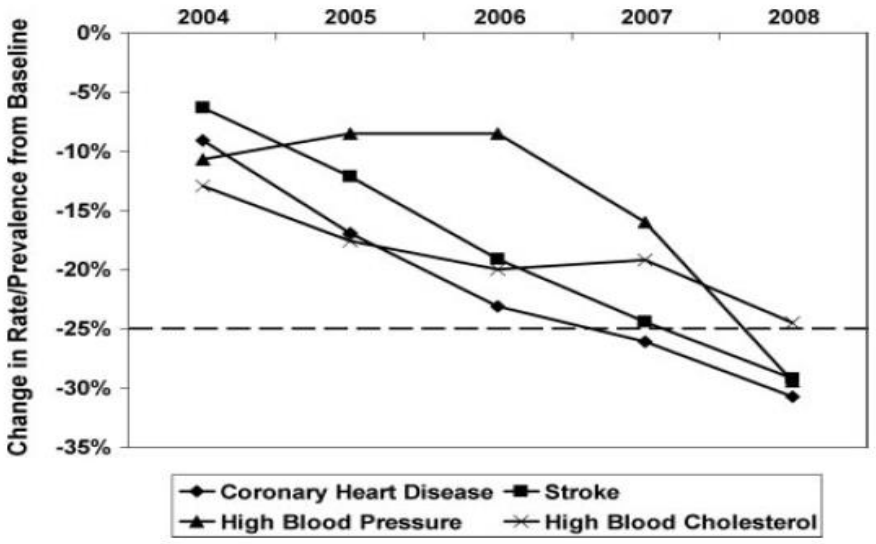


Figure 2.1. Trajectory of mortality rates from coronary heart disease (CHD) and stroke, rate of uncontrolled high blood pressure, and prevalence of high blood cholesterol from 2004 to 2008 (Lloyd-Jones, Adams et al. 2009)

Previous literature has shown an inverse relationship between physical activity and physical fitness and the incidence of CHD. [48,51-53] Clinicians seldom consider cardiorespiratory fitness when evaluating their patient's risk for CHD. [25,51] One theory behind the lack of consideration CRF receives in clinical assessment of CHD is a poorly established association between CRF and CHD. [51]

A meta-analysis determined that individuals who were moderately physically active had a lower risk of CHD than sedentary individuals. [54] Following this theory, a more recent meta-analysis of 33 eligible studies depicted an association between CRF and CHD. [51] The individuals with a low CRF had an RR for all-cause mortality of 1.40 (95% CI 1.23-1.48, p-value<0.001) and for CHD/CVD events of 1.47 (95%CI 1.35-1.61, p=value<0.001) while adjusting for heterogeneity of study design. [51]

The meta-analysis performed by Kodama, 2009 showed a dose-response relationship between a 1-MET increase of MAC (maximum aerobic capacity) and a 13% and 15% decrements in risk of all-cause mortality and CHD/CVD, respectively. [51] In categorical analysis, individuals with a low CRF had significant higher risk for CHD/CVD compared to individuals with intermediate or high CRF. [51]

Current Public Health Undertakings

The AHA recognized the need to expand their 2010 goals for their 2020 proposal. AHA decided to broaden its scope beyond CHD to include all of cardiovascular disease (CVD) mortality and CVD health. To evaluate CHD and CVD health, a comprehensive metric was developed. [4] This metric recognized physical activity as a significant factor in CVD and CHD, as well as smoking status, body mass index, diet score, cholesterol, blood pressure, and fasting plasma glucose. The 2020 goal of the American Heart Association is to reduce the deaths caused by CVD and stroke by 20% [5] and to improve the cardiovascular health of Americans by 20%.

Health Care Costs

The US continues to spend more money per capita than any other country on health care. [55] CHD and CVD remain among the leading causes of death in the United States and comprise approximately 17% of the overall national health care expenditures. [1-3] In the past ten years, the medical costs of CVD have grown at an average of 6% per year. [56] However the US also has observed a longer life expectancy [57] and as the US population ages, the cost of CVD is expected to increase significantly.

Heidenreich et al produced a detailed methodology to project and predict the future costs of CVD and related diseases from 2010 to 2030 (Table 1). [55] The CVD conditions that Heidenreich et al included in their analysis were hypertension, CHD, heart failure, and stroke. [55]

Table 2.1. Projections of Crude CVD Prevalence (%), 2010-2030 in the United Stated (Heidenreich, Trogdon et al. 2011)

Year	All CVD*	Hypertension	CHD	HF	Stroke
2010	36.9	33.9	8.0	2.8	3.2
2015	37.8	34.8	8.3	3.0	3.4
2020	38.7	35.7	8.6	3.1	3.6
2025	39.7	36.5	8.9	3.3	3.8
2030	40.5	37.3	9.3	3.5	4.0
% Change	9.9	9.9	16.6	25.0	24.9

CVD indicates cardiovascular disease; CHD, coronary heart disease; HF, heart failure.

*This category includes hypertension, CHD, HF, and stroke.

The primary data source utilized by Heidenreich and his colleagues was the 2001-2005 Medical Expenditure Panel Survey. [55] Cost associated to each CVD condition was calculated as the difference between predicted expenditures for an individual with the condition compared to an individual without the condition. [55] Total direct (Table 2.2) and indirect (Table 2.3) medical costs of CVD were estimated by multiplying the per person cost of each CVD condition by the projected number of individuals with the condition. [55]

Table 2.2. Projected Direct (Medical) Costs of CVD, 2010-2030 (in Billions 2008$) in the United Stated (Heidenreich, Trogdon et al. 2011)

Year	All CVD*	Hypertension	CHD	HF	Stroke	Hypertension as Risk Factor†
2010	$272.5	$69.9	$35.7	$24.7	$28.3	$130.7
2015	$358.0	$91.4	$46.8	$32.4	$38.0	$170.4
2020	$470.3	$119.1	$61.4	$42.9	$51.3	$222.5
2025	$621.6	$155.0	$81.1	$57.5	$70.0	$293.6
2030	$818.1	$200.3	$106.4	$77.7	$95.6	$389.0
% Change	200	186	198	215	238	198

CVD indicates cardiovascular disease; CHD, coronary heart disease; HF, heart failure.

*This category includes hypertension, CHD, HF, stroke, and cardiac dysrhythmias, rheumatic heart disease, cardiomyopathy, pulmonary heart disease, and other or ill-defined "heart" diseases. It does not include hypertension as a risk factor.

†This category includes a portion of the costs of complications associated with hypertension, including CHF, CHD, stroke, and other CVD. The costs of hypertension as a risk factor should not be summed with other CVD conditions to calculate the costs of all CVD.

Table 2.3. Projected Indirect (Lost Productivity) Costs of CVD, 2010-2030 (in Billions 2008$) in the United Stated (Heidenreich, Trogdon et al. 2011)

Year	All CVD*	Hypertension	CHD	HF	Stroke	Hypertension as Risk Factor†
2010	$171.7	$23.6	$73.2	$9.7	$25.6	$25.4
2015	$195.7	$27.2	$82.8	$11.3	$29.7	$29.3
2020	$220.0	$31.0	$92.0	$13.0	$34.0	$33.3
2025	$246.1	$35.1	$101.5	$15.1	$38.9	$37.8
2030	$275.8	$39.8	$112.3	$17.4	$44.4	$42.8
% Change	61	69	53	80	73	69

CVD indicates cardiovascular disease; CHD, coronary heart disease; HF, heart failure.

*This category includes hypertension, coronary heart disease, heart failure, stroke, and cardiac dysrhythmias, rheumatic heart disease, cardiomyopathy, pulmonary heart disease, and other or ill-defined "heart" diseases.

†This category includes the costs of CVD complications attributable to hypertension.

The authors also calculated indirect costs based on lost productivity for two reasons: CVD related morbidity, and premature mortality. [55] This projection determined that approximately 40% of the US population will have some form of CVD by the year 2030. [55] This increase in CVD prevalence will result in the total direct medical costs tripling and indirect costs increasing from $171.1 billion to $275.8. [55]

The AHA estimates that more than one in three adults have one or more types of CVD with approximately 50% of this population over the age of 59 (Figure 2.2)[5]. Within the 45 million adults reporting having a functional disability, heart disease is among the 15 leading conditions that caused those disabilities. Disability was defined as difficulty with daily activities and limitation in ability to do work around the house or on the job. [5]

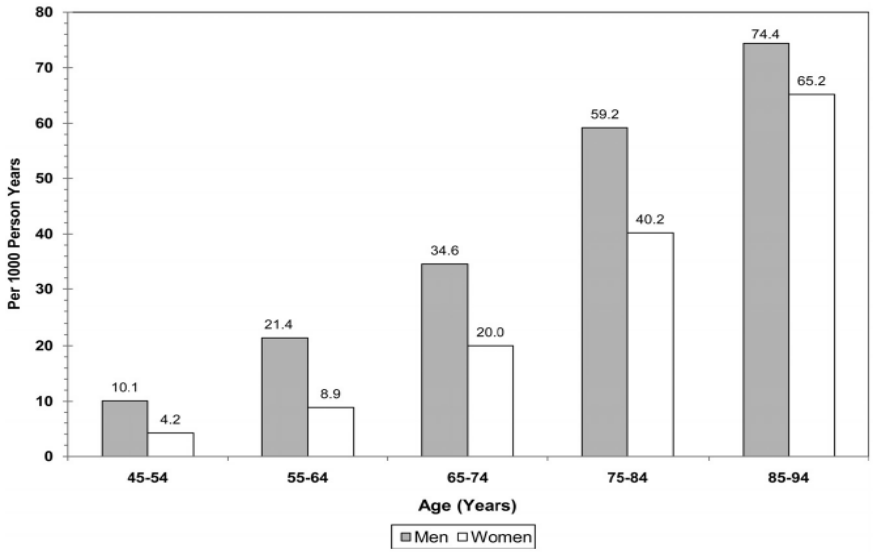


Figure 2.2. Incidence of cardiovascular diseases' by age and sex (Framingham Heart Study, 1980-2003). Coronary heart disease, heart failure, stroke, or intermittent claudication. Does not include hypertension alone. (American Heart Association 2013)

Quality of Care

Institute of Medicine defines quality of care as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge." [58] There are six specific domains that quality of care envelops: safety, effectiveness, patient-centered, timely, efficient, and equitable.

Effective care involves providing scientifically based services for those individuals that could benefit while refraining from causing harm to those who will not benefit. [5] Medicare data from July 2005- June 2008 was employed to determine the 30-day mortality and 30-day readmission after hospitalization for heart failure and acute myocardial infarction. [59,60] The results showed the median risk-standardized mortality rate was 11.1% for heart failure and 16.6% for acute myocardial infarction. The median

risk-standardized readmission rate was 24.4% and 19.9% for heart failure and acute myocardial infarction, respectively. [59,60]

Timely care is an integral factor of any CHD service and is an important service for health care and other industries to focus on. A study titled Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) depicted that for non-ST-elevation myocardial infarction (NSTEMI) patients, the median delay from symptom onset to hospital presentation was 2.6 hours. This was significantly related to within-hospital mortality and did not change from 2001-2006. [61]

Biological Mechanisms

CHD is the accrual of plaque in the arteries of the heart [6] that supply the heart with blood to maintain normal function. The accumulation of plaque narrows the heart's arteries forcing the heart muscle to work harder. The form of CHD depends on the extent of plaque build-up, reduce blood flow, and damage caused to the heart muscle. The deprivation of oxygen to the heart muscle may create dead muscle cells or scar tissue to form, decreasing the pump efficiency of the heart and often the accumulation of blood on the right side. Another main cause of CHD is the depositing of fat beneath the endothelium reducing the elasticity of arteries. Decreased elasticity coupled with high blood pressure could lead to the artery hemorrhaging, also called an aneurysm.

Lipoprotein lipase (LPL) has been linked to the risk of CHD. [62] Many studies have documented strong inverse relationship between LPL activity and CHD [62]. Previous literature has reported even slight reductions in LPL activity have increased the relative risk for mortality or CHD five times higher compared to healthy controls. [63] LPL is an

enzyme essential for lipolysis of triglycerides and can have various effects on metabolism. [64,65] Jensen et al investigated that overexpressing LPL in the muscle fat of mice would prevent feeding-induced obesity by diverting the lipoprotein-derived triglyceride fatty acids away from being stored by the body and would then, in turn, be oxidized by the muscle. [65] Mice were examined before and after the high fat feeding intervention. At the conclusion of the 13 week high fat feeding, the mice that were targeted for overexpression of LPL in skeletal muscle had lower diet-induced lipid accumulation. [65]

A more recent rat study focused on three long-standing biological mechanisms associated with CHD: physical activity, insulin sensitivity, and fat storage. [66] Booth et al employed a wheel-lock model on the group of rodents. The wheel-lock model was to simulate the physiological changes that take place when there are changes from high physical activity levels to a more sedentary lifestyle. [66] Four week old rats were allowed access to running wheels for 3 weeks where they were running an average of ~5km/day by the third week. [67] The rats were then divided in to four groups: sedentary (rats who never run), and rats with their wheels locked for 5, 29, or 53 consistent hours. The group of rats with a wheel-lock for 5 hours was classified as the referent or healthy group. The sedentary group and the group that experienced wheel lock for 53 hours showed a significant reduction in insulin sensitivity compared to the referent group. Booth et al's findings are concurrent with previous human studies that depicted a loss of whole-body sensitivity at 38 and 60 hours after termination of endurance training. [68,69] Figure 2.3 shows decreased insulin sensitivity in muscles diverts energy away from muscle

glycogen synthesis [70] and may cause lower mitochondrial density in skeletal muscle resulting in metabolic dysfunction [67].

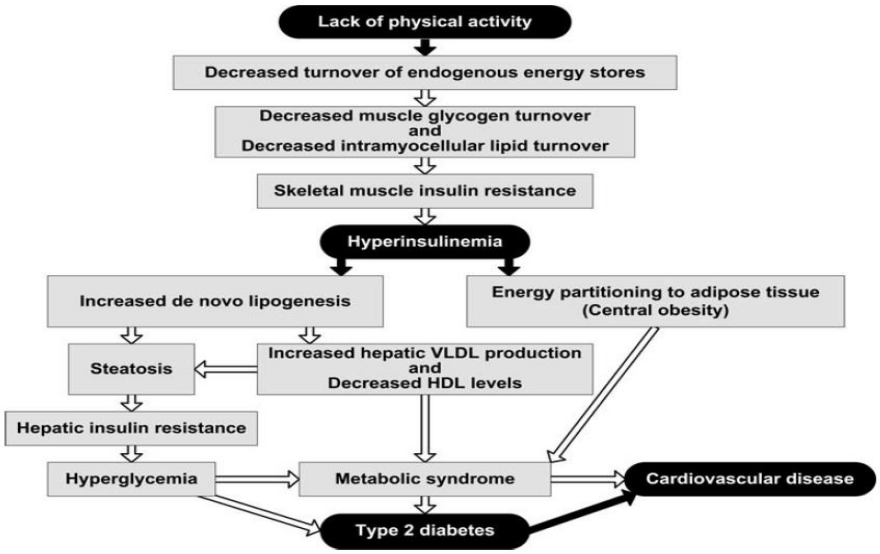


Figure 2.3. A hypothetical sequence to type 2 diabetes is shown (see text for description) (Booth, Laye et al. 2008)

Patient History: Overview

CHD has substantially decreased worldwide in the past 30 years [7,8] primarily due to the improvements of modifiable lifestyle characteristics. [9,10] The modifiable lifestyle characteristics include smoking, high blood pressure, high cholesterol, physical inactivity, cardiorespiratory fitness, body mass index, and diabetes mellitus.

Patient History: Smoking

Doyle et al published one of the first studies examining the association between smoking and CHD. [71] Doyle published findings derived from two prospective studies: The Framingham Study and the Albany, New York Civil Servant study and had a combined study population of over 1,800 men without CHD. [71] The study concluded that

while problems with blood pressure and cholesterol were absent, the participants that reported being a smoker had an increased risk of CHD mortality compared to non-smokers. [71]

An American Cancer Society Cancer Prevention Study compared two different groups derived at different time points with a 20 year gap between them: group one was surveyed between 1959-1965 while group two was surveyed between 1982-1988. [11] The survey of these volunteers in both groups showed that there was a noticeable decline in deaths related to CHD between the two sampling periods. Although both lifelong nonsmokers and smokers at enrollment experienced a decline in CHD mortality, the smokers at enrollment still had a higher mortality risk. [11]

This decreasing prevalence of smoking continues. A recent 2012 article published in the American Journal of Public Health reported similar results from the Minnesota Health Study[72]. The Minnesota Health Study is a population-based cross-sectional study to examine the trends of risk factors associated with cardiovascular disease. The age-adjusted prevalence of smoking significantly decreased more than 15% in both men and women (p-value<0.001) .[72] National studies present similar results. [73]

Patient History: High Blood Pressure

Elevated blood pressure creates more strain for the heart which can lead to thickening and rigidity of the muscle [6]. This stiffness significantly increases an individual's risk for a CHD. High blood pressure can also subject an individual's arteries to increase force that creates microscopic tears in the walls that may develop in to scar tissue. [6] This scar tissue creates a lattice for plaque to accumulate within the artery and

may eventually lead to a partial or full blockage. [6] Most deaths related to high blood pressure are attributed to CHD .[13]

An important cause of the decrease of CHD mortality in recent years is improvement of blood pressure management. [14] This also is supported by a recent publication on a population based Canadian study. They reported a 1.4 mmHg decrease in mean systolic blood pressure from 1994 to 2005 that could be associated with a 20% reduction in CHD deaths. [14 9] Myocardial ischemia is common in patients with hypertension. [16,74,75] In early patients with hypertension, decreased ventricular relaxation during diastole impairs the heart's ability to fill [76] while the more severe hypertensive cases experience myocardial wall thickness. [16] A continued decline in ventricular function could lead to heart failure. Reports from the Framingham study showed that hypertension was the primary cause of congestive heart failure for 35% of cases. [77]

Patient History: High Cholesterol

Cholesterol is a substance that contributes to plaque formation .[12] High cholesterol coupled with high blood pressure and scar tissue formation within arteries may increase an individual's risk for CHD. [6,13]

The aforementioned Canadian study also reported the prevention of over 1,700 CHD deaths due to a 23% reduction in mean cholesterol level. [14] Data from the National Health and Nutrition Examination Study depicted a decrease in the mean of total cholesterol in the United States between two survey time points: 1988-1994 and 1999-2000. [78] Hypercholesterolemia is an asymptomatic disease and regular blood screenings are important for detection. [6] Ford et al reported that nearly 60% of 20-44 year olds have ever had their cholesterol checked while 85% of 45-64 year olds have completed

screening. [78] Ford also reports that those individuals reporting being diagnosed with hypercholesterolemia, only a total of 24% were regularly treating their high cholesterol (≥6.2 mmol/L), with men reporting a high prevalence of treatment compared to women. [78]

Patient History: Diabetes mellitus

When food is consumed, it is usually broken down in to sugar for the body's energy source. The pancreas produces insulin that enables the cells within the body to utilize these sugars. [6] Diabetes is diagnosed when the body cannot adequately utilize these synthesized sugars because of 1) reduced insulin production within the pancreas, or 2) the body becomes insulin resistant. [6] Research shows that individuals with diabetes and hypertension have a higher incidence of heart disease compared to those with diabetes or hypertension alone. [16] Diabetes can cause impairment in the cardiac muscle that may lead to cardiomyopathy, congestive heart failure, or ischemic heart disease and can increase the 5-year mortality rate after a myocardial infarction. [16] Diabetic patients without heart disease can experience abnormal diastolic function.[79]

Prevention of diabetes is crucial. Obesity and physical inactivity can increase the risk of diabetes in men and women. [80-82] Men and women with diabetes are at an increase for CHD. [83,84] Sullivan et al employed the Medical Expenditure Panel Survey to determine the association between diabetes and related comorbidities among overweight and inactive adults. [82]The study was a survey conducted on a representative sample from the United States from 2000-2002. Sullivan reported that inactive and obese participants were 5.6 (95% CI 4.2-7.8) times more likely to be diagnosed with diabetes and heart disease than active participants with a normal BMI (20.0-24.9 m/kg^2). [82]

Patient History: Physical Inactivity

Physical inactivity is defined by the lack of voluntary movement of skeletal muscles that results in energy expenditure. [85] and has been shown to cause chronic diseases [32] such as CHD. Physically inactive people have twice the risk of CHD compared to physically active people. [31] Physical activity has various physiological mechanisms to that lead to the prevention of CHD through the improvement of blood pressure, cholesterol levels, and glucose tolerance. [31,32]

Regular physical activity promotes higher levels of high density lipoproteins that help control low density lipoproteins, improve the efficiency of pumping in the heart, and retard clotting formation within arteries. [6,32]

Patient History: Low Cardiorespiratory Fitness

Cardiorespiratory fitness is associated with the ability of respiration and circulation to supply oxygen throughout the body during sustained physical activity. [85 86] Research from the Aerobics Center Longitudinal Study (ACLS) has examined the independent effects fitness has on all-cause and CVD mortality in men [43,46,87-89] and women; [90 34] results that may be more robust across populations than fatness. [91] Lee et al reported that lean, unfit men had three times higher risk of dying from CVD(RR=3.16, 95% CI 1.12, 8.92) compared to lean, fit men. [46] Lee also reports that obese, fit men's risk for CVD death was not significantly different than lean, fit men. [46]

A meta-analysis was published where the authors analyzed 16 different cohorts with combined person-years over one million. [85] Williams' meta-analysis reported that fit individuals have a lower risk for CHD compared to unfit individuals, which is congruent

with previous findings. [43,46,88] The association between CRF and CHD will be discussed in more detail later in this chapter.

Patient History: Overweight and Obesity

Overweight and obese status are based on a person's body mass index. Body mass index (BMI) was developed by Adolphe Quetelet and is based on an individual's body weight and height (weight in kg/height in meters^2). [92] Overweight is defined as a BMI of 25.0-29.9 and a BMI of 30.0 or greater is classified as obese. The positive trends in blood pressure and cholesterol control have unfortunately been partially offset by the increasing trends in obesity. [14] The prevalence of overweight and obesity has increased across the world, especially in the United States. [93]

Excess weight can lead to an increase in uncontrolled blood pressure which, as previously stated, puts more strain on the heart muscle. A prospective study conducted with more than 115,000 female registered nurses showed that a higher BMI increases the risk for CHD. [94] This nurses' cohort also showed that weight gain after 18 years of age increases the CHD risk for middle-aged women. [94] The relative risk for women with experiencing 20 or more pounds of weight gain since age 18 was 2.7 (95% CI 2.2-3.2) compared to women who changed less than 5 pounds since they were 18. [94] A meta-analysis involving 31 cohorts concluded that calendar periods had no influence on the relationship between BMI and CHD and that the strongest affect was attributed to the age of the population. [93]

Patient History: Family History and Genetics

First degree relatives (siblings, offspring) share roughly 50% of their genetic variation. [5] Individuals within a specified racial/ethnic group are more likely to share their genetic variation within their demographic group compared to other individuals outside their demographic group. [5] Roger et al also reported that 13.3% of adults 20 years old or greater reported having a first degree relative with a heart attack or angina before the age of 50. [5]

One limitation of investigating this relationship between family history and heart disease mortality worth noting is survival bias. More plainly, the risk for heart disease increases with age; individuals without a family history of heart disease may simply live longer compared to those who have a family history. Another limitation was the potential for recall bias. The Framingham Study performed a multigenerational cohort study collecting information on various health outcomes and behaviors. They reported that among those participants with documented parental history of heart disease, only 75% accurately reported their family history when asked. [5]

Brown et al utilized the longitudinal design of the Framingham Study and their inclusion of spouses and offspring of original participants to examine the heritability of phenotypic determinants of CVD. [95] The study stratified on three age groups (Age Group 40 ± 9, Age Group 55 ± 5, and Age Group 70 ± 9) and focused on determining the strength of heritability of four major CVD risk factors: BMI, height, weight, and systolic blood pressure. [95] The study found that BMI (h^2=0.64), weight (h^2=0.63), and height (h^2=0.88) exhibit high heritability when stratified on age. [95]

Other heritability studies from FHS shows moderate heritability in other CVD risk factors such as diastolic blood pressure (h^2=0.39), [96] subcutaneous abdominal fat (h^2=0.57), [97] HDL cholesterol (h^2=0.52), [98] LDL cholesterol (h^2=0.59), [98] and total cholesterol (h^2=0.57). [98]

Heritability (h^2) is the ratio (measured on a scale 0 to 1) of genetically caused variation to the total variation of a trait or measure. As h^2 approaches 1, the heritability becomes stronger. [95] Heritability of a trait is the proportion of observable differences in a trait between individuals within a population that is due to genetic differences.

Treatment

Various treatment options for CHD are available depending on the severity of the problem and the underlying cause. The first form of treatment is to reduce blood pressure through the employment of drug therapies that regulate heartbeat, normalize cholesterol, or prevent blood clotting. When addressing high blood pressure, physicians also need to be aware of hypercholesterolemia and control this condition through lipid-lowering drugs. [99] Shepherd reported that controlling for high cholesterol significantly reduces the risk of a nonfatal myocardial infarction (p-value<0.0001) and produces a 32% (p-value=0.033) reduction in death from CHD. [99]

More serious treatment options are available for more severe CHD cases such as by-passing a failed artery in the heart (heart by-pass), implementation of a stint or balloon to clear an arterial blockage (angioplasty), or a complete organ transplant for extreme cases. [6]

Inpatient cardiovascular operations and procedures increased 22% between 1999 and 2009. [5]

A comparison analysis of Medicare data from 1992 and 2001 depicted that racial disparities within the high-priced CVD treatment procedures was still evident [100] although minimizing in some treatment areas. In 1992 the procedure rate difference between White males receiving a coronary artery bypass graft compared to Black males was 6.29 (in favor of White males). This disparity between White and Black males was reduced in 2001 to 5.69, a non-significant 0.60 reduction (according to a multivariable linear regression). [100]

The recent impression cardiothoracic surgeons have is that patients being referred for coronary artery bypass graft are, on average, "sicker and older" than patients referred ten years prior. [101] This shift in treatment can be explained partly by extensive previous literature showing that lower risk patients that may only have one or two-vessel blockage benefit more from percutaneous coronary intervention [102] while clinical trials document that patients with a higher baseline risk (usually with triple-vessel disease) are better treated with coronary artery bypass graft compared to percutaneous coronary intervention. [103] Ferguson et al analyzed the data from The Society of Thoracic Surgeons National Cardiac Database from 1990 to 1999. This database included more than 1.5 million adult cardiac procedures and 520 sites. [101] The extensive analysis showed a decline in risk-adjusted mortality as well as the observed vs expected mortality ratio for the patients receiving coronary artery graft bypass. [101]

Risk Scores

Framingham Risk Score

Investigators from the Framingham Heart Study have developed CHD risk equations for physicians to employ in order to predict their patient's risk for developing

of CHD. [22] These equations were derived for the purpose of application on patients free of disease. [23] In 1991, the Framingham Heart Study published an update to the previous risk equations. [22] The more recent equations were derived from a more expansive data base which included older individuals. [22] The most recent risk score also accounts for the influence of high density lipoprotein cholesterol, a variable that the Framingham Heart Study (FHS) has been collecting since 1968. [22]

HeartScore

The guidelines that were first issued by the First Joint Task Force of the European Societies on Coronary Prevention [21] was based on the Framingham Heart Study. [22] The Task Force had a number of concerns basing their risk chart on this study that included: 1) risk function derived from US data and not European based data 2) definition of nonfatal endpoints in Framingham Heart Study differed from other definitions of nonfatal endpoints 3) difficult to adjust the model to account for local variances. [21] The Second Joint Task Force instigated the development of a risk score that was based on European cohorts in 12 different countries. [21] The result was a sex and age stratified risk chart that assessed the individual's smoking history and cholesterol profile. This risk chart is aimed to estimate the total cardiovascular risk rather than just CHD [21] and enable its utilization in different European countries. Although this was a risk score based on several cohorts throughout Europe, the HeartScore still neglects to account for strong predictors of CVD such as a diabetes diagnosis [80-82] that are included in the FRS.

Prospective Cardiovascular Münster (PROCAM) Study.

Assmann et al reports that there are certain limitations to the Framingham Heart Study's risk chart and that it might not account for family history or triglycerides [20]. The

completion of the Prospective Cardiovascular Münster Study (PROCAM), which consisted of a cohort of middle-aged men, allowed for a risk score to be compiled to address Framingham's limitations. PROCAM accounts for age, low density lipoprotein, high density lipoprotein, triglycerides, smoking status, diabetes diagnoses, family history of myocardial infarction, and systolic blood pressure to create a score ranging from zero to over 60. [20] The PROCAM risk chart adds to FRS by inclusion of family history, but disregards the difference men and women experience with these risk factors. This lack of stratification is caused by PROCAM's limited data on only men that started collection in 1985; compared to Framingham's initiation of data collection 15 years prior. [22]

Summary of Coronary Heart Disease

The mere presence of a risk score does not perfectly correlate with the clinical use and adherence to the risk score. A 2009 report details the findings of physicians' attitudes and adherence to CVD risk scores. [24] Sposito et al administered a survey throughout Europe, Africa, North America, Central America, and South America to physician groups commonly associated with CHD prevention: cardiologists, general practitioners, and endocrinologists. [24] The survey consisted of brief questions describing a hypothetical patient. Forty-eight percent of surveyed physicians indicated that they used a CVD risk score. [24] Among this 48%, the majority of physicians reported they used the FRS while less than a combined 15% specified other risk scores [24] such as HeartScore [21] and PROCAM. [20] A primary reason cited by physician's for not utilizing these risk scores is that "I don't believe they add value to the clinical evaluation." [24] Sposito et al concludes to stress the importance of early identification of CHD risk and the need for

refinement of the current risk scores. [24] It is important to recognize that risk scores can only provide insight in to the risk of CHD and not a robust image. Currently the FRS is the most common CHD risk score implemented throughout the world. [24] FRS has been shown to be applicable in various race and ethnic cohorts. [28] Researchers have attempted to refine the FRS through the addition of other risk factors, only to come up with less meaningful conclusions than the original risk score. [29,104-108] All of these studies had various flaws including data compilation, analysis, or reporting. The current study aims to go beyond these limitations with a more complete, valid data base that will be utilized to initially assess the prediction power of FRS and then expand on its estimation power through the addition of cardiorespiratory fitness.

Overview of Framingham Risk Score

The estimation of risk for cardiovascular disease events can be a dynamic and convoluted task. The FHS wanted to provide a simplified method to predict the risk for initial CHD events for individuals free of disease. [22,25]

Population

The FHS originated in 1948 with a sample of more than 5,000 men and women free of coronary heart disease at the study's initiation and residing in Framingham, Massachusetts. [23] Clinical examinations were conducted every two years. These clinical exams included blood chemistry values, electrocardiogram, blood pressure, physical exam, and a thorough cardiovascular examination. [23]

The original risk score was derived more than forty years ago and has since been updated. In 1991 The FRS was updated utilizing the original Framingham population as

well as the offspring cohort. [22] The inclusion criteria for the population was 1)age 30-74 years at baseline examination; 2)data available on systolic and diastolic blood pressure, cigarette smoking, cholesterol levels, diabetes diagnosis, and electrocardiogram; and 3) individual was free of cardiovascular disease at baseline. [23] This study included more than 5,500 men and women. [22] The Framingham Research group updated the score a few years later in 1998 utilizing the same population from Anderson et al analysis. [25]

Derivation of Variables for Risk Score

Host and environmental factors can contribute to coronary heart disease. These characteristics include atherogenic personal attributes including serum cholesterol levels, blood pressure, and glucose intolerance, lifestyle choices (physical inactivity and nutrition) that may exacerbate these attributes, and preclinical signs for cardiovascular disease. [23] When the risk factor score was updated in 1991, the risk factors considered remained the same: age, systolic blood pressure, diastolic blood pressure, cholesterol (total cholesterol and high density lipoproteins), smoking status, diagnosis of diabetes, and electrocardiogram to determine CHD. [22] Risk scores also took sex in to account based on previous findings that men and women experience different risks for coronary heart disease. [22,23] Blood pressure and cholesterol were defined as continuous variables, smoking status was dichotomized between currently smoking or quit within past 12 months or otherwise, and diabetes was dichotomized as positive or negative diagnosis. [22] Parametric regression analysis was utilized to determine significant association between CHD outcome and the aforementioned risk factors; Values for blood pressure and the ratio between HDL and total cholesterol were analyzed using the log-scale and age for women was transformed in to a quadratic term. [22] The result from the regression model

was translated in to a worksheet that clinicians can employ for the approximation of the five and ten year risk for CHD. [22]

Wilson et al continued to refine this worksheet by comparing the prediction power of continuous risk factors versus categorized risk factors. [25] Blood pressure and cholesterol level were continuous variables for the 1991 worksheet derived by Anderson et al [22] and Wilson categorized the variables on five and four levels, respectively. [25] Systolic and diastolic blood pressure was transformed in to a scale for hypertension based on JNC-V definition; [109] optimal, normal, high normal, hypertension stage I, and hypertension stage II and III. [25] The higher category for hypertension was chosen when systolic and diastolic fell in to different groups. [25] Total cholesterol was defined as <200, 200-239, 240-279, and ≥280 mg /dL; high density lipoprotein was defined as: <35, 35-59, and ≥60 mg /dL; low density lipoprotein was categorized as follows: <130, 130-159, and ≥160 mg /dL. [25] Linear regression was employed to determine the existence of significant trends within each risk factor [25] and then age-adjusted Cox Proportional Hazard Models were applied to test the relationship between the risk factors and the outcome of CHD and assigning point values based on the β-coefficients. [25] Wilson et al tested this categorization method against Anderson et al's 1991 model that utilized continuous variables transformed on the log scale. Sex-specific receiver operating characteristic was generated for each methodology and a plot was generated to determine the difference between each model. [25] No statistical difference in predictive power was found for either method. [25]

Results

The probability for developing cardiovascular disease by age 65 within the Framingham cohort was 37% for men and 18% for women. [23] The score sheet developed by Anderson et al assigns points to each risk factor with a point value ranging from -12 to 19; age is the only risk factor stratified by gender. [22] A more detailed description can be seen in Table 2.4.

Wilson et al refined Anderson et al's score sheets to incorporate the categorized variables with a sex-specific final product summarizing an individual's 10-year CHD risk that may range from 1% to ≥56% (see appendix Figure 3 for an example of this score sheet for men). [25] The refined score sheet produced by Wilson et al envelops the same predictive capability as the continuous model. [22,25] The categorical model also incorporates the categorical approach utilized by JNC-V [109] to measure blood pressure. The categorized score sheet lessens the physician burden by allowing the clinician to utilize either total cholesterol or low density lipoprotein. It is important to note that the Framingham Heart Study was a free-living population based research and the results might be altered if the blood pressure or cholesterol levels are aggressively treated.

Wilson et al also evaluated the possible inclusion of other variables in this risk score. Family history was considered but was found not to be uniformly available within the birth cohort population. [25] The suggestion to include the presence of estrogen replacement therapy for postmenopausal women was made but could not be followed through due to a change in treatment recommendations throughout the decades. [25,110] Regular physical activity and exercise are known to lower your risk of CHD. [39,111,112] The Framingham Heart Study did not capture information on physical activity at the

baseline examination and the Framingham researchers did not discuss the decision not to include other risk factors such as BMI. [25]

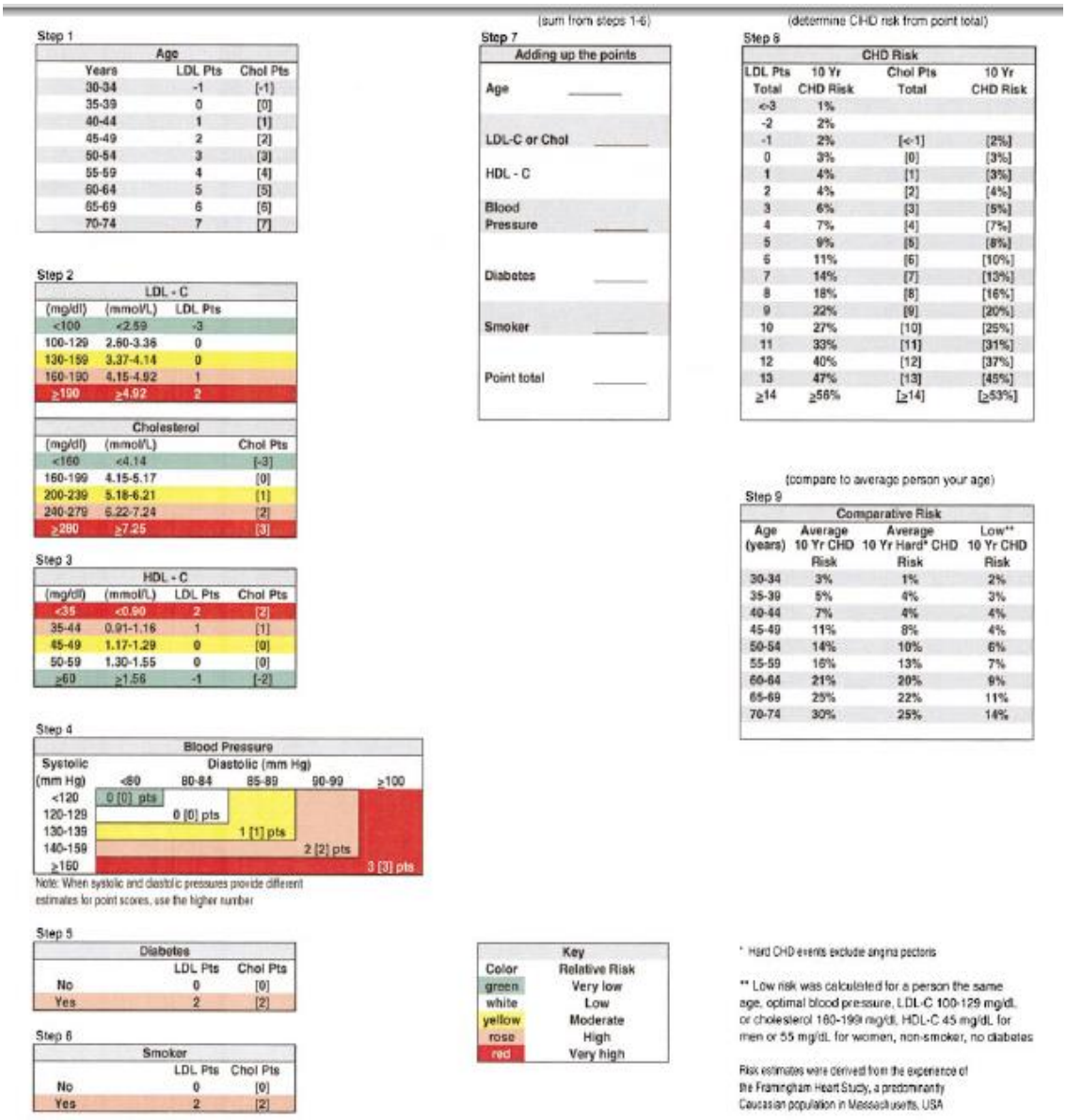


Figure 2.4. CHD score sheet for men using total cholesterol (TC) or low density lipoprotein cholesterol (LDL-C) categories. Uses age, TC (or LDL-C), high density lipoprotein cholesterol (HDL-C), blood pressure, diabetes, and smoking. Estimates risk for CHD over a period of 10 years based on Framingham experience in men 30 to 74 years old at baseline. Average risk estimates are based on typical Framingham subjects, and estimates of idealized risk are based on optimal blood pressure, TC 160 to 199 mg/dL (or LDL- 100 to 129 md/dL), HDL-C of 45 mg/dL in men, no diabetes, and no smoking. Use of the LDL-C categories is appropriate when fasting LDL-C measurement are available. Pts indicates points. [113]

Clinical Utilization and Adherence

Prevention of CHD and the reduction of certain risk factors can be crucial to an individual's life. FRS is a tool physicians can utilize as a primary source of prevention. Sposito et al surveyed physicians across the globe to quantify their perspective on risk scores and the extent that physicians utilize the risk score. Forty-eight percent of respondents self-reported utilizing the FRS more often than other scores. [24] Of the remaining 52% of physicians that reported not using a risk score, approximately 75% of those physicians claimed the risk score 'took up too much time' with another 21% adding that they do not believe the risk score adds anything to the clinical evaluation.' [24]

Physicians were also asked to apply the FRS to a hypothetical scenario. The physicians were asked to rank the risk of the hypothetical scenario with the options as low, intermediate, or high. The results were split across the population with the majority (59%) of physicians ranking the hypothetical case as intermediate; most cardiologists classified this case as low risk. [24] The disagreement using the FRS varies across countries and ranged from 29% to 54%. [24]

Although there is still a large need to change physicians' attitudes regarding the added benefit of risk scores, patient-physician communication and decision making is still the primary focus. Framingham researchers urge clinicians to exercise caution when generalizing the FRS. [22,25] One of the limitations cited from the authors and researchers of the Framingham Study is that the risk measure was created on an American population comprised of Non-Hispanic White individuals with moderate socioeconomic status. Extrapolating the FRS for other populations should be done cautiously.

Validation Within Other Populations

The population recruited for the Framingham Heart Study was derived from a suburb west of Boston and is comprised of primarily Non-Hispanic White men and women. [25] However, since its origination, FRS or similar scores have been applied to various racial and ethnic populations.

The Honolulu Heart Study initiated in 1965with the overall concept of standardizing cardiovascular examination. [26] The cohort is comprised of Japanese men born between 1900 and 1919 and updated their World War II Selective Service Files; the final population with a baseline examination was approximately 8,000 individuals. [26] The majority of this population were first generation immigrants. 50% never attended high school and only 15% had any technical or university training. [26]

Similar to FRS, all men were free of disease with the primary outcomes consisting of: myocardial infarction, acute coronary insufficiency, angina pectoris, and death by coronary heart disease. Independent variables analyzed for inclusion in the final model were the same as FRS with the addition of skinfold of back and arm, and a diabetes diagnosis based on history of diagnosis, urinalysis, or glucose intolerance. [26]

Although the incidence of CHD in the Honolulu Heart Study was half the incidence reported in the Framingham Heart Study, the independent relationships to CHD were very similar. Cigarette smoking, cholesterol levels, and blood pressure all were significant predictors of CHD but glucose intolerance showed no significant relationship. [26]

Similar to the need for standardization of cardiovascular examinations in Japanese American men that Kagan et al explore, researchers from the University of

Oklahoma acknowledged the inadequacy of information on cardiovascular disease on Native American. [114] Lee et al created the Strong Heart Study with an objective to use a retrospective cohort design and create a standardized risk estimate of cardiovascular disease. The study consisted of three components: 1. Mortality survey, 2.Morbidity survey to estimate initial and follow up hospitalizations due to myocardial infarction or stroke, and 3.Clinical examination .[114] The study's population consisted of Native American tribes in Arizona, North Dakota, and South Dakota. Men and women in the study population were segmented in to two age groups comparing 35-44 years (n=5,179) and 45-74 years of age (n=8,072). [114] The Strong Heart Study investigated similar covariates to the FRS and found the only significant predictive capabilities between diabetes diagnosis and a total cholesterol level over 280mg/dL. [28,114]

Validation of the Framingham Risk Factor also was done in the Physician's Health Study. Male physicians in the United States between 40-84 years of age (n=22,071) were randomized in a double-blinded, placebo-controlled, study of beta-carotene and aspirin. [27] Coronary risk factors were collected through questionnaires prior to randomization and surveys were mailed to the participants every 6 months. Individuals would self-report nonfatal CHD incidence, and the non-responders were followed up with a telephone based survey. [27] Stampfer et al also found similar effects of the FRS covariates with the exception of smoking. The Physician's Health Study also reported the significant joint effects HDL and total cholesterol have on CHD's relative risk. [27,28]

D'Agostino et al evaluated the level of agreement between the FRS applied to the Framingham Heart Study cohort and the FRS applied to non-Framingham Heart Study populations. They concluded that the level of agreement was reasonably sound between

the predicted and actual CHD events, with the exception of the study implemented using the Japanese American cohort. [28] The suggestion from D'Agostino and his co-authors for future application of the FRS to non-Framingham Heart Study populations was to obtain the cross-sectional information on risk factor prevalence in conjunction with population rates of CHD over time [28]. However, application of the FRS to dissimilar populations is not the only form of modification researchers have undertaken since the FRS's development.

Potential Risk Score Modifications

There are various risk factors that have a significant relationship with CHD and other cardiovascular events. However, it is not enough for these risk factors to have independent predictive power. The risk factor has to improve the predictability traits that the traditional, FRS, encompasses.

A recent review article assessed various risk scores that claimed to improve the prediction power of the Framingham Risk Score. The review contained studies that include one or more factors in addition to the original variables present in the FRS. [104] Articles were included if they demonstrated analyses comparing the FRS performance against the predictive performance of the modified FRS. [104] The review article included articles making additions to the FRS: BMI, alcohol intake, and racial group; deletions that included diabetes diagnosis and blood pressure definition; and also the modifications to the definitions of smoking to include pack years, and blood pressure to include the prevalent hypertension diagnoses. [104]

Pischon et al investigated the predictive power of C-reactive protein (CRP) and the feasibility to substitute this for low-density lipoprotein cholesterol measure. [29] CRP

has been shown to be a strong independent predictor of cardiovascular events including myocardial infarction and stroke. [115,116] The study population consisted of more than 27,000 participants age 35-65 years in the city of Potsdam, Germany between the years 1994-1998. [29] Myocardial infarction and stroke were self-reported by the study's participants and CRP was measured through highly sensitive assays and then applied to the FRS. [29] Cox regression analysis showed that the FRS plus CRP was a significant prediction model for myocardial infarction and stroke although the inclusion of CRP did not add prediction power to the original FRS. [29] However, a limitation to Pischon et al's publication was the lack of calibration or test for goodness-of-fit through comparison of the FRS to Pischon's revised risk score.

Ingelsson investigated apolipoprotein's predictive power in FRS instead of including low-density lipoprotein. [106] The Framingham Offspring Study population was used for this analysis and the lipid measures were captured after a 12-hour fast. [106] The model including the apolipoproteins was subjected to a test for Goodness-of-Fit as well as model calibration. Goodness-of-Fit was analyzed through the C index produced by the Cox models. [106] The C index is calculated through the summation of the concordance values divided by the number of comparable pairs and has been shown to be analogous to the area under the curve obtained through the receiver operating characteristic curve. [117] The study showed that the apolipoproteins predicted 10 year CHD risk well but there was no significant difference in prediction ability between the traditional cholesterol measures and the apolipoprotein [106] and therefore no benefit of the substitution. This is similar to other findings that attempted to include CRP in the FRS. [105,118]

Instead of attempting to modify the FRS with biological factors, Gallo et al studied the value of augmenting the FRS with social factors that may increase the risk of CHD. [30] Gallo et al. explored the effect of involuntary job loss after the age of 50 may have on 10-year risk on myocardial infarction and stroke. A Cox regression model was used to analyze the first ten years of data in the US Health and Retirement Survey with the outcome as self-reported myocardial infarction or stroke. Job loss was the main independent variable and was treated as a time dependent variable. [30] Gallo and his associates found that individuals who lost their job involuntarily had a 2.48 times higher risk (95% CI 1.49-4.14) for myocardial infarction and a 2.43 high risk of stroke compared to individuals who did not experience involuntary job loss. [30] Although this study displays the predictive ability of the FRS augmented with job loss, Gallo et al did not perform goodness-of-fit tests to determine if this model was truly a better predictor of 10 year cardiovascular disease risk than the original FRS.

Summary of Framingham Risk Score

Framingham Risk Score has been proven to be a strong predictor of CHD risk in dissimilar populations. [26-28,114] Researchers have also attempted to improve the FRS through modification of current risk factors or the addition/deletion of FRS covariates [29,30,105,106,118] although various limitations did not allow these studies to achieve strong agreement with FRS or producing a more robust predictive model than FRS.

During Wilson et al's augmentation of the 1991 FRS model, the analysis tested the addition of other risk factors. [25] Physical activity has been shown to have a predictive effect on CHD [32] although the Framingham Heart Study did not capture this information

at the baseline examination prohibiting its inclusion in the model. [25] Another risk factor that has a well-documented significant protective effect over CHD mortality and non-fatal CHD events is cardiorespiratory fitness. [39,43,87,88,119]

Overview of Cardiorespiratory Fitness

Physical Activity

Physically active individuals have a lower risk for coronary heart disease compared to people less physically active. [54] Berlin et al conducted a meta-analysis on previous literature surrounding physical activity. Her analysis grouped the papers in to work-related and leisure physical activity while examining non-fatal coronary heart disease, fatal coronary heart disease, and myocardial infarction. [54] Summaries and characteristics from 27 different cohorts were analyzed to generate a Mantel-Haenszel Odds Ratio. [54] One pattern that emerged from the data was an inverse dose-response association; increasing physical activity decreased the risk for CHD. [54] In non-occupational physical activity, nine studies reported that low physically active individuals have a pooled relative risk of 1.5 (95% CI 1.4-1.7) for CHD compared to high physically active individuals. [54]

A more recent meta-analysis was done by sports medicine researchers in Japan. Their focus was to determine the effects of physical activity on women's health and preventions of CHD in women, since physical activity has been shown to have different effects in women and men. [33] Oguma and colleagues identified 30 articles originating from 23 different studies, the majority with a cohort study designs. [33] The paper confirmed that physical activity has a protective relationship with CHD in women.

Physical inactivity has been shown to cause CHD. [32,67] A recent review published focused on the biological mechanisms behind the link of physical activity and exercise to CHD. In essence, Booth and his contributors reported that the lack of physical activity or decrease from an active lifestyle to a sedentary lifestyle can cause a decreased turnover of energy stores and decreased lipid turnover causing hyperinsulinemia to occur. [67] Hyperinsulinemia can lead to several other conditions including accumulation of adiposity in the abdominal region, insulin resistance, metabolic syndrome, and type 2 diabetes with the latter two conditions leading to an increased risk of CHD. [67]

Limitations of Physical Activity

As noted in the meta-analysis conducted by Oguma et al, measuring physical activity is not entirely standardized. Physical activity has been categorized differently across studies which may vary the results and makes comparisons to previous findings difficult. [33] In addition to this, the primary components that calculate the volume of physical activity (duration, intensity, and frequency) performed cannot be captured accurately. [33] This type of misclassification is common in physical activity [120] and can dilute the effect size determined between physical activity and CHD. [33] It could be this misclassification that has caused various results of physical activity's effect on CHD and all-cause mortality throughout the literature. [41] Although Kampert et al presented that physical active men had a lower relative risk of all-cause mortality compared to physically inactive men; this significant relationship between physical activity and all-cause mortality was not present in women. [41]

In a meta-analysis that examined 16 cohorts totaling more than 1 million person-years, the authors were able to assess the various affects physical activity and

cardiorespiratory fitness may have on CHD. [85] The risk reduction for fitness was significantly greater than the risk reduction for physical activity. [85] This report discusses how physical activity and cardio respiratory fitness have significantly different relationships on CHD risk, although both are protective factors. [85] Cardiorespiratory fitness (CRF) resolves the limitation of physical activity measures not being able to capture energy expenditure consistently.

Cardiorespiratory Fitness: Definition

Cardiorespiratory fitness (CRF) is defined as the ability of the circulatory system to supply and utilize oxygen during sustained physical activity. [38] CRF is typically measured in epidemiological studies through maximal or submaximal exercise tests [39]. CRF has been shown to be strongly correlated with measured maximal oxygen uptake in women (r=0.94) [121] and men (r=0.92)[122] and is the most accepted index of CRF. [43] CRF is typically categorized using treadmill performances normalized based on age and sex. [43] CRF has been shown to be protective against all-cause mortality even when taking in to account various health conditions. For example, Blair et al described that current smokers with high CRF have reduced relative risk of all-cause mortality compared to current smokers with low CRF. [43] In an observational cohort of more than 6,000 women, low CRF was described as being a significant predictor of type 2 diabetes incidence cases. [34]

Cardiorespiratory Fitness: Comparison with Physical Activity

Usual physical activity habits are the primary determinant of fitness [34] in addition to CRF's genetic component. [35-37] Church et al [123] showed that even a modest exercise

program of 4 kcal/kg a week increase in physical activity was associated with significant improvement in CRF. A recent meta-analysis was performed to compare the effects physical activity and CRF had on CHD. [85] Williams plotted the relative risk (Figure 2.5) as functions of the cumulative percentages within the samples when ranked from least active or fit to most active or fit creating a weighted average for the 16 physical activity cohorts and seven CRF cohorts. [85] Physical activity presented a linear relationship with CHD with a 1% increase in physical activity being equivalent to a 0.0031 reduction in CHD relative risk. [85] CRF also produced a protective effect on CHD risk although, unlike physical activity's relationship with CHD, CRF did not have a linear association with CHD and could be more appropriately described as a dose-response curve with the largest improvement occurring between unfit and moderate fitness. [85] The relative risk reduction for CHD was almost twice as much for CRF than for physical activity (Figure 2.5). [85] This conclusion is similar to other findings and reviews of physical activity compared to CRF and the relationship with CHD and other outcomes such as all-cause mortality. [39,124] In preliminary multivariate modeling analyses using the Aerobic Center Longitudinal Study (ACLS) database, fitness still showed a significant protective association with all-cause mortality even when physical activity and comorbidities were included [39,120].multivariate modeling analysis employing the Aerobic Center Longitudinal Study (ACLS), fitness still showed a significant protective association with all-cause mortality even when physical activity and comorbidities were included. [39,120]

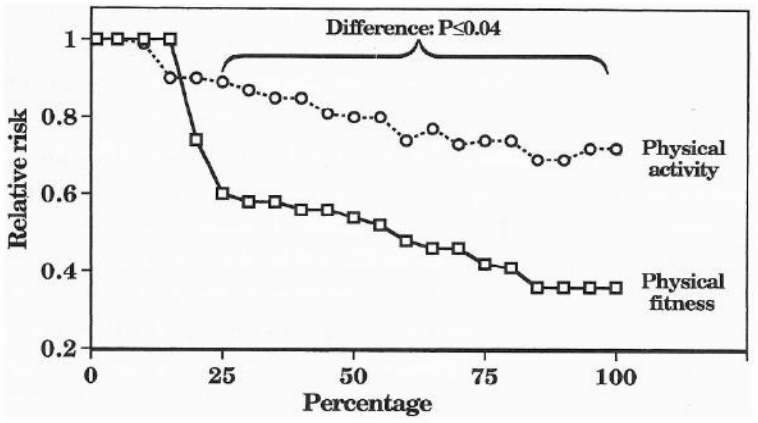


Figure 2.5. Estimated dose-response curve for the relative risk of either coronary heart disease (CHD) or cardiovascular disease (CVD) by sample percentages of fitness and physical activity. Studies weighted by person-years of experience (Williams 2001)

Cardiorespiratory Fitness: Predicting Capabilities

All-Cause Mortality

One of the first articles to publicize the protective relationship CRF may have on adverse health outcomes originated from the Aerobic Center Longitudinal Study (ACLS) report in 1989. [43] More than 13,000 participants, comprised of mainly White males, completed a thorough medical examination that included family history, recording of current medical diagnoses, blood chemistry, and maximal exercise test. The maximal exercise test was used to estimate maximal oxygen uptake and was performed on a treadmill with start position of 0% grade and 88m/min. [43] The treadmill increased to 2% after the first minute, and then 1% each minute for 25 minutes. After 25 minutes was completed, the incline did not change and the speed began to increase 5.4 m/min until termination. The ACLS population was divided in to age and sex specific quintiles. [43] Participants were followed from their first clinic visit through 1985 to determine the occurrence of the event, all-cause mortality. [43] The study population was divided in to

quintiles of fitness and then analyzed for joint effects of fitness and various comorbidities on all-cause mortality. [43] In men with cardiovascular disease, there was a significant protective linear trend relationship between CRF and all-cause mortality. [43] Women with cancer in the unfit group had a relative risk of all-cause mortality of 16.3 compared to women in the fit group. [43]

Diabetes

The Centers for Disease Control and Prevention has predicted that American lifestyle and choices coupled with improved diabetes management, will result in an estimated prevalence of diabetes mellitus of 48.3 million by the year 2050. [125] Obesity and physical inactivity are two strong predictors of diabetes incidence. [80,82,126] A large prospective cohort focused on determining the independent and joint associations CRF and obesity may have on the incidence of type 2 diabetes in American women. [34] More than 140 women developed diabetes in a 17 year follow up period. [34] Age-adjusted incidence rates were calculated for increments of CRF and the results showed that women with a low exercise capacity (<7 METs) had a three times higher risk of developing type 2 diabetes compared to women with a higher exercise capacity (≥10 METs). [34] When the combined effects of CRF and BMI were analyzed, normal-weight (BMI <25 kg/m^2) unfit women (lowest CRF tertile) did not present an increased risk for diabetes incidence while overweight/obese (BMI≥25 kg/m^2) unfit women had twice the risk for diabetes incidence; both groups were compared to the referent group comprised of normal weight fit women. [34]

A similar prospective study with 18 years of follow up was conducted in men [127] and found CRF protective against incidence of type 2 diabetes. Men in the upper two

CRF quintiles with a fasting glucose <100 mg/dL had a 60% decreased risk of developing diabetes compared to unfit men with similar fasting glucose levels, [127] which was similar to findings from other study populations. [44,112,128,129]

Diabetes is not commonly recorded as the primary cause of death. [130-133] A 1992 study reported that, among individuals with a history of diabetes, diabetes was captured as the cause of death only 36% of the time. [133,134] A more recent study from 2006 reported that diabetes was recorded on 39% of death certificates and was only listed as the underlying cause of death on 10% of decedents with diabetes. [135] It is much more likely for cardiovascular disease to be listed as the primary cause of death for individuals with diabetes than for diabetes to be listed as a cause of death. [135]

This limitation in vital statistics has led researchers to investigate all-cause or cardiovascular disease specific mortality within a subpopulation with a diabetes diagnosis. [40,136] All-cause mortality was the outcome of interest for a study published in 2000 investigating the predictive effects of CRF and physical inactivity in men with type 2 diabetes. [136] Average follow-up time for 1,260 diabetic men was 12 years, and it was noted that 180 individuals died during the study period. [136] A fully adjusted model reported that low fit, diabetic men had twice the risk of all-cause mortality compared to fit men. [136] Similarly, physically inactive men with diabetes had 1.7 times higher risk for all-cause mortality compared to their physically active counterparts. [136]

A comparable study including more than 2,300 men in a subpopulation with a diabetes diagnosis but no history of stroke or myocardial infarction; 179 deaths due to a cardiovascular event were identified in this population. [40] When CRF was analyzed as a protective factor while controlling for body mass index, it was shown that low fit males

categorized as normal weight (18.0<BMI<25.0) had a higher risk for CVD-specific mortality (HR 2.7, 95% CI 1.3-5.7) compared to fit males with normal weight. This significant relationship was also present in low fit males classified as overweight (HR 2.7, 95% CI 1.4-5.1) or class I obese (HR 2.8, 95% CI 1.4-5.1) [40]. CRF's protective relationship with type 2 diabetes incidence may be explained through glucose homeostasis. [137,138] CRF could assist in glucose homeostasis by improvement of blood flow, fiber size, or kinetics involved in insulin and noninsulin signaling. [138]

Cancer

A prospective observational cohort was employed to determine the relationship of CRF and cancer mortality. [41] The prospective observational study contains a large group of men (n=25,341) and women (n=7,080) with an average age around 42 years and originating from a middle to upper socioeconomic status. [41] The cohort is also from the ACLS and the method of obtaining CRF is aforementioned. [41,43] This report stratified CRF in to quintiles and concluded a significant protective linear trend for all cancer caused mortality for both men and women. [120] The treadmill maximal exercise test is an objective measure of fitness and minimizes the misclassification common for the subjective, self-reported measures of physical activity. [41,85] However both have shown protective relationships against cancer including prostate, colon, lung, and breast cancer. [139,140] CRF's strong linear protective trend against all types of cancer may be caused through the enhancement of the immune system. [120] However, Kampert et al was careful to note that this protective relationship may be mediated by genetic predispositions. [41]

Self-Rated Health

Self-rated health (SRH) is a subjective measure that is used to capture an individual's perception of their health. This perception can incorporate biological, psychological, and social constructs that may be unavailable to the external observer. [141] SRH has been shown to be independently associated with all-cause mortality. [142] In a recent large cohort study, SRH was also determined to have a dose-response relationship with CRF predicting all-cause mortality [141]. The researchers analyzed this significant protective relationship taking in to account the presence of a chronic medical condition including diabetes, hypertension, cardiovascular disease, and cancer. [141] Men diagnosed with one or more chronic health conditions and a good/excellent SRH experienced a lower risk of all-cause mortality compared to men with one or more chronic health conditions and a poor/fair self-rated health. [141] The relationship between SRH and all-cause mortality was only attenuated when CRF was added to the model. When compared to unfit men reporting poor/fair SRH, fit men with good/excellent SRH had a 58% smaller risk of all-cause mortality. [141]

Quality of Life

Along with CRF's protective effect on diabetes, [34,127] cancer, [41,143] and chronic obstructive pulmonary disease,[144] research has shown the improvement of overall quality of life. [145] Previous epidemiological studies have reported a protective association between CRF and quality of life. [146-148] Martin et al surpassed the conclusions from these studies and investigated the effects RF may have on quality of life with The Dose-Response to Exercise in postmenopausal Women (DREW) randomized controlled trial.

[145] This study population encompassed more than 400 women age 45-75 years. The women were randomized in to four different groups and the Medical Outcomes 26-Item questionnaire was utilized to measure quality of life. [145] At baseline, there were no significant differences in the mean scores of the DREW participants and the national mean. [145] Women were either assigned to a control group that did not perform any exercise, or to one of three physical activity intervention groups that expended 4, 8, or 12 kcal/kg of body weight each week. [145] The results depicted a positive dose-response relationship between CRF and quality of life; this relationship was not attenuated by weight change. [145] As the demographics for the 65 years of age or older population begin to shift, this paper holds important public health implication for this sub-population. The aging population of the United States can benefit from exercise and improved CRF by preventing certain chronic conditions and improving their quality of life.

Coronary Heart Disease

A 1987 review article summarized the protective effects of habitual physical activity and coronary heart disease. [149] The review paper concluded that there was a significant effect between physical inactivity and CHD. [149] The authors continue to state that physical activity is a complex measure without standardization. [149] [150] The lack of standardization leads to imprecise findings with only 66% of the reviewed literature showing a significant relationship. [149] On the other hand, CRF is a very objective measure with a standardized operating procedure and variable definition. [150]

An early study portrayed the significant effect CRF has on CHD risk factors in women. [42] Women ages 18-65 years who completed a comprehensive medical exam

between 1971 and 1980 were included in the regression analysis to determine the relationship between CRF and CHD, a relationship already found to be significant in men. [47-49] The CHD risk factors employed in the analysis were based on the Framingham Risk Score. [23] CRF was shown to have significant impact on the CHD risk factors including current smoking, total cholesterol, HDL cholesterol, and blood pressure. [42]

Ekelund continued the study of this association through the utilization of the Lipid Research Clinics Prevalence Survey. [45] The primary aim of this study was to determine the relationship physical fitness, obtained through a maximal exercise test, has on coronary heart disease mortality. [45] Cox proportional hazard models were used in a cohort of approximately 4,000 men divided in to a healthy group and a group with cardiovascular disease diagnosis. [45] Healthy men with a higher CRF were shown to have a lower CHD and CVD mortality compared to healthy men with low CRF; similarly, men with a CVD history and low CRF are 5.6 times more likely to die from CHD (95% CI 2.5-12.6) or 4.8 times more likely to die from CVD (95% CI 2.5-9.2) compared to men with a CVD history and high CRF. [45] Ekelund et al concluded that mortality was higher in the least fit group regardless of health history and that physical fitness and physical training improve heart rate, heart rate recovery, and improve myocardial oxygen supply. [45] This study provides further evidence to Oja et al's results from a physical training program in men. [47] The men were divided up in to four training groups based on their preference for type of exercise with two groups serving as the control training group whom did not receive any exercise. At the end of the 18 month training, a significant change (p-value <0.001) was seen in the experimental groups regarding their heart rate recovery, and max VO2. [47]

To better assess the risk factors for CHD mortality and the impact CRF may have, Lee et al (1999) conducted an analysis to examine the relationship between body composition, CRF, and CHD mortality. Approximately 22,000 men who completed a medical examination between 1971 and 1989 received a body composition assessment and reached ≥85% of their age-adjusted maximal heart rate during a treadmill test. [46] Body composition of these men was measured either through hydrostatic weighing, skinfold-thickness measurements, or both and percentage of body fat was calculated with Siri's [151] two-component model. Body composition was defined as a three level variable: lean (<25th percentile), normal (25th to <75th percentile), or obese (≥75th percentile). Hazard ratios were adjusted for smoking habit, alcohol use, and parental history of heart disease with the referent group represented by fit, lean men. [46] A significant interaction was reported between body composition and CRF. Unfit lean men had a significantly three times higher risk for CHD mortality compared to fit lean men; unfit men with normal body composition had a 2.94 (95% CI 1.48, 5.83) times higher risk compared to fit lean men. [46] The largest effect was found in unfit obese men who had a four times higher risk for CHD mortality compared to fit lean men. [46] Although there were significantly higher risk of CHD mortality across the body composition groups, this significant relationship was attenuated in fit men. Fit men with a normal body composition had a 1.43 (95% CI 0.77, 2.67) higher risk of CHD mortality compared to fit lean men while fit obese men had a 1.35(95% CI 0.66, 2.76) times higher risk compared to referent group. [46]

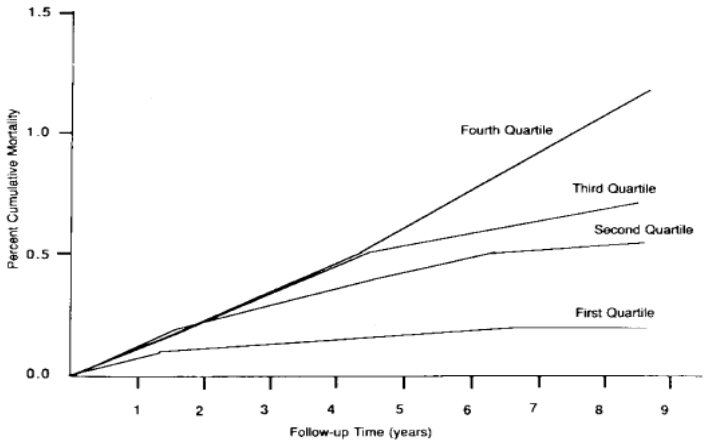


Figure 2.6. Cumulative Rate of Death from Cardiovascular Disease in Health Men, According to Quartiles of Stage 2 Exercise Heart Rate (Ekelund, Haskell et al. 1988)

These findings build on a previous report from Ekelund et al [45] who investigated the relationship between CRF and CHD in asymptomatic men. A treadmill maximal exercise test was used to determine fitness category and the participants were divided in to four categories depending on their heart rate during the second stage of the treadmill test with the fourth quartile representing the least fit individuals. [45] The participants were followed for nine years for event occurrence (CHD mortality). A cumulative growth curve for CHD mortality depicts the most fit group (first quartile) having the least risk compared to the fourth quartile. [45]

The biological mechanisms behind this protective relationship is primarily based on peripheral mechanism [152,153] such as improvements in skeletal muscles and enhancement in arterial oxygen content. [153] Research has shown that CRF can increase the double-product threshold for ischemic ST-segment depression, [154,155] a decrease in the magnitude of ST depression, and a diminished maximal ST depression. [154] CRF may also have a positive effect on coagulation [156,157] and protect against thrombosis. [45]

This protective relationship between CRF, CHD diagnosis, and CHD cause mortality has been demonstrated numerous times. [88,111,119,123,158-161] Despite this strong and continuous relationship, the American Heart Disease and Stroke do not mention CRF's protective effects against CHD in their annual report. [5,6,162]

Cardiorespiratory Fitness: Utilization in Coronary Heart Disease Risk Factor Scores

Barlow et al recently investigated prognostic factors of long-term cardiovascular risk in "low risk" men and women. [163] Low risk for coronary heart disease was defined utilizing the 10-year risk of CHD <10% by the Framingham Risk Score. [163] Through the analysis of cardiorespiratory fitness, Barlow et al showed that a 1-MET increase in CRF resulted in an 18% lower risk of CVD mortality during a 30 year follow up period. [163]

Gupta et al sought to determine CRF's contribution to traditional CHD risk factors [50]. Gupta utilized the ACLS cohort with data ranging from 1970 through 2006. The researchers utilized a traditional CHD risk factor model that adjusted for age, systolic blood pressure, diabetes, total cholesterol, and smoking status [50] and measured the predictability of the traditional model on the ACLS cohort and the predictability of the traditional risk factor score after the addition of CRF. Harrell's C statistics were calculated for each model. All variables included in the traditional risk factor score and all quintiles of CRF were significant with CHD mortality. [50] When comparing the traditional versus CRF augmented model in men, the CRF augmented CHD risk factor model correctly reclassified participants with CHD death based on their 10-year risk [50]. For instance, among male participants with CHD death, the CRF augmented risk model reclassified 49 high risk participants that the traditional model classified as low risk. [50]

A potential limitation of this study is the use of a very basic model to represent the traditional CHD risk factor model. Gupta et al's traditional CHD risk factor model accounts for variables that other popular models, such as the Heart Study, [21] do not while neglecting to include significant CHD risk factors that other models include. A popular CHD risk factor score derived from the PROCAM cohort adjusts for similar covariates in Gupta et al's study with the addition of family history of myocardial infarction, HDL, and LDL. [20] The FRS adjusts for sex similarly to Gupta et al and also includes diastolic blood pressure and high density lipoproteins in their risk calculation. [22]

Each CHD risk factor model has its own specific limitations. Gupta et al reported the improvement in calibration and risk classification CRF added to their 'traditional' risk score derived from the ACLS cohort. [50] Other researchers have taken the FRS and added covariates such as apolipoproteins, [106] C-reactive protein, [29] and social factors. [30] The aforementioned evidence and research states the strong protective effect CRF has on CHD. Previously presented literature also reports the validity of the FRS. The culmination of this literature suggests that the addition of CRF in the Framingham Risk Score may provide a stronger predictive model than the original equation.

CHAPTER III

METHODS

This research encompasses three manuscripts focusing on the predictive power of cardiorespiratory fitness. The overarching goal is to create a prediction equation that includes CRF and is modeled after the Framingham Heart Study's Framingham Risk Score. Each manuscript addresses specific research topics through the utilization of the Aerobics Center Longitudinal Study data.

Aerobics Center Longitudinal Study (ACLS)

ACLS is an ongoing, cohort study that encompasses a large group of men and women. The participants were patients of the Cooper Clinic, where they received a preventative medical examination and counseling on health behaviors during periodic visits. The Cooper Clinic serves anyone who elects to come for an examination and patients come from all 50 states. During the patients' medical examination, they were informed of the ACLS cohort study, asked to participate, and, if they agreed to participate, consented to follow-up surveillance.

The participants were examined at least once during 1970 to 2003 at the Cooper Clinic, Dallas, TX. The cohort consists of mostly individuals within the middle and upper socioeconomic groups with approximately 80% holding college degrees. [41] The mean age of the cohort is 42 years at baseline and consists primarily of Non-Hispanic White

(>95%) individuals. Although a large number of women were enrolled in ACLS, the majority of patients were men (~75%). The following primary inclusion criteria were used:

1. Age at baseline examination between 30-74 years
2. Complete data for outcome and predictor variables
3. Free of CHD diagnosis or cancer diagnosis at baseline

Women were excluded from analysis due to the small proportion of events. The sample population for Hypothesis I is larger compared to the sample population utilized for Hypothesis II and III. The change in sample size is cause by second inclusion item and ensuring there was not missing data. Hypothesis II and III include the CRF variable that is missing in 13.61% of the sample population for Hypothesis I.

While ACLS is not a representative sample of the entire US population, a comparison of median values of specific physiological variables show similarity to representative population data. [164] A comparison between ACLS and two large population based cohorts found that ACLS' results were similar to the results of the Lipid Research Clinics Prevalence Survey and the Canada Fitness Survey. [165] A notable advantage of ACLS' homogeneity is controlling for potential confounding by demographic characteristics such as education, socioeconomic status, and race/ethnicity. Although ACLS' homogeneity characteristic improves the internal validity, generalizations must be made cautiously and future research should be conducted in more diverse populations.

Baseline Examination

Trained technicians followed standardized protocols for each measurement. The baseline clinical exam included a personal and family medical history, anthropometric measurements, a 12-hour fasting blood chemistry including glucose and cholesterol measurements, ECG, blood pressure assessment, and a maximal exercise test [112,164,166]. Smoking was assessed through a standardized questionnaire and participants were classified as current or non-smoker.

CRF was determined using the Balke maximal exercise test [167]. Treadmill time converted to METs is analogous to peak VO2 [121] and is an accepted object laboratory measure of CRF. At initialization of test, the treadmill speed was 88m/min for the first 25 minutes. The initial grade of the treadmill was set at 0%, increased to 2% after the first minute, and then increased 1% grade for the second minute and continued this pattern of progression for each subsequent minute until 25minutes elapsed. After 25 minutes, the treadmill's grade remained constant and the speed increased at the rate of 5.4m/minute until termination of the exercise test. Technicians encouraged participants to give maximal effort. The following regression formula was employed to convert maximal treadmill time to METs [48]:

$$METs = \frac{(1.44 * MinutesOfExerciseDuration) + 14.99}{3.5}$$

One MET is equal to energy expenditure of an average person at rest. [168] Factors other than physical activity may influence both health status and fitness levels through various biological pathways. Because of this, CRF provides an objective measure of recent physical activity habitat compared to self-report physical activity levels; CRF also offers an objective measure of the physiological consequences a sedentary lifestyle may have

and CRF is less prone to misclassification bias. Many ACLS participants have several clinical examinations at varying intervals. Table 3.1 depicts the main assessments included in their clinical exam and interview.

Table 3.1. Data available on Cooper Clinic patients (baseline and repeat visits)

A. Demographics
Age, Sex, Race, Education, Income, Occupation, Marital Status

B. Medical History
1. Medication history
2. Extensive series of questions on past or present diseases/conditions
3. Hospitalizations
4. Physician visits
5. Days lost from work
6. Family medical history

C. Health Habits
1. Smoking history
2. 3-day diet record
3. Brief nutritional pattern questionnaire
4. Alcohol intake
5. Extensive exercise and sports participation questionnaire
6. Weight history

D. Laboratory
1. Maximal exercise treadmill test (ECG, heart rate, and blood pressure during exercise and recovery)
2. Pulmonary function
3. Body composition (7 skinfolds, girths, and hydrostatic weighing)
4. Blood chemistries (lipids, glucose, uric acid)
5. Urinalysis
6. Height and weight
7. Physical examination (complete physician's examination findings including ECG interpretation)

Framingham Risk Score (FRS)

FRS was derived from the Framingham Heart Study, which is an ongoing observational study that initiated in 1948 and primarily recruits residents of Framingham, Massachusetts. [23] The Framingham Heart Study involved clinical exams conducted every other year. The inclusion criteria applied to the Framingham Heart Study to derive the study population were 1)age 30-74 years at baseline examination; 2)data available on

systolic and diastolic blood pressure, cigarette smoking, cholesterol levels, diabetes diagnosis, and electrocardiogram and 30individual was free of cardiovascular disease at baseline. [22] The most recent FRS is presented with categorical variables for hypertension, total cholesterol, high density lipoprotein, smoking, and diabetes. [25]

The main outcome of the FRS was a CHD event defined as a myocardial infarction, coronary insufficiency, or CHD death. These events were recorded from self-report or medical chart review. The original FRS has been updated since its origin in 1976. [23,25] FRS stratifies by sex and adjusts for age. Age is treated as a continuous variable within the survival model. Anderson et al [22] updated the FRS and the risk factors included the continuous variables: systolic blood pressure, diastolic blood pressure, total cholesterol, high density lipoproteins, and dichotomous variables for smoking status and diagnosis of diabetes. In 1998 all risk factors, with the exception of age, were analyzed as categorical variables. [25] The predictability of the categorical FRS was compared to the FRS containing the continuous variables and the results showed that the more recent version maintained Anderson et al's predicting power [25]. The risk factors included in the age-adjusted analysis were: hypertension, total cholesterol, high density lipoprotein, smoking status, and diabetes diagnosis.

ACLS Measurements

Definition of Outcome

Coronary heart disease (CHD) was the primary endpoint being investigated. CHD was defined as the self-report of myocardial infarction or revascularization (including, bypass, coronary balloon, angioplasty, or stent) or death due to CHD. Deaths among study participants were identified from the National Center for Health Statistic's National

Death Index. International Classification of Disease (ICD) codes: 410.0-414.0 (Ninth edition) and I20-I25 (Tenth edition), were used to identify CHD as the primary cause of death. In accordance with FRS' follow-up time definition, the maximal follow up time was 12 years. The 12-year follow up was used in the regression and survival analysis and then adapted to provide a 10-year CHD incidence estimates.

Derivation of Covariates

The covariates considered for analysis in the ACLS population mimicked the variables included in the recently-updated Framingham Risk Score. Hypertension (HTN) was defined through the categorization of systolic blood pressure and diastolic blood pressure. Systolic blood pressure was categorized in to five levels: <120 mm Hg, 120-129 mm Hg, 130-139 mm Hg, 140-159 mm Hg, or ≥160 mm Hg. Diastolic blood pressure was categorized in to five levels: <80 mm Hg, 80-84 mm Hg, 85-89 mm Hg, 90-99 mm Hg, ≥ 100 mm Hg. When an individual's blood pressure fell into different categories for systolic and diastolic blood pressure, the higher category was chosen for categorization. (For example, if a participant's blood pressure was 130/80 (SBP/DBP), the corresponding categories for systolic blood pressure would be 2, and the diastolic blood pressure category would be 1. To determine the HTN category, the highest classification would be chosen, in this example the HTN categorization would be 2.) HTN definition was made without regard to a participant's use for antihypertensive medication. The definition of HTN parallels FRS' definition. [22,25]

Total cholesterol was grouped in to four levels: <200 mg/dL, 200-239 mg/dL, 240-279 mg/dL, and ≥ 280 mg/dL. High density lipoproteins were categorized as: <35 mg/dL, 35-59 mg/dL, and ≥ 60 mg/dL. A 12-hour fasting glucose >140 mg/dL classified

an individual as having diabetes. Smoking status was dichotomized as current or non-smoker. All categorizations and definitions were analogous to FRS' covariate groupings.[25]

The volume of participant-level measurements is rare and unusual in a large, single center epidemiological study. The major assessment variables cover a range of clinical and physical examination data, although limitations are still apparent. One limitation of ACLS' measurements is the lack of nutritional and dietary measures. A second limitation is the absence of participant's medication information. Despite these limitations, the analyses employed for this research do not require either piece of data.

The ACLS study protocol was annually reviewed and approved by the Cooper Institute Institutional Review Board.

PAPER 1: Framingham Risk Score applied to the Aerobic Center Longitudinal Study (ACLS)

Purpose

This manuscript will address Hypothesis 1: the Framingham Risk Score will be a significant predictor of CHD events for men within the ACLS population.

Study Design

Analysis were performed using the ACLS prospective cohort. Predictor variables were determined at baseline examination and each participant and follow-up was conducted to ascertain information on the occurrence (or non-occurrence) of a CHD event.

Study Population

Men who completed a baseline examination at the Cooper Clinic in Dallas, TX between 1970 and 2003 and were free of CHD were included in the study population. Participants were volunteers and consented to follow up examinations prior to baseline exam. The exclusion criteria initially applied omitted individuals age less than 30 years or older than 75, with a body mass index less than 18.5kg/m^2, a history of CHD, stroke, or cancer at baseline, and follow-up time less than one year. Individuals needed complete data on all variables of interest: systolic and diastolic blood pressure, cigarette smoking, cholesterol levels, diabetes diagnosis, and electrocardiogram. Participants must have completed a baseline examination between 1970 and 2003 and all participants were followed until death or 31 December 2003. Men comprised 76% (n=34,557) of the study population (n=45,833). Women were excluded from analysis due to the small number of CHD events (n=45) among this subgroup. The average age for men was 44 years. The majority of participants were Non-Hispanic, white, and well-educated. The Cooper Institute's Institutional Review Board annually reviewed and approved the ACLS protocol.

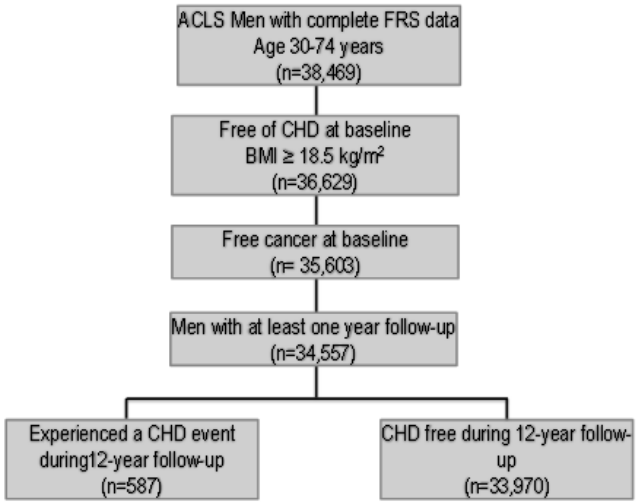


Figure 3.1. Study flow for Paper 1 and Aerobic Center Longitudinal Study (ACLS) inclusion criteria depicting final sample size and coronary heart disease (CHD) event frequency. Men with complete Framingham Risk Score (FRS) data and body mass index (BMI) ≥ 18.5 kg/m^2 were included in the analysis.

Measures

Measurements from the ACLS cohort involved in this analysis were previously described in detail at the beginning of Chapter III. The following is an overview of the variables used to investigate Hypothesis I.

Definition of Outcome

The outcome of interest was coronary heart disease (CHD). This event was defined as the self-report of myocardial infarction or revascularization (including, bypass, coronary balloon, angioplasty, or stent) at a return clinic visit or on a mail-back questionnaire; or death due to CHD. The time to follow-up began at the baseline examination and continued until CHD event or 1 July 2004. Deaths among study participants were identified from the National Center for Health Statistic's National

Death Index. International Classification of Disease (ICD) codes: 410.0-414.0 and I20-I25, were used to identify CHD as the primary cause of death. In accordance with FRS follow-up time definition, the maximal follow up time was 12 years.

Predictor Variables

The covariates considered for analysis in the ACLS population mimicked the variables included in the Framingham Risk Score. Age was defined as a continuous variable. Hypertension (HTN) was defined through the categorization of systolic blood pressure and diastolic blood pressure. Systolic and diastolic blood pressure were categorized in to five levels. When an individual's blood pressure fell in to different categories for systolic and diastolic blood pressure, the higher category was chosen for categorization. HTN definition was made without regard to a participant's use for antihypertensive medication. The definition of HTN parallels FRS' definition that utilized the measured systolic and diastolic blood pressure. [22,25]

Total cholesterol and high density lipoprotein measures were grouped in to four levels. : <200 mg/dL, 200-239 mg/dL, 240-279 mg/dL, and ≥ 280 mg/dL. High density lipoproteins were categorized as: <35 mg/dL, 35-59 mg/dL, and ≥ 60 mg/dL. A 12-hour fasting glucose >140 mg/dL classified an individual as having diabetes. Smoking status was dichotomized as current or non-smoker. All categorizations and definitions were analogous to FRS' covariate groupings. [25]

Statistical Analysis

Descriptive statistics were generated to compare the ACLS population to the Framingham Heart Study population. The variables compared for the male populations of each cohort were mean age, percentage within each category in HTN, total cholesterol,

and HDL, percent diabetic, and percent whom are current smokers. Univariate Cox Proportional Hazard models were performed for the outcome of interest and each covariate to determine each characteristic's prediction power. Survival analyses were conducted to determine the 5 and 10 year CHD risk for the ACLS male population. The full, age-adjusted survival model contained the outcome and all covariates. Statistical tests were two sided and a p-value<0.05 signified statistical significance.

Predictive accuracy for both models, 10 and 20-year CHD risk, was determined through the concordance-statistic (c statistic) associated with the receiver operating characteristic (ROC) curve. The ROC curve estimates the concordance probability between the observed and expected number of CHD events. The Hosmer-Lemeshow statistic is used to assess calibration and is a chi-square test by sorting the sample by estimated probability of success. [169] A limitation of the Hosmer-Lemeshow test is that it is not recommended for sample sizes larger than 25,000. A sensitivity analysis was performed following Paul et al's (2013) recommendations and the ACLS sample (n=34,557) was randomly divided in to two equal groups. The c-statistic from the randomly divided sample cohorts and the full cohort were compared and no significant statistical difference was found. All analyses were performed with the statistical software, SAS version 9.3 (SAS).

PAPER 2: Augment the Framingham Risk Score (FRS) applied to the Aerobic Center Longitudinal Study (ACLS) with the addition of Cardiorespiratory Fitness (CRF)

Purpose

This manuscript will address Hypothesis 2: the CRF variable will significantly improve the Framingham Risk Score predictive ability of CHD events for men within the ACLS population.

Study Design

Survival analysis and predictive modeling was performed using the ACLS prospective cohort. Predictor variables were determined at baseline examination and each participant and follow-up was conducted to ascertain information on the occurrence (or non-occurrence) of a CHD event.

Study Population

The current analyses include men from the Cooper Clinic who completed a baseline medical exam between 1970 and 2003. Participants between the ages of 30-74 were included in the analysis. Participants were excluded if they reported a history of CHD, stroke, or cancer at baseline or did not have data available on systolic and diastolic blood pressure, cigarette smoking, cholesterol levels, diabetes diagnosis, and electrocardiogram. Participants were patients of the Cooper Clinic and asked to participate in ACLS. Individuals were only included if they achieved ≥85% age-predicted maximal heart rate at each visit. Participants were primarily from the middle to upper socioeconomic group and had a median age of 44 years. The Institutional Review Board at Cooper Clinic, Dallas, TX annually reviewed and approved ACLS' protocol.

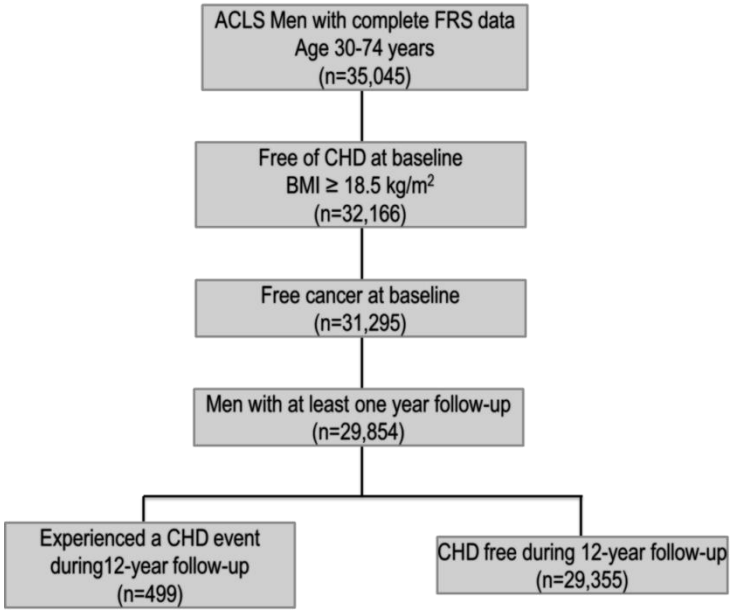


Figure 3.2. Study flow for Paper 2 and Aerobic Center Longitudinal Study (ACLS) inclusion criteria depicting final sample size and coronary heart disease (CHD) event frequency. Men with complete Framingham Risk Score (FRS) data and body mass index (BMI) ≥ 18.5 kg/m^2 were included in the analysis.

Measures

Measurements from the ACLS cohort involved in this analysis were previously described in detail at the beginning of Chapter III. The following is an overview of the variables used to investigate Hypothesis II.

Definition of Outcome

Coronary heart disease (CHD) was defined as the self-report of myocardial infarction or revascularization (including, bypass, coronary balloon, angioplasty, or stent) at a return clinic visit or on a mail-back questionnaire; or death due to CHD. The time to follow-up began at the baseline examination and continued until CHD event or 1 July

2004. Deaths among study participants were identified from the National Center for Health Statistic's National Death Index using ICD codes: I11 and I20-I25 that identify CHD as the primary cause of death. In concordance with FRS follow-up time definition, the maximal follow up time was 12 years. The risk of CHD was tested for a 5-year and 10-year follow up.

Predictor Variables

The measures utilized to test Hypothesis 2 are inclusive of the covariates described to test Hypothesis 1, with the addition of cardiorespiratory fitness (CRF). In brief, the objectively measured predictor variables included in the analysis were a five level categorical variable for hypertension defined through systolic and diastolic blood pressure, five levels of total cholesterol, high density lipoprotein categorized in five different groups, diagnosis of diabetes defined as either yes or, and dichotomized current smoking status. Age was included as a continuous variable. This version of FRS [25] incorporated categorical variables for age, hypertension, total cholesterol, HDL-C, smoking, and diabetes to determine a point value that could be summed and interpreted as an overall 10-year risk for CHD. The FRS was applied to every individual, and men were stratified based on their level of 10-year CHD risk. A point summation ≤5 points was classified as 'low' risk and a point summation >5 points was categorized as 'moderate or high' risk for CHD.

The main predictor variable of interest was cardiorespiratory fitness (CRF). A maximal exercise test was performed to determine each participant's CRF. The technicians administered the Balke protocol for maximal exercise test while encouraging the participant to reach the maximal capacity. Total treadmill time was used as an

indicator of aerobic power. CRF is a gender-specific, age-adjusted Metabolic Equivalent of Task (MET) value at the final grade and speed of the treadmill test. One MET is equal to the amount of energy expended by an average person at rest. [168]

Statistical Analysis

Descriptive statistics were generated to analyze the population's representation among the predictor variables. Univariate survival models were performed for CHD event and each covariate to determine each characteristic's prediction power. Men with and without incident CHD were compared on mean age, mean fitness defined through maximally achieved METs, proportion of men with low, moderate, or high CRF, the average FRS point summation, proportion of men with 'moderate or high' 10-year CHD risk, hypertension classification, cholesterol levels, diabetes diagnosis, and smoking status. To determine each of the aforementioned covariate's association with CHD events, univariate survival analysis was performed. Cox Proportional Hazard Models, adjusted for baseline examination year, also were fit to determine the association between CRF and CHD events while controlling for 10-year CHD risk. To test for an interaction between CRF and FRS, survival analysis was performed on a population stratified by 'low' and 'moderate or high' 10-year CHD risk, while adjusting for age and baseline examination year. SAS® version 9.3 (SAS) was used to perform all analyses.

PAPER 3: Determine the association between non-exercise estimated Cardiorespiratory Fitness (e-CRF) and Coronary Heart Disease. Utilize e-CRF and Framingham Risk Score (FRS) to predict the risk of CHD.

Purpose

This manuscript will address Hypothesis 3: the e-CRF will be significantly protective against CHD. We also hypothesize that e-CRF and FRS will have a significant association with CHD.

Study Design

Survival analysis and predictive modeling was performed using the ACLS prospective cohort. Predictor variables were determined at baseline examination and each participant and follow-up was conducted to ascertain information on the occurrence (or non-occurrence) of a CHD event.

Study Population

Patients of the Cooper Clinic in Dallas, TX who consented to participation in the ACLS cohort are considered for inclusion in the analysis. To be included in the following analysis, participants had to complete their baseline examination between 1979 and 2002 and have at least one year of follow up. Only men were considered in this analysis because of the low number of CHD events in women in the ACLS. Individuals were between the age of 30-74 with a BMI higher than 18.5 kg/m^2. Only individuals with complete information on all the possible covariates were included in the analysis.

The majority of participants were Non-Hispanic, White, with a median age of 44 years. Most participants were well-educated and represented the middle to upper

socioeconomic group. The Cooper Clinic's Institutional Review Board annually reviewed and approved ACLS' protocol.

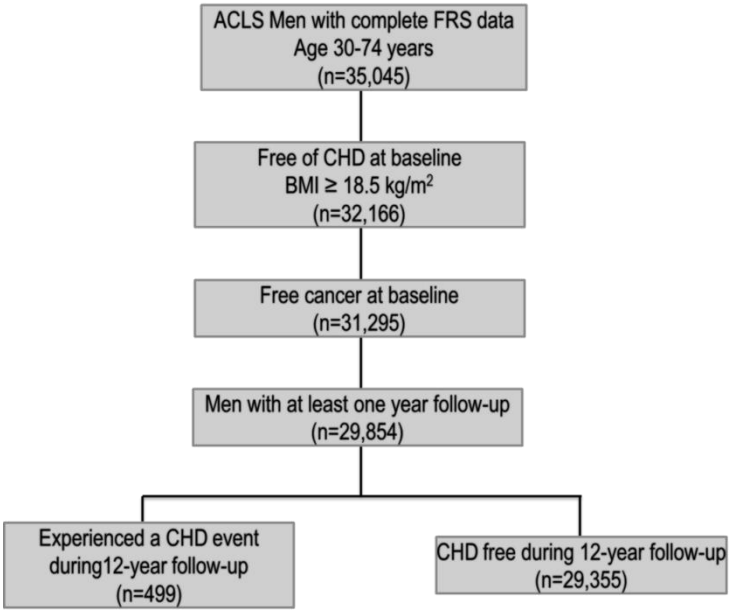


Figure 3.3. Study flow for Paper 3 and Aerobic Center Longitudinal Study (ACLS) inclusion criteria depicting final sample size and coronary heart disease (CHD) event frequency. Men with complete Framingham Risk Score (FRS) data and body mass index (BMI) ≥ 18.5 kg/m^2 were included in the analysis.

Measures

Measurements from the ACLS cohort involved in this analysis were previously described in detail at the beginning of Chapter III. The following is an overview of the variables used to investigate Hypothesis III.

Definition of Outcome

Coronary heart disease (CHD) was the outcome of interest for the proceeding analyses. CHD was recorded if there was a presence of self-reported myocardial infarction or revascularization (including, bypass, coronary balloon, angioplasty, or

stent), or death due to CHD. Follow up was measured at the baseline examination and continued until occurrence of CHD event or 1 July 2004. Deaths among study participants were identified from the National Center for Health Statistic's National Death Index through December 31, 2003. In concordance with FRS follow-up time definition, the maximal follow up time was 12 years.

Predictor Variables

The variables considered in the age-adjusted reduced model for Hypothesis 3 are estimated MET values for CRF, systolic and diastolic blood pressure classified as a five level hypertension variable, objectively measured cholesterol levels: total cholesterol and high density lipoprotein, diabetes diagnosis assessed through a 12-hour fasting glucose, and a self-report current smoking status. A composite score was derived from FRS and point values were tabulated for each participant based on Wilson et al's study [113] and the cohort was stratified based on their 'low' or 'moderate or high' 10-year CHD risk. A point summation > 5 points was considered 'moderate or high' risk. A non-exercise predictor variable of CRF based on the prediction modeling of Jurca et al (2005) [170] will replace CRF that was measured by a maximal exercise test.

Estimated CRF (e-CRF) is a non-exercise estimation of CRF generated from a 6-item, non-exercise, scale estimating CRF (e-CRF) [171] was recently developed and incorporates age, body mass index (BMI), waist circumference, resting heart rate, smoking status, and physical activity. Physical activity was captured through a medical history questionnaire where participants reported their regular physical activity for the past 3 months. [41,172] Physical activity was then dichotomized in to two levels: none or low, and moderate or high physical activity. The accuracy of the developed algorithm

was determine by computing the random intercept's square root of the sum and the residual variances. [171,173] Estimated CRF (e-CRF) was expressed in metabolic equivalent of task (MET) units. METs were estimated using a 6-item questionnaire [170,174]. The sex-specific questionnaire is composed of a participant's age, BMI, waist circumference (WC), resting heart rate (RHR), two-level physical activity (activity), and smoking status (smoke). These variables are applied to Jackson et al's algorithm [171] below.

$$e - CRF = 21.2870 + (Age \times 0.1654) - (Age^2 \times 0.0023) - (BMI \times 0.2318) - (WC \times 0.0337) - (RHR \times 0.0390) + (Active \times 0.6351) - (Smoke \times 0.4263)$$

The estimated METs were categorized into three age-adjusted e-CRF tertiles: low, middle, or high e-CRF. This classification is similar to previous e-CRF studies. [171]

Statistical Analysis

Descriptive statistics were calculated for the total study population and stratified by e-CRF. Chi-square tests were conducted to determine significant differences between the e-CRF levels and each risk factor. Death rate per 10,000 person-years for follow-up was calculated for e-CRF and 10-year CHD Risk. Crude Cox Proportional Hazard Models, adjusting for baseline examination year, were generated to determine the association between e-CRF and CHD, and the relationship between 10-year CHD risk and CHD. A fully adjusted Cox Proportional Hazard Model was used to determine the relationship between e-CRF, 10-year CHD risk and CHD. The effect of e-CRF on CHD also was investigated on population subsets defined by age, smoking status, hypertension

status, and diabetes diagnosis. To investigate if there was a significant interaction between e-CRF and 10-year CHD risk, the male ACLS participants were stratified by 'low' or 'moderate or high' CHD risk and hazard ratios between e-CRF and CHD were calculated. The receiver operating characteristic (ROC) curves were plotted to determine if there was a significant improvement in the predictive accuracy of CHD by augmenting the FRS point summation with e-CRF. The chi-square test determined if there was a significant difference between the models. The Hosmer-Lemeshow statistics was used to asses calibration and goodness of fit; the statistics compares the predictive and observed events but is limited to sample sizes smaller than 10,000 observations. [169] To control for this limitation, a random sample population was generated from the larger study population to perform this goodness of fit test. SAS® version 9.3 was used to perform all descriptive, survival, and predictive analyses.

CHAPTER IV

Factors Related to Coronary Heart Disease Risk in Men: Validation of the Framingham Risk Score[1]

[1]Gander J, Sui X, Hazlett LJ, Cai B, Hébert JR, Blair SN. Accepted by *Preventing Chronic Disease*. Reprinted here with permission of publisher, 06/24/2014.

Abstract

Coronary heart disease (CHD) remains a leading cause of death in the United States. The Framingham Risk Score (FRS) was developed to help clinicians in determining their patients' CHD risk. We hypothesize that the FRS will be significantly predictive of CHD events in men within the Aerobics Center Longitudinal Study (ACLS) population.

Methods

The study included 34,557 men who attended the Cooper Clinic in Dallas, TX for a baseline clinical exam between 1970 and 2003. CHD events included self-reported myocardial infarction or revascularization, or death due to CHD. There were 587 CHD events during the 12-year follow-up. Multivariable-adjusted hazard ratios generated from ACLS analysis were compared to the FRS' application to the Framingham Heart Study (FHS).

Results

The ACLS cohort produced similar hazard ratios to the FHS. The adjusted Cox proportional hazard model revealed men with total cholesterol of ≥280mg/dL were 2.21 (95% Confidence Interval (CI) 1.59, 3.09) times more likely to have a CHD event compared to men with total cholesterol between 160-199mg/dL; men with diabetes were 1.63 (95% CI 1.35, 1.98) times more likely to experience a CHD event compared to men without diabetes.

Conclusion

The FRS significantly predicts CHD events in the ACLS cohort. To the best of our knowledge, this is the first report of a large, single-center cohort study to validate the FRS using extensive laboratory and clinical measurements.

Introduction

Coronary heart disease (CHD) remains one of the leading causes of death in the United States, accounting for approximately 17% of the overall national health care expenditures. [3] CHD is the accrual of plaque in the arteries of the heart [6] that supply the blood for maintaining normal cardiac function. The accumulation of plaque narrows the heart's arteries and reduces blood flow to the heart muscle. The lack of oxygen-rich blood to portions of the heart muscle leads to ischemia of myocardial tissues and consequent alteration of heart function. CHD also can be caused by the deposition of fat beneath the endothelium, reducing the elasticity of arteries. [6] This arterial damage has been shown to be caused by an array of significant risk factors such as hypertension, [74] hypercholesterolemia, [14] diabetes, [16] and smoking. [11] However, because these risk factors are modifiable through individual and population-level behavior change, medical prevention through closely monitoring cholesterol, blood glucose, and other risk factors, and treating any of these risk factors that are above acceptable ranges with medication such as statins or insulin, many countries have experienced a decrease of CHD incidence in the past 30 years. [8]

Several risk scores have been developed to provide guidance to clinicians on their patients' risk for CHD. [18,23] The Framingham Risk Score (FRS) [23,25] is the CHD risk score most widely utilized by clinicians across the globe. [24] The FRS originated from the Framingham Heart Study (FHS), a relatively homogeneous cohort residing in Framingham, Massachusetts, [23] and has been applied and validated in a variety of different populations. [26,114] However, Kagan et al's [26] study lacked complete congruency with FRS methodology and other studies such as Lee et al's [114] and Fried et al's [175] had

relatively small sample sizes. A recent publication updated the 1998 FRS and developed a new risk score that predicted an individual's cardiovascular disease risk, instead of the CHD outcome. [176] For the purposes of this study, we have chosen to investigate CHD outcomes as they comprise the majority of CVD events. [177]

The current research aims to expand on the recent validation studies [28] employing the Aerobics Center Longitudinal Study (ACLS) cohort and the measured outcome of 10-year risk for CHD. ACLS provides a larger cohort to validate FRS compared to FHS or previous studies and FRS has yet to be applied to this cohort. This cohort includes extensive measures of FRS components and CHD outcomes on more than 40,000 participants. [43] We hypothesize that the FRS will be significantly predictive of CHD events for men within the ACLS population.

Methods

Study Population

ACLS is an observational longitudinal study whose members were patients of the Cooper Clinic, Dallas, TX, where they received a preventive medical examination and counseling on health behaviors during periodic visits. The Cooper Clinic serves anyone who elects to come for an examination and patients come from all 50 states. During the patients' medical examination, they were informed of the ACLS, asked to participate, and, if they agreed to participate, consented to follow-up surveillance. The ACLS protocol was annually reviewed and approved by the Cooper Institute Institutional Review Board.

The participants were examined at least once during 1970 and 2003 at the Cooper Clinic. The cohort consists mostly of individuals within the middle and upper socioeconomic groups, with approximately 80% holding college degrees. [41] The mean baseline age of the cohort was 42 years [34] and consisted mostly of men (75%) and non-Hispanic Whites (>95%).

Although ACLS is not a representative sample of the entire US population, a comparison of median values of specific physiological variables show similarity to representative population data [164]. A large number of women were enrolled in ACLS (n=11,276), however, women were excluded from this analysis due to the small number of CHD events (n=45) during the follow-up period. The following inclusion criteria were applied to the ACLS cohort for the current study: 1) Age at baseline examination between 30-74 years; 2) Complete data for outcome and predictor variables; and 3) Free of CHD diagnosis or cancer diagnosis at baseline. To control for any unmeasured confounders that may have caused early drop-out, men with less than one year of follow-up were excluded from the study's cohort. Figure 1 shows the flow diagram of the study participants.

Clinical Examination

Trained technicians followed standardized protocols while conducting each measurement. The baseline clinical exam included a personal and family medical history, anthropometric measurements, a 12-hour fasting blood chemistry including glucose and cholesterol measurements, ECG, blood pressure assessment, and a maximal exercise test. [112,164]

Measures

Definition of Outcome

CHD was the primary endpoint being investigated. CHD was defined as the self-report of myocardial infarction or revascularization (including, bypass, coronary balloon, angioplasty, or stent), or death due to CHD. Participants reported their history of infarction or revascularization and incident date through a mail-back questionnaire administered in 1982, 1986, 1990, 1995, 1999, and 2004. Deaths among study participants were identified from the National Center for Health Statistic's National Death Index. International Classification of Disease (ICD), Ninth and Tenth Revisions, codes: 410.0-414.0 and I20-I25, respectively, were used to identify CHD as the primary cause of death. According to FRS' follow-up time definition, the maximal follow up time was 12 years. The 12-year follow up was used in the regression and survival analysis and then adapted to provide a 10-year CHD incidence estimates.

Predictor Variables

The covariates considered for analyses in the ACLS population mimicked the variables included in the recently-updated Framingham Risk Score. [25] Hypertension (HTN) was divided into four categories according to systolic blood pressure and diastolic blood pressure. Systolic blood pressure was categorized into four levels: <130 mm Hg, 130-139 mm Hg, 140-159 mm Hg, or ≥160 mm Hg. Diastolic blood pressure was categorized into four levels: <85 mm Hg, 85-89 mm Hg, 90-99 mm Hg, and ≥ 100 mm Hg. When an individual's blood pressure fell into different categories for systolic and

diastolic blood pressure, the higher category was chosen for categorization. For example, if a participant's blood pressure was 130/80 (SBP/DBP), the corresponding categories for systolic blood pressure would be 2, and the diastolic blood pressure category would be 1. To determine the HTN category, the higher classification would be chosen and the HTN categorization would be 2 in this example. HTN definition was made without regard to a participant's use of antihypertensive medications. The definition of HTN parallels FRS' definition. [25]

Total cholesterol was grouped into four levels: <200 mg/dL, 200-239 mg/dL, 240-279 mg/dL, and ≥ 280 mg/dL. High density lipoprotein was categorized as: <35 mg/dL, 35-59 mg/dL, and ≥ 60 mg/dL. A 12-hour fasting glucose >140 mg/dL classified an individual as having diabetes. Smoking status was dichotomized as current or non-smoker. All categorizations and definitions were analogous to FRS' covariate groupings. [25]

Statistical Analysis

Descriptive statistics were generated to compare the ACLS population to the Framingham Heart Study population. Males in each cohort were compared on mean age, percentage within each category in HTN, total cholesterol, and HDL, percent diabetic, and percent of current smokers. Univariate Cox Proportional Hazard models were performed for the CHD events and each covariate to determine each characteristic's predictive power. Cox Survival analyses were conducted to determine the 10-year CHD risk for the ACLS male population. The fully adjusted Cox Proportional Hazard model

included age, blood pressure, total cholesterol, high density lipoprotein cholesterol, diabetes diagnosis, and smoking status.

Predictive accuracy was determined through the concordance-statistic (c-statistic) associated with the receiver operating characteristic (ROC) curve. The ROC curve measures the discrimination power of these diagnostic markers for the CHD outcome. The Hosmer-Lemeshow statistic is used to assess calibration and is a chi-square test calculated by sorting the sample by estimated probability of success [169]. The higher the c-statistic the better the prediction. A limitation of the Hosmer-Lemeshow test is that it is not recommended for sample sizes larger than 25,000. A sensitivity analysis was performed following Paul et al's [169] recommendations and the ACLS sample (n=34,557) and a smaller 10,000 sample cohort was randomly selected. To satisfy this limitation, the Hosmer-Lemeshow test was performed on a randomly selected cohort (n=10,000) and a p-value>.05 represent no significant difference between predicted and observed events. All analyses were performed using SAS® version 9.3 (SAS).

Results

During a 12-year follow- period (284,572 person-years of exposure), 587 men had a CHD event. The incidence rate was 20 per 10,000 person-years. The ACLS cohort had approximately 32,000 more participants (Table 4.1) compared to the Framingham Heart Study (FHS) and were, on average, younger ($p<0.0001$). FHS had a higher proportion of diabetics (5.0%) and smokers (40.0%) compared to the ACLS cohort of 1.5% and 17.0% respectively ($p<0.0001$) (Table 4.2).

When the ACLS cohort is stratified by CHD status, men who experienced a CHD event during the 12-year follow-up period were significantly different on all predictor variables; i.e. they were older, had higher blood pressure and were in the upper two categories for high-density lipoprotein cholesterol. Among those men who experienced CHD during follow-up, 4.6% were diabetic and 23.3% were smokers compared to 1.47% ($p<0.001$) and 16.8% ($p<0.001$) who did not experience CHD, respectively (Table 4.3).

Table 4.3 displays the unadjusted and fully adjusted survival models. The covariates that were based on the FRS were all significant when applied to the men in ACLS. The hazard ratios reported from FHS by D'Agostino et al (2001)[28] are similar to the ACLS fully adjusted hazard ratios. The fully adjusted HRs show men with Stage I HTN (HR=1.41; 95%CI 1.16, 1.72) have significantly higher risk of CHD compared to men with optimal or normal blood pressure. Men with total cholesterol of ≥280mg/dL were more than twice (HR=2.21; 95% CI 1.59, 3.09) as likely to have a CHD event compared to men with total cholesterol between 160-199mg/dL Men with diabetes were 1.82 (95% CI 1.23, 2.70) times more likely to experience a CHD event compared to men without diabetes. Smokers also experienced a significantly higher risk (HR=1.63; 95%CI 1.35, 1.98) for CHD compared to past/nonsmokers during the 12-year follow-up.

Figure 4.2 portrays the receiver operating characteristic (ROC) curve. The c-statistic (Area Under the Curve) obtained from the ROC curve was 0.77 (95% CI 0.7523, 0.7871). The Hosmer-Lemeshow test reported there was not a significant lack of fit for the model (p-value 0.88) and we failed to reject the null hypothesis that states there is no significant difference between the predicted and observed values of the outcome variable.

Discussion

The FRS significantly predicts CHD events occurring during a 12-year follow-up in the Aerobics Center Longitudinal Study, which was a much larger study than the original Framingham Heart Study. In addition to our main finding, age, blood pressure, total cholesterol, high density lipoprotein cholesterol, diabetes diagnosis, and smoking status were associated with CHD events. The relative risks were congruent with the those reported from the FHS [28] and previous literature. [26,114]

Elevated blood pressure creates more strain for the heart which can cause stiffness of the muscle [6] or create microscopic tears in the walls that may develop in to scar tissue [6]. Myocardial ischemia is common in patients with hypertension [16,74] and reports from the FHS showed that hypertension was the primary cause of congestive heart failure in 35% of cases. [77] Diabetic men are also at increased risk for CHD [83] and additional research shows that individuals with both diabetes and .hypertension have a higher incidence of heart disease compared to people with diabetes or hypertension alone. [16]

Doyle et al published one of the first studies examining the association between smoking and CHD [71] in two prospective studies: The FHS and the Albany, New York Civil Servant study, with a combined study population of over 1,800 men without CHD [71]. The study concluded that men with elevated systolic blood pressure and total cholesterol who smoked were at a 1.8 ($p<0.05$) times higher risk of mortality compared to men with elevated systolic blood pressure and total cholesterol who did not smoke. [71] Our findings are also in line with The Physicians' Health Study that reported significant effects of HDL and total cholesterol on CHD. [28]

Researchers have previously investigated FRS' predictability in various populations. The Honolulu Heart Study was initiated in 1965 with the overall goal of standardizing cardiovascular examination. [26] The cohort is comprised of Japanese men born between 1900 and 1919 and updated with their World War II Selective Service Files; approximately 8,000 individuals free of CHD at study initiation, with a baseline examination constituted the final population[26]. Cigarette smoking, cholesterol levels, blood pressure, sum of skinfolds, and uric acid levels were significant predictors of CHD; however glucose intolerance showed no significant relationship. The lack of congruency in the significant results between the Honolulu Heart Study, FHS, and ACLS may be due to the Honolulu Heart Study population being at low risk of CHD (i.e. CHD incidence observed in the Honolulu Study was about half that of the FHS).

To the best of our knowledge, this is the first large, single-center, prospective cohort to validate the FRS with the same level of precision as that in the FHS. The present study expands on previous research through the improvement of internal validity by utilizing objectively measured clinical data.

Similar to FHS, a potential limitation of the ACLS cohort is the homogeneity of the study population's sociodemographic factors. This limitation was explored through comparison analysis between ACLS and two large population-based cohorts and found that ACLS' results were similar to the results of the Lipid Research Clinics Prevalence Survey and the Canada Fitness Survey. [165] It should be noted that ACLS' homogeneity may be a strength through the improvement of internal validity by controlling for potential demographic confounders such as education, socioeconomic status, and race/ethnicity; however, generalizations must be made cautiously and future research

should be conducted in more diverse populations. Unlike the FHS, stage II-IV hypertension was not significantly associated with CHD and may be due to the limitation in the small proportion (4.93%) of ACLS' cohort was categorized in to this group.

Conclusion

Although CHD remains one of the leading causes of death in the United States, the prevalence of CHD has decreased since 2004;[4] a reduction that can be largely attributed to better medical treatment and improvement in CHD risk profiles. The FRS was developed to assist clinicians in estimating their patients' absolute risk for CHD. [28] This study further evaluates FRS' performance in the larger ACLS cohort, and strictly followed the FHS methodology which does not control for other CHD risk factors such self-rated health, [141] family history [95] of CHD, and cardiorespiratory fitness. [43] Future research should focus on the expansion of the FRS to include other modifiable risk factors. Community interventions and education programs should continue to target these CHD risk factors to further the prevention of heart disease.

Table 4.1. Comparison of Demographic Characteristics Between men free of coronary vascular disease at baseline the Framingham Heart Study (FHS) and the Aerobics Center Longitudinal Study (ACLS)[a].

RISK FACTOR	Study Comparison[b]	
	FHS[d]	**ACLS**
	n=2,439	n=34,557
Age, range (years)	30-74	30-74
Mean age, y	48.30	44.82
Blood Pressure, (mm HG)		
Optimal and Normal (S<130, D<85)	44.00	59.85
High Normal (S<140, D<90)	20.00	16.24
Stage I HTN (S<160, D<100)	23.00	18.98
Stage II-IV HTN (S≥160, D≥100)	13.00	4.93
Total Cholesterol (mg/dL)		
<160	7.00	9.34
160-199	31.00	34.36
200-239	39.00	36.67
240-279	17.00	15.10
≥280	6.00	4.53
HDL-C (mg/dL)		
<35	19.00	16.24
35-59	70.00	70.97
≥60	11.00	12.79
Diabetes	5.00	1.52
Current Smoking	40.00	16.95

Abbreviations: CI; confidence interval; HTN, hypertension; HDL-C, high density lipoprotein cholesterol

[a] The numbers displayed are percentages unless otherwise stated

[b] Independent t-test was used to determine statistically significant difference of age between FHS and ACLS; Proportion test calculated the statistical difference for each level of blood pressure, total cholesterol, HDL, diabetes, and current smoking between FHS and ACLS. All proportion tests were significant with a p-value<0.001.

[c] FHS, Framingham Risk Score descriptive statistics referenced from D'Agostina et al (17)

Table 4.2. Comparison in Demographic Characteristics Between Men With and Without a Coronary Heart Disease (CHD) Event in the Aerobic Center Longitudinal Study (ACLS)[a].

	CHD Event Comparison within ACLS[b]	
RISK FACTOR	**No CHD**	**With CHD**
	n=33,970	n=587
Median Follow-up Time (IQR)	10.94 (3.82, 12.00)	5.66 (2.94, 8.93)
Age, range (years)	30-74	30-73
Mean age, y	44.70	51.91
Blood Pressure, (mm HG)		
Optimal and Normal (S<130, D<85)	60.06	47.53
High Normal (S<140, D<90)	16.18	19.76
Stage I HTN (S<160, D<100)	18.85	26.41
Stage II-IV HTN (S≥160, D≥100)	4.90	6.30
Total Cholesterol (mg/dL)		
<160	9.44	3.92
160-199	34.62	19.59
200-239	36.60	40.37
240-279	14.88	27.60
≥280	4.46	8.52
HDL-C (mg/dL)		
<35	16.08	25.55
35-59	71.05	66.44
≥60	12.88	8.01
Diabetes	1.47	4.60
Current Smoking	16.84	23.34

Abbreviations: HTN, hypertension; HDL-C, high density lipoprotein cholesterol

[a] The numbers displayed are percentages unless otherwise stated

[b] Chi-square test was performed to calculate statistical difference between the group with and without CHD. All comparisons were significant with p-value<0.05

Table 4.3. Hazard Ratios for coronary heart disease (CHD) Events for Framingham Heart Study (FHS) Cohort Compared to Aerobics Center Longitudinal Study (ACLS) Cohort

	FHS[a]			ACLS 12y Follow-up					
				Unadjusted			Fully Adjusted[b]		
	HR	95% CI		HR	95% CI		HR	95% CI	
Age (years)	1.05	1.04	1.06	1.09	1.08	1.10	1.09	1.08	1.10
Blood Pressure, mm HG									
Optimal and Normal (S<130, D<85)	1.00	Referent		1.00	Referent		1.00	Referent	
High Normal (S<140, D<90)	1.31	0.98	1.76	1.66	1.33	2.06	1.33	1.07	1.66
Stage I HTN (S<160, D<100)	1.67	1.28	2.18	1.95	1.60	2.38	1.41	1.16	1.72
Stage II-IV HTN (S≥160, D≥100)	1.84	1.37	2.06	1.94	1.37	2.73	1.23	0.87	1.74
Total Cholesterol (mg/dL)									
<160	0.69	0.31	1.52	0.77	0.49	1.21	0.82	0.52	1.28
160-199	1.00	Referent		1.00	Referent		1.00	Referent	
200-239	1.77	1.25	2.50	1.85	1.48	2.31	1.59	1.27	1.99
240-279	2.10	1.43	3.10	2.90	2.28	3.68	2.37	1.86	3.01
≥280	2.29	1.39	3.76	2.74	1.97	3.83	2.21	1.59	3.09
HDL-C (mg/dL)									
<35	1.47	1.16	1.86	1.59	1.32	1.92	1.60	1.32	1.94
35-59	1.00	Referent		1.00	Referent		1.00	Referent	
≥60	0.56	0.37	0.83	0.66	0.49	0.90	0.60	0.44	0.81
Diabetes	1.50	1.06	2.13	3.45	2.34	5.07	1.82	1.23	2.70
Smoking Status	1.68	1.37	2.06	1.60	1.32	1.93	1.63	1.35	1.98

Abbreviations: CI; confidence interval; HR, Hazard Ratio; HTN, hypertension; HDL-C, high density lipoprotein cholesterol

[a] Framingham Heart Study hazard ratios from Wilson et al 1998 (10)
[b] Fully adjusted model included age, blood pressure, total cholesterol, high density lipoprotein levels, diabetes diagnosis, and smoking status

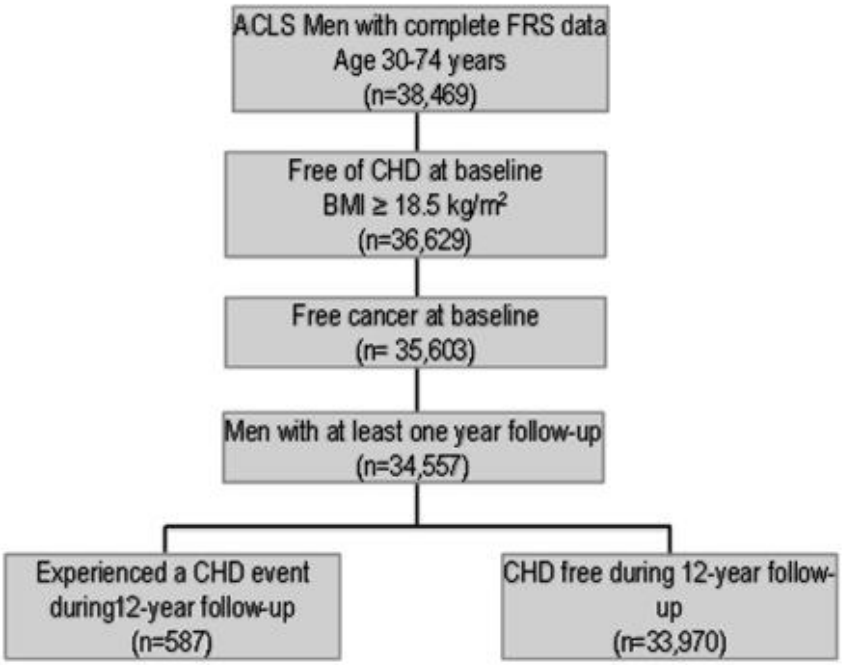


Figure 4.1. Study flow and Aerobic Center Longitudinal Study (ACLS) inclusion criteria depicting final sample size and coronary heart disease (CHD) event frequency. Men with complete Framingham Risk Score (FRS) data and body mass index (BMI) $\geq$ 18.5 kg/m^2 were included in the analysis.

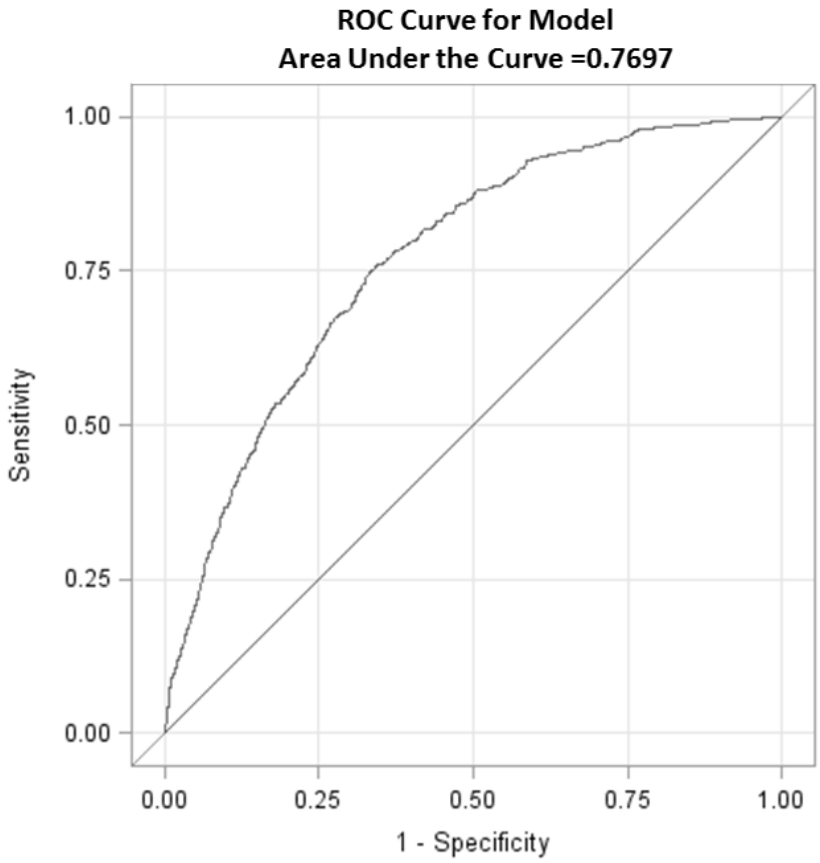


Figure 4.2.Receiver Operating Characteristic Curve representing the predictive ability of the Framingham Risk Score (FRS) applied to the ACLS cohort with a 12 year follow-up. The Hosmer-Lemeshow c-statistic is represent by the Area Under the Curve (c=0.7697, 95% Confidence Interval 0.7523, 0.7871)

CHAPTER V

Incorporation of Cardiorespiratory Fitness in the Framingham Risk Score in Asymptomatic Men[1]

[1]Gander J, Sui X, Hébert JR, Hazlett LJ, Cai B, Lavie CJ, Blair SN. Submitted to *Circulation*, 06/12/2014.

Abstract

Background

The Framingham Risk Score (FRS) includes a limited set of risk factors and does not include cardiorespiratory fitness (CRF), which has been shown to have a strong protective effect on coronary heart disease (CHD). We aim to examine the association of CRF on 10-year risk of CHD while controlling for individuals' FRS.

Methods and Results

The study included 29,854 men from the Aerobics Center Longitudinal Study (ACLS) who received a baseline examination from 1979 to 2002. CHD events included self-reported myocardial infarction or revascularization, or CHD death. Multivariable survival analysis investigated the association between CRF, FRS, and CHD. CRF was analyzed as both a continuous and categorical variable. The population was stratified by 'low' and 'moderate or high' risk for CHD to test for interaction between CRF and FRS.

Men with incident CHD were older (mean age = 51.6 years), had an average maximally achieved fitness of 10.9 metabolic equivalent of task (METs), and were more likely to have 'moderate or high' 10-year CHD risk, compared to men without incident CHD (p-value<0.001). CRF, defined as maximal METs, showed a 20% lower risk of CHD (HR=0.80, 95% CI 0.77, 0.83) for each 1 unit MET increase. Men within the 'low' 10-year CHD risk strata and high (HR=0.62, 95% CI 0.45, 0.84) CRF had a lower CHD risk compared with men in the same strata, but with low CRF *(p-value <0.001).*

Conclusion

Clinicians should emphasize the promotion of physical activity to improve CRF to reduce CHD risk, even in patients with otherwise low CHD risk.

Introduction

The American Heart Association stated one of its 2020 Impact Goals was to reduce the deaths from cardiovascular disease (CVD) by 20%;[4] coronary heart disease (CHD) comprised the majority of CVD deaths in 2006 and 2007.[177] CHD is classified as plaque accumulation in the arteries of the heart, decreasing the supply of oxygen-rich blood.[177] Several risk factors have been shown to significantly predict CHD, including: smoking,[11] diabetes, [16] hypertension,[74] and hypercholesterolemia.[14]

CHD risk equations, such as the Framingham Risk Score (FRS), have been developed and employed to account for these and other risk factors .[23] The FRS provides a sex-specific, age-adjusted risk score that accounts for systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol (HDL-C), diabetes diagnosis, and smoking status.[25] Previous studies [29,30,104] have modified the FRS to include additional risk factors. Tzoulaki et al [104] conducted a meta-analysis on 63 studies and examined how each study modified the FRS, including the addition of C-reactive protein,[29] deletion of diabetes diagnosis,[30] and alterations to blood pressure definitions.[178]

None of these modifications involved the addition of cardiorespiratory fitness (CRF), a characteristic that has shown significant protective effects for all-cause mortality, [43,136] cancer-related mortality,[139] diabetes incidence,[34] and CHD incidence [47] and mortality.[25,45,46] Barlow et al [163] showed that a 1-MET increase in CRF resulted in an 18% decrease in CVD mortality over a 30-year follow-up period in "low-risk" adults, as defined by the FRS. However, this result reflects control for additional factors besides CRF, such as body mass index (BMI) and early family history of CHD, which are not included in the FRS.

The aim of this study is to examine the association of CRF on 10-year risk of CHD while controlling for an individual's FRS. Our secondary aim is to investigate if the relationship between CRF and 10-year risk of CHD differs in 'low risk' males.

Methods

Study Population

The Aerobics Center Longitudinal Study (ACLS) is a prospective cohort study involving a large group of men and women. The participants were patients of the Cooper Clinic, where they received a preventive medical examination and counseling on health behaviors during periodic visits. The participants were examined at least once from 1979 to 2002 at the Cooper Clinic, Dallas, Texas. The protocol for ACLS was reviewed annually and approved by the Cooper Institute Institutional Review Board. Women were excluded from these analyses due to a small number of CHD events (n=45). Men were included based on the following criteria: 1) Age at baseline examination between 30-74 years; 2) Complete data for outcome and predictor variables; and 3) Free of CVD or cancer diagnosis at baseline. A flow diagram of the study population is depicted in Figure 5.1.

Clinical Examination

The baseline, clinical exam included an ECG, a 12-hour fasting blood chemistry analyses including cholesterol and glucose measurements, blood pressure assessment, and a maximal exercise test.[112,164,166] A standardized questionnaire was used to assess smoking status.

Measures

Definition of Outcomes

CHD was defined through either self-report of revascularization (including, bypass, coronary balloon, angioplasty, or stent) or myocardial infarction (MI), or CHD specific mortality. A mail-back questionnaire was administered in 1982, 1986, 1990, 1995, 1999, and 2004 in which participants were asked to report their history of revascularization or MI along with the incident date. The National Center for Health Statistic's National Death Index was used to identify CHD deaths in the ACLS cohort; International Classification of Disease (Ninth and Tenth Revisions) codes 410.0-414.0 were used to determine CHD as the primary cause of death. In accordance with FRS's follow-up time definition, the maximal follow-up time for the ACLS study population was 12 years.

Application of Framingham Risk Score

FRS was derived from the Framingham Heart Study, which is an ongoing observational study initiated in 1948 and primarily recruits residents of Framingham, Massachusetts.[23] In a study published in 1998,[25] the main outcome was a CHD event defined as a MI, coronary insufficiency, or CHD death. This version of FRS[25] incorporated categorical variables for age, hypertension, total cholesterol, HDL-C, smoking, and diabetes to determine a point value that could be summed and interpreted as an overall 10-year risk for CHD. The FRS was applied to every individual, and men were stratified based on their level of 10-year CHD risk. A point summation ≤5 points was classified as 'low' risk and a point summation >5 points was categorized as 'moderate or high' risk for CHD.

Cardiorespiratory Fitness

The Balke maximal exercise treadmill test [167] was used to determine CRF, which was analyzed as a continuous and categorical variable. The continuous variable was the maximally achieved metabolic equivalent of task (MET). The following regression formula was employed to convert maximal treadmill time to METs :[48]

$$METs = \frac{(1.44 * Minutes\ of Exercise Duration) + 14.99}{3.5}$$

Treadmill time converted to METs is analogous to peak VO2.[121]

The categorical definition of CRF was based on a participant's age-specific treadmill time from the entire ACLS cohort and consisted of three levels: "low (least fit 20%)", "moderate (next fit 40%)", and "high (most fit 40%)".

Statistical Analysis

Descriptive statistics were computed for the total ACLS male population and stratified by incidence of CHD. Men with and without incident CHD were compared on mean age, mean fitness defined through maximally achieved METs, proportion of men with low, moderate, or high CRF, the average FRS point summation, proportion of men with 'moderate or high' 10-year CHD risk, hypertension classification, cholesterol levels, diabetes diagnosis, and smoking status. To determine each of the aforementioned covariate's association with CHD events, univariate survival analysis was performed.

Cox Proportional Hazard Models, adjusted for baseline examination year, also were fit to determine the association between CRF and CHD events while controlling for 10-year CHD risk. To test for an interaction between CRF and FRS, survival analysis was performed on a population stratified by 'low' and 'moderate or high' 10-year CHD risk, while adjusting for age and baseline examination year. SAS® version 9.3 (SAS) was used to perform all analyses.

Results

During a 12-year follow-up period (248,890 person-years of exposure), there were 499 incident CHD events. This ACLS cohort used the FRS on approximately 30,000 men (Table 1). At baseline, the males in the overall ACLS cohort had an average age of 44.7 years, 60.6% had either optimal or normal blood pressure, 4.7% had stage II-IV hypertension, 1.4% had diabetes, and 16. 6% reported being current smokers. Men with incident CHD were older, had higher prevalence of stage I hypertension, a lower HDL-C <35 mg/dL, a lower mean fitness, and were more likely to have 'moderate or high' 10-year CHD risk, compared to men without incident CHD (p-value <0.0001 for all stated comparisons).

Table 2 reports the univariate analyses between the risk factors that comprise the FRS and the risk for CHD. Men with optimal blood pressure were 33% less likely to experience a CHD event compared to men with normal blood pressure (HR=0.67, 95% CI 0.52, 0.87), while men with stage I hypertension were at a significantly higher risk (HR=1.55 95% CI 1.23, 1.97) for CHD. Men with HDL-C ≥60 mg/dL were at a

significantly lower risk for CHD compared to men with HDL-C 45-49 mg/dL. Men diagnosed with diabetes and current smokers also were at a significantly higher risk for CHD compared to non-diabetics and non-smokers. For every FRS point increase, the relative risk for a CHD event increased 36% (HR=1.36 95% CI 1.32, 1.40). Similarly, men with a 'moderate or high' 10-year CHD risk had an almost 6-fold (HR=5.66 95% CI 4.25, 7.55) higher risk for CHD compared to men with a 'low' 10-year CHD risk. A univariate analysis showed an inverse association between CRF and CHD. CRF, defined as maximal METs showed a 20% lower CHD risk (HR=0.80, 95% CI 0.77, 0.83) for each 1 MET increase. CRF also was categorized into low, moderate, and high and men with high CRF had 33% (HR=0.67, 95% CI 0.51, 0.88) lower risk for CHD compared with men who had low CRF (Table 3). Table 3 also reports the various survival models fit to test the association between FRS point, CRF, and risk of CHD. Model four reports the maximal METs protective effect on CHD (HR=0.82) while controlling for 'moderate or higher' 10-year CHD risk. Model 5 evaluates a similar association, but defines CRF as a categorical variable and shows that men with high CRF have 26% lower CHD risk while controlling for 'moderate or high' 10-year CHD risk.

Figure 2 shows the association between CRF, FRS, and risk of CHD through stratification of the population by low and 'moderate or high' 10-year CHD risk. Compared with men in the same strata with low CRF there was a significant inverse trend among men within the 'low'10-year CHD risk strata; Men with moderate (HR=0.92 95% CI 0.68, 1.25) and high (HR=0.62, 95% CI 0.45, 0.84) CRF had a lower probability of experiencing CHD *(P_{trend} <0.001).* These associations were similar for men with 'moderate or high' 10-year CHD risk, although not significant at □=0.05 *(P_{trend} =0.22).*

Discussion

Both FRS and CRF were strong independent predictors of CHD. CRF had a significant protective effect on CHD in men, after controlling for 10-year CHD risk based on the FRS point summation. When men were stratified by 'low' and 'moderate or high' 10-year CHD risk, CRF's protective effect became more apparent, with a significant inverse trend in low-risk adults. To our knowledge, this is the first study to investigate the association between CRF and CHD in males with 'low' and 'moderate or high' 10-year CHD risk.

The FRS is comprised of CHD risk factors such as hypertension, cholesterol levels, diabetes diagnosis, and smoking.[25] Various versions [22,25,26,176] that have included these risk factors repeatedly have shown the predictive power of the FRS. [179] Myocardial ischemia is common in patients with hypertension;[16,74,75] although a recent study reported a 1.4 mm Hg decrease in mean systolic blood pressure from 1994 to 2005 that could be associated with a 20% reduction in CHD deaths.[9] A diabetes diagnosis also previously has been shown to significantly increase a person's risk for CHD.[83,84] Diabetes can cause impairment in the cardiac muscle that may lead to cardiomyopathy, congestive heart failure, or ischemic heart disease and can increase the 5-year mortality rate after a myocardial infarction.[16] Doyle et al published one of the first studies examining the association between smoking and CHD.[71] That study concluded that while problems with blood pressure and cholesterol were absent, participants who reported being smokers were at a significantly higher risk for CHD mortality compared to nonsmokers.[71]

Our finding that CRF has a significant protective effect on CHD is similar to findings previously reported in the literature.[34,43,46,87] Ekelund et al investigated the relationship

between CRF and CHD in asymptomatic men and found during a nine year follow-up the more fit men had the least CHD risk compared to the fourth quartile.[45] Lee et al built on these findings by analyzing CRF's association with CVD while controlling for body composition. That study reported that lean, unfit men had three times higher risk of dying from CVD (RR=3.16, 95% CI 1.12, 8.92) compared to lean, fit men.[46] Improved CRF may reduce CHD risk through improved muscle mass [152,153] and enhancement in arterial oxygen content.[180] Research has shown that CRF can increase the double-product threshold for ischemic ST-segment depression,[154,155] a decrease in the magnitude of ST depression, and a diminished maximal ST depression.[154] CRF also may have a positive effect on coagulation [156,157] and may protect against thrombosis.[45]

Our findings regarding the association between CRF, FRS, and risk for CHD are consistent with recent findings. Barlow et al [163] investigated the association of CRF and CVD mortality in men and women that were at low risk for CHD events. The study concluded that a 1-MET increase in CRF resulted in an 18% decrease in CVD mortality during a 30 year follow up period.[163] Gupta et al [50] utilized the ACLS cohort with data ranging from 1970 through 2006 and employed a traditional CHD risk factor model that adjusts for age, systolic blood pressure, diabetes, total cholesterol, and smoking status and reported that CRF augmented CHD risk factor model correctly reclassified participants with CHD death based on their 10-year risk,[50] compared to the traditional FRS model.

The current study builds on the aforementioned research by applying the FRS to a large, single-center, longitudinal cohort with the same level of precision as the Framingham Heart Study that generated the FRS. The previous studies either modified the outcome of interest or the predictor variables included in the risk score. The American College of Cardiology and the American Heart Association recently developed the Pooled Cohort Equation for estimating artherosclerotic cardiovascular disease (ASCVD) [181] that encompassess similar risk factors as FRS but offers risk estimates for myocardial infarction, CHD death, stroke, and stroke death. This project decided to focus on prevoiusly defined CHD that includes angioplasty and revascularization while excluding stroke and stroke death. Future research should investigate the potential effect the Pooled Cohort Equation may have on ASCVD with the addition of CRF.

To the best of our knowledge, this is the first prospective cohort to investigate CRF's associations with 10-year risk of CHD while controlling for the FRS [25] in its entirety. A possible limitation to the current study is the homogeneity of the ACLS population. At the time of enrollment, ACLS consisted of mostly men, mean age 42 years , and was predominantly non-Hispanic Whites (>95%). However, a comparison study between ACLS and two large population-based cohorts found ACLS's results were similar to that of those cohorts.[165] It also should be noted that ACLS' homogeneity improves internal validity by controlling potential confounders such as socioeconomic status and education, although generalizations from this study should be made cautiously.

Conclusion

Our study found that CRF and FRS are both significant predictors of CHD events. Moderate and high fit men have lower risk for CHD compared to men with low CRF; this association remains significant when the population was stratified into 'low' and 'moderate or high' risk for CHD. It may be advantageous for clinicians to evaluate a patient's CRF to provide a more accurate assessment of the 10-year risk for CHD. CRF is a modifiable predictor of CHD and improved CRF may lead to an improvement in the FRS and 10-year CHD risk, as well as an improvement in the ability to predict long-term CHD risk. Clinicians should vigorously promote exercise therapy and increases in physical activity to their patients in efforts to increase CRF in the long-term prevention of CHD.[182,183] Researchers should consider developing a randomized clinical trial to determine the effect that CRF changes may have on an individual's FRS overall, the individual components of the risk score, and ultimately, the effect on 10-year risk for CHD.

Table 5.1. Comparison of demographic characteristics between men (n=29,854) with incident coronary heart disease (CHD) and no incident CHD, from the Aerobics Center Longitudinal Study (ACLS) prospective cohort

RISK FACTOR	Total Population n=29,854	Incident CHD n=499	No incident CHD n=29,355	p-value*
Age, range (years)	30-74	31-73	30-74	
Mean Age, y	44.72	51.57	44.60	<0.0001
Mean Fitness, maximally achieved MET	11.95	10.92	11.97	<0.0001
Cardiorespiratory Fitness				
Low	11.58	13.43	11.54	0.19
Moderate	38.45	43.29	38.37	0.03
High	49.97	43.29	50.09	0.0029
Mean FRS, points	3.51	6.15	3.47	<0.0001
'Moderate or High' 10year CHD risk	2.05	10.42	1.91	<0.0001
Blood Pressure, mm HG				
Optimal (S<120, D<80)	28.82	19.44	28.98	<0.0001
Normal (S<130, D<85)	31.82	30.26	31.85	0.45
High Normal (S<140, D<90)	15.97	19.64	15.91	0.02
Stage I HTN (S<160, D<100)	18.72	25.45	18.61	<0.0001
Stage II-IV HTN (S≥160, D≥100)	4.67	5.21	4.66	0.56
Total Cholesterol, mg/dL				
<160	9.15	3.81	9.25	<0.0001
160-169	34.11	19.24	34.36	<0.0001
200-239	36.90	40.48	36.84	0.09
240-279	15.30	27.25	15.10	<0.0001
≥280	4.54	9.22	4.46	<0.0001
HDL-C, mg/dL				
<35	15.60	25.25	15.43	<0.0001
35-44	34.13	38.68	34.05	0.03

	45-49	15.58	13.03	15.62	0.11
	50-59	21.42	15.83	21.52	0.0021
	≥60	13.28	7.21	13.38	<0.0001
Diabetes		1.39	4.41	1.34	<0.0001
Current Smoking		16.56	21.84	16.47	0.001

Abbreviations: CHD, coronary heart disease; FRS, Framingham Risk Score; HDL-C, high density lipoprotein- cholesterol; HR, hazard ratio; MET, metabolic equivalent of task

*Student t-test was used to calculate the difference between incident CHD and no incident CHD for age, mean fitness, and mean Framingham Risk Score points. Chi-square test was performed to determine statistical significant difference for remaining categorical variables.

Table 5.2. Univariate survival analyses between the Framingham Risk Score (FRS) risk factors and 10-year risk for coronary heart disease (CHD)

	Model One, Univariate		
RISK FACTOR	**HR**	**95% CI**	
Age	1.09	1.08	1.10
Blood Pressure, mm HG			
Optimal (SBP<120, DBP<80)	0.67	0.52	0.87
Normal (SBP <130, D<85)	1.00	- -	- -
High Normal (SBP <140, DBP<90)	1.36	1.06	1.76
Stage I HTN (SBP <160, DBP<100)	1.55	1.23	1.97
Stage II-IV HTN (SBP ≥160, DBP≥100)	1.34	0.89	2.04
Total Cholesterol, mg/dL			
<160	0.77	0.47	1.26
160-169	1.00	- -	- -
200-239	1.87	1.47	2.38
240-279	2.89	2.22	3.75
≥280	3.03	2.14	4.31
HDL-C[a], mg/dL			
<35	1.82	1.35	2.46
35-44	1.33	1.01	1.76
45-49	1.00	- -	- -
50-59	0.89	0.64	1.23
≥60	0.64	0.43	0.96
Diabetes	3.54	2.31	5.42
Current Smoking	1.51	1.22	1.87

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; HDL-C, high density lipoprotein- cholesterol; HR, hazard ratio; SBP, systolic blood pressure

Table 5.3. Model Building to assess the association between Framingham Risk Score (FRS) assessment, cardiorespiratory fitness (CRF), and coronary heart disease (CHD)

	Model I, Univariate model			Model II*			Model III†			Model IV±			Model V§		
RISK FACTOR	**HR**	**95% CI**		**HR**	**95% CI**		**HR**	**95% CI**		**HR**	**95% CI**		**HR**	**95% CI**	
FRS, points	1.36	1.32	1.40	1.34	1.29	1.39	1.36	1.32	1.41						
10 year CHD risk‖															
Low Risk	1.00	- -	- -							1.00	- -	- -	1.00	- -	- -
'Moderate or High' Risk	5.66	4.25	7.55							3.50	2.59	4.73	5.38	4.03	7.19
Maximally achieved METs Cardiorespiratory Fitness	0.80	0.77	0.83	0.95	0.91	1.00				0.82	0.79	0.85			
Low	1.00	- -	- -				1.00	- -	- -				1.00	- -	- -
Moderate	0.93	0.71	1.22				1.15	0.88	1.52				0.98	0.75	1.30
High	0.67	0.51	0.88				1.11	0.84	1.47				0.74	0.56	0.98

Abbreviations: CI, confidence interval; CHD, coronary heart disease; HR, hazard ratio

[*]Model II investigates the association between maximal METs achieved and CHD events while controlling for FRS point summation and baseline examination year

[†]Model III investigates the association between CRF categorized in to low, moderate, and high fitness and CHD events while controlling for summation of FRS points and baseline examination year

[±]Model IV investigates the association between maximally achieved METs and CHD events while controlling for 'moderate or high' 10 year CHD risk and baseline examination year

[§]Model V investigates the association between CRF categorized in to low, moderate, and high fitness and CHD events while controlling for 'moderate or high' 10 year CHD risk and baseline examination year

[‖]Low and ''moderate or high'' 10 year CHD risk is a comparative risk calculated from the summation of FRS points. 'moderate or high' risk is defined as a sum > 5 points.

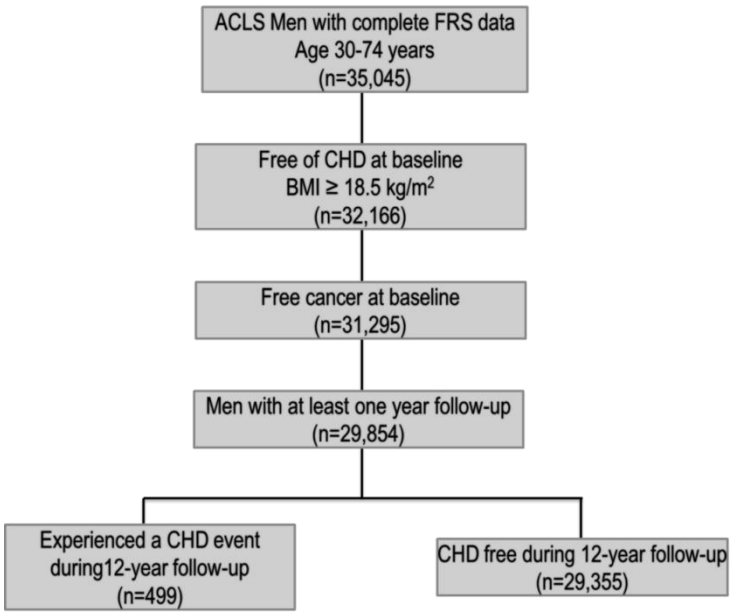


Figure 5.1. Study flow and Aerobic Center Longitudinal Study (ACLS) inclusion criteria depicting final sample size and coronary heart disease (CHD) event frequency

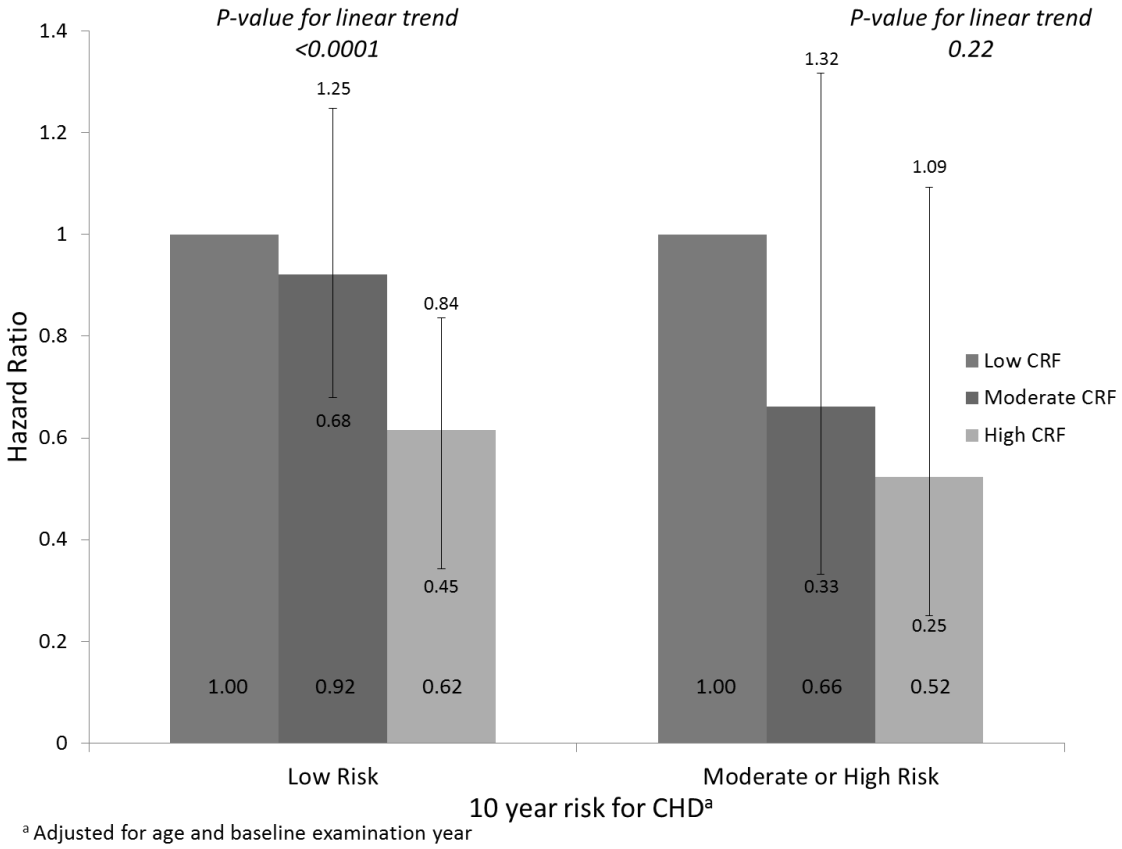


Figure 5.2. Adjusted Hazard Ratios and 95% confidence intervals (95% CI) for the relationship between cardiorespiratory fitness (CRF) and 10-year coronary heart disease (CHD) risk stratified by 'low' and 'moderate or high' risk. A significant inverse association is present among men with 'low' 10-year risk for CHD.

CHAPTER VI

Addition of Estimated Cardiorespiratory Fitness to the Clinical Assessment of 10-Year Coronary Heart Disease Risk in Asymptomatic Men[1]

[1]Gander J, Sui X, Hébert JR, Hazlett LJ, Cai B, Lavie CJ, Blair SN. To be submitted to *Journal of the American College of Cardiology*.

Abstract

The Framingham Risk Score (FRS) was developed to quantify a patient's CHD risk; although, many clinicians recognize its limitations. Cardiorespiratory fitness' (CRF) is protective of CHD events, however the measurement is often not clinically viable. Non-exercise estimated CRF (e-CRF) is a practical alternative that was computed and tested in relation to the FRS and CHD.

Methods

Male participants (n=29,854) enrolled in the Aerobics Center Longitudinal Study (ACLS), completed a baseline examination between 1979-2002, and were followed for 12 years to determine incident CHD defined either by self-report of myocardial infarction or revascularization, or CHD mortality. Estimated CRF was defined from a 6-item questionnaire and categorized using age-specific tertiles (low, middle, and high). Multivariable survival analysis determined the crude and adjusted association between FRS, e-CRF, and CHD. Interaction between e-CRF and FRS was tested by survival analysis on a population stratified by 'low' and 'moderate or high' 10-year CHD risk.

Results

Compared to men with low e-CRF, men with high e-CRF group was significantly (p-value < 0.0001) younger, had a higher proportion of optimal blood pressure, had a lower proportion of total cholesterol ≥ 240 mg/dL, and were less likely to be smokers. Unadjusted Cox analysis showed men with high e-CRF had a 36% (HR=0.64; 95% CI 0.51, 0.80) CHD risk reduction compared to the men with low e-CRF (p-value for trend <0.001). In men with 'low' 10-year FHS predicted CHD risk, men with high e-CRF were

28% (HR=0.72; 95% CI 0.0.57, 0.91) less likely to experience an incident CHD event compared to men with low e-CRF.

Discussion

Among men with 'low' risk for CHD, those who were more fit had a decreased risk for CHD compared to men in the lowest third of fitness. Estimated CRF can add clinical value to the FRS and help clinicians predict long-tern CHD risk.

Introduction

Despite the decrease in coronary heart disease (CHD) incidence worldwide in the past 30 years, [7,8] a decrease in age-adjusted CHD mortality in the United States (US), [184] and decrease in self-reported CHD [185] from 2006-2010, CHD remains one of the leading causes of death in the U.S. [186] CHD risk factors include diabetes, [16] hypercholesterolemia, [14] hypertension, [74] and smoking. [11] Risk scores have been developed to enable clinicians to quantify risk factors from their patients' medical histories in order to provide an estimate of CHD risk. [18,21,113]

Sposito et al [24] reports from a cross-sectional survey among physicians that those utilizing CHD risk scores primarily chose to use the Framingham Risk Score (FRS) [23]. The FRS was developed from the Framingham Heart Study (FHS) [23] and a 1998 version by Wilson et al [113] categorized the aforementioned risk factors to determine 10-year CHD risk and provide a score sheet for clinical implementation. The FRS' predictive power has persisted through validation in various populations [26,27] as well as modifications such as

the inclusion of apolipoproteins, [106] C-reactive protein, [29] and involuntary job loss. [30] Despite FRS' strengths and predictive power, clinicians from Sposito et al's analysis reported that the FRS was time-consuming and "does not add value to the clinical examination." [24]

Similar to the FRS, cardiorespiratory fitness (CRF)' protective effect on CHD [45,46] and other adverse events has been well documented. [34,43,88,127,141] In a study with more than 22,000 men, a significant interaction between body composition and CRF reported that unfit lean men had a significantly three times higher risk for CHD mortality compared to fit lean men; unfit men with normal body composition had a 2.94 (95% CI 1.48, 5.83) times higher risk compared to fit lean men. [46] CRF has traditionally been determined by an individual's sex- and age-specific maximal oxygen uptake that is ascertained through a maximal exercise test. Due to the methodologic rigor and associated high costs, CRF has not been easily captured in clinical settings.

Recently, a 6-item, non-exercise, scale estimating CRF (e-CRF) [171] was recently developed and incorporates age, body mass index (BMI), waist circumference, resting heart rate, smoking status, and physical activity. Physical activity was captured through a medical history questionnaire where participants reported their regular physical activity for the past 3 months. [41,172] Physical activity was then dichotomized in to two levels: none or low, and moderate or high physical activity. The accuracy of the developed algorithm was determine by computing the random intercept's square root of the sum and the residual variances. [171,173] Since the scale to calculate e-CRF was developed, no study has

investigated the association between e-CRF and CHD independently or in addition to a CHD risk score such as the FRS. This study was designed to expand on previous literature by determining the relationship between e-CRF and CHD. A second aim was to evaluate the potential for the e-CRF to add clinical value to the FRS by testing for improvement in predicting 10-year CHD risk.

Methods

Study Population

This study focused on men from the ACLS prospective cohort. The ACLS participants were recruited from patients attending the Cooper Clinic in Dallas, TX for a preventive medical examination and health behavior counseling. The participants completed a baseline examination at the Cooper Clinic from 1979-2002. Men were included in the analyses if they were between the ages of 30-74 years, had a BMI $\geq$18.5 kg/m^2, were free of a previous CHD, cancer, or stroke diagnosis at baseline, reached a $\geq$ 85% age-predicted maximal exercise heart rate at each visit, and had complete data with a minimum of one year of follow-up. Figure 1 displays the inclusion and exclusion criteria for this study.

Clinical Examination

Standardized protocols were followed by trained technicians at every clinical exam. Personal and family medical history was taken during the baseline examination.

Other clinical baseline measures included a 12-hour fasting cholesterol and glucose measurement, blood pressure assessment, electrocardiogram, anthropometric measurements, and a maximal exercise test. [112,164,166] A standardized questionnaire was used to capture an individual's current smoking status and medical history.

Measures

Definition of Outcome

CHD was defined either by self-reported myocardial infarction (MI), bypass, coronary balloon, angioplasty, or stent placement, or by CHD mortality. Self-reported history of CHD was collected through a mail-back survey administered in 1982, 1986, 1990, 1995, 1999, and 2004. CHD specific mortality was determined through linking the ACLS cohort with the National Center for Health Statistic's National Death Index. The primary cause of death was determined by International Classification of Disease Ninth (ICD-9) and Tenth (ICD-10) revisions. CHD mortality was classified with ICD-9 codes 410.0-414.0 and ICD-10 codes I20-I25. In accordance with FRS's follow-up definition, the cut-off for maximum follow-up time for CHD event was 12 years.

Primary Exposure

Estimated CRF (e-CRF) was expressed in metabolic equivalent of task (MET) units. METs were estimated using a 6-item questionnaire. [170,174] The sex-specific questionnaire is composed of a participant's age, BMI, waist circumference (WC), resting heart rate (RHR), two-level physical activity (activity), and smoking status (smoke). These variables are applied to Jackson et al's algorithm [171] below.

$$e - CRF = 21.2870 + (Age \times 0.1654) - (Age^2 \times 0.0023) - (BMI \times 0.2318) - (WC \times 0.0337) - (RHR \times 0.0390) + (Active \times 0.6351) - (Smoke \times 0.4263)$$

The estimated METs were categorized into three age-adjusted e-CRF tertiles: low, middle, or high e-CRF. This classification is similar to previous e-CRF studies [171].

Application of Framingham Risk Score

A composite 10-year CHD risk score was generated for each participant using the FRS. The FRS was derived from the Framingham Heart Study and the 1998 modeling [113] to predict 10-year CHD risk. The FRS is a sex-specific and age-adjusted risk score that incorporates categorical variables for blood pressure, total cholesterol, high density lipoprotein cholesterol (HDL-C), diabetes diagnosis, and smoking status. Point values were tabulated for each participant based on Wilson et al's study [113] and the cohort was stratified based on their 'low' or 'moderate or high' 10-year FHS predicted CHD risk. A point summation > 5 points was considered 'moderate or high' risk of FHS predicted CHD.

Statistical Analysis

Descriptive statistics were calculated for the total study population and stratified by e-CRF. Chi-square tests and Cochran Armitage trend tests were conducted to determine significant differences between the e-CRF levels and each risk factor. Death rate per 10,000 person-years for follow-up was calculated for e-CRF and 10-year FHS predicted CHD Risk. Crude Cox Proportional Hazard Models, adjusting for baseline

examination year, were generated to determine the association between e-CRF and CHD, and the relationship between 10-year FHS predicted CHD risk and actual CHD events. A fully adjusted Cox Proportional Hazard Model was used to determine the relationship between e-CRF, 10-year FHS predicted CHD risk and CHD. The effect of e-CRF on CHD also was investigated on population subsets defined by age, smoking status, hypertension status, and diabetes diagnosis. To investigate if there was a significant interaction between e-CRF and 10-year FHS predicted CHD risk, the male ACLS participants were stratified by 'low' or 'moderate or high' FHS predicted CHD risk and hazard ratios between e-CRF and CHD were calculated. The receiver operating characteristic (ROC) curves were plotted to determine if there was a significant improvement in the predictive accuracy of CHD by augmenting the FRS point summation with e-CRF. The chi-square test determined if there was a significant difference between the models. The Hosmer-Lemeshow statistics was used to asses calibration and goodness of fit; the statistics compares the predictive and observed events but is limited to sample sizes smaller than 10,000 observations. [169] To control for this limitation, a random sample population was generated from the larger study population to perform this goodness of fit test. SAS® version 9.3 was used to perform all descriptive, survival, and predictive analyses.

Results

There were 499 CHD events among 29,854 men (contributing 248,890 person-years of observation) (Figure 6.1). Table 1 displays the comparisons between men stratified by their e-CRF. Men with low e-CRF had a higher proportion of CHD events

compared to high fit men. Men with low e-CRF were also less likely to have optimal or normal blood pressure compared to men with moderate or high e-CRF. High-fit men were more likely to have increased levels of HDL-C ≥60 mg/dL, be nondiabetic, and be a nonsmoker compared to moderate or low-fit men.

Crude survival analysis, adjusted for baseline examination year, reported that both e-CRF and 'moderate or high' 10-year FHS predicted CHD risk were statistically significant with CHD (Table 6,2). In the crude Cox analysis, men with high e-CRF had a 36% (HR=0.64; 95% CI 0.51, 0.80) lower CHD risk compared to low fit men (p-value for trend <0.001). This significant association between e-CRF and CHD remained in a subsequent model controlling for 'moderate or high' 10-year FHS predicted CHD risk, although effect size was slightly attenuated. The significant protective effect between e-CRF and CHD was also found in subpopulations of male ACLS cohort members. Figure 2 reports that among men age ≥ 60 years, high fitness reduced CHD risk by 44% (HR=0.56; 95% CI 0.32, 0.97). Among non-smokers, men within the highest fitness tertile (HR=0.62; 95% CI 0.48, 0.79) had a smaller probability of a CHD event compared to non-smokers with low e-CRF. Although similar protective effects were present for the different classifications of hypertension, high e-CRF proved to be significantly protective against CHD in men with optimal blood pressure.

Figure 6.3 portrays the association between e-CRF and CHD stratified by 'low' and 'moderate or high' FHS predicted CHD risk. Men with 'low' 10-year FHS predicted CHD risk and high e-CRF have a 28% (HR=0.72; 95% CI 0.57, 0.91) lower risk of CHD

compared to men with low 10-year FHS predicted CHD risk and low e-CRF. In men with 'moderate or high' 10-year FHS predicted CHD risk, men with middle e-CRF were 38% (HR=0.62; 95% CI 0.32, 1.22) less likely to experience a CHD incident event compared to men with low e-CRF. High e-CRF also was associated with a protective effect (HR=0.69; 95% CI 0.31, 1.51) of CHD in men with 'moderate or high' FHS predicted CHD risk, although neither relationship was not statistically significant.

The receiver operating characteristic (ROC) curves were plotted for 'FRS point summation only' model and the 'FRS point summation with e-CRF' (Figure 6.4). The Area Under the Curve was higher for the 'FRS point summation with e-CRF' (c-statistic=0.7987; 95% CI 0.7813, 0.8161) compared to the model 'FRS point summation only' (c-statistic=0.7972; 95% CI 0.7798, 0.8146). The predictive power of these models was not significantly different (p-value=0.90) but the goodness of fit test reported that the predicted events were not different from the observed events with a Hosmer-Lemeshow p-value>0.05.

Discussion

Men with middle or high e-CRF were at a significantly lower risk for CHD compared to men with low e-CRF. Among men with 'low' FHS predicted risk for CHD, high fit men had a significantly lower risk for CHD compared to men with low fitness. To our knowledge, this is the first study to examine the relationship between e-CRF and CHD and the protective effect of e-CRF on CHD among men with 'moderate or high' risk for CHD by the FRS assessment.

The FRS has been validated in various populations with similar results to ours. Male physicians in the US, enrolled in the Physician's Health Study, reported their coronary risk factors through a questionnaire at enrollment and completed follow-up surveys every 6 months to capture CHD incidence. [27] The study found similar risk factors associated with CHD as those reported in the Framingham Heart Study, with the exception of smoking status. Additionally, D'Agostino et al conducted a comparison analysis to determine the level of agreement between the FRS applied to the Framingham Heart Study cohort and the FRS applied to non-Framingham Heart Study populations. They concluded that the level of agreement was reasonably sound between the predicted and actual CHD events, with the exception of the study implemented using the Japanese-American cohort. [28]

For the purposes of our study, 'moderate or high' CHD risk was defined through the 1998 FRS that quantified categorically-defined risk factors in to a composite score. [113] The age-adjusted composite score included CHD risk factors of hypertension, hypercholesterolemia, diabetes diagnosis, and smoking status. Many researchers report that the decrease in CHD-related mortality and CHD incidence could be attributed to the modification of these risk factors through prevention and close monitoring, improvements of modifiable lifestyle characteristics, [9,10] and pharmacologic treatment of risk factors out of acceptable ranges. [8]

Similar to the FRS, which was comprised by several risk factors, CRF also is a significant predictor of CHD and a modifiable risk factor. The Lipid Research Clinics Prevalence Survey [45] divided approximately 4,000 men in to a healthy and unhealthy group. Their investigation found that healthy men with high CRF had a lower risk for CHD mortality compared to men with low CRF; unhealthy men with a history of CVD and low CRF were 5.6 times more likely to die from CHD compared to men with a history of CVD and high CRF. [45] CRF's protective effect on CHD can be explained through moderate and high fit individual's having increased muscle mass [152], enhanced arterial oxygen content, [152,153] improved glycemic control, [66] increased double-product threshold for ischemic ST-segment depression, [154,155] and may protect against thrombosis [187] Several studies have reported on the modifiable qualities of CRF in various populations. [47,188-190] Oja et al's reported the significant improvement of heart rate recovery and maximal oxygen uptake (traditionally used to determine CRF) [47] after an 18-month, exercise training program. A meta-analysis reported similar findings to Oja et al's and concluded that exercises, varying in duration and intensity, also improved CRF with an average VO_{2max} increase of 11.8%. [137]

The current study expands on previous literature by investigating the protective effects of e-CRF on CHD. Estimated CRF offers the predictive capability of traditionally measured CRF [170] while reducing the cost/burden to the patient and clinician. As stated above, improvements in fitness as estimated by e-CRF may lead to additional improvements in other CHD risk factors such as hypertension and glycemic control and should be considered as part of primary and secondary prevention.

The limitations of this study should be noted and considered when determining generalizability. Due to the small number of CHD events occurring in women, only men were included in the present analysis. Future research should investigate the association between e-CRF and CHD in asymptomatic women. The non-significant association between e-CRF and CHD among stage II-IV hypertensive men may be due to the small proportions and generalizations toward this group should also be made cautiously. It also should be noted that the ACLS cohort consists predominately of non-Hispanic White individuals from middle to upper socioeconomic status who were relatively young (i.e., with a mean age of 42 years). Although this limitation may be considered a strength because of its tendency to improve internal validity while exerting inherent control for possible demographic confounders, generalizations and implementations of e-CRF should be made cautiously.

Conclusion

Our study found that among men with 'low' risk for CHD by the FRS, those with high fitness had a lower risk for CHD when compared to men with low fitness. Increasing awareness through early quantification of a patient's risk for CHD is important for CHD prevention. Although the FRS is a validated tool that enables physicians to assess an individual's risk, many clinicians have questioned the ability of the FRS to add to the standard overall clinical evaluation. Our results suggest that an assessment of e-CRF may add considerably to the clinicians' overall risk assessment for CHD. The results of this 6-item survey (age, waist circumference, BMI, physical activity, resting heart rate, and

smoking status) which can be quickly and easily collected during a clinical exam by paramedical staff, can help clinicians predict adverse CHD events and provide ammunition for the promotion of physical activity and exercise training for improving CRF and CHD risk. [182,183]

Table 6.1. Demographics of participants stratified by estimated cardiorespiratory fitness

RISK FACTOR	Total Population	Low e-CRF	Moderate e-CRF	High e-CRF	Cochran-Armitage Trend p-value
Number of CHD Events (%)	499 (1.67)	174 (1.75)	182 (1.83)	143 (1.44)	0.08
Age, range (years)	30-74	30-74	30-74	30-70	
Mean Age, y	44.7	49.7	46.8	42.1	<0.001
Moderate or High 10-year CHD risk	2.1	3.7	1.7	0.8	<0.001
Blood Pressure, mm HG					
Optimal (SBP<120, DBP<80)	28.8	16.6	29.4	40.4	<0.001
Normal (SBP <130, D<85)	31.8	29.2	33.7	32.6	<0.001
High Normal (SBP <140, DBP<90)	16.0	18.6	16.1	13.2	<0.001
Stage I HTN (SBP <160, DBP<100)	18.7	26.9	17.4	11.9	<0.001
Stage II-IV HTN (SBP ≥160, DBP≥100)	4.7	8.7	3.4	1.9	<0.001
Total Cholesterol, mg/dL					
<160	9.2	6.8	8.2	12.5	<0.001
160-169	34.1	28.7	33.3	40.3	<0.001
200-239	36.9	38.5	37.9	34.3	<0.001
240-279	15.3	19.6	15.7	10.6	<0.001
≥280	4.5	6.4	4.8	2.3	<0.001
HDL-C, mg/dL					
<35	15.6	24.8	14.2	7.9	<0.001
35-44	34.1	39.9	36.0	26.5	<0.001
45-49	15.6	13.8	16.7	16.2	<0.001
50-59	21.4	15.1	21.4	27.7	<0.001
≥60	13.3	6.5	11.7	21.7	<0.001

Diabetes	1.4	2.8	0.9	0.6	<0.001
Current Smoker	16.6	24.4	17.1	8.1	<0.001

Abbreviations: DBP, diastolic blood pressure; e-CRF, estimated cardiorespiratory fitness; HDL-C, high density lipoprotein- cholesterol; SBP, systolic blood pressure

Table 6.2. Adjusted survival risks for coronary heart disease (CHD) events by estimated cardiorespiratory fitness (e-CRF) or 10-year CHD risk group

	N	Number of Deaths	Death Rate*	HR (95% CI)†	HR (95% CI)‡
Estimated CRF (e-CRF)					
Low	5970	152	31.93	1	1
Moderate	11942	211	18.90	0.93 (0.76, 1.14)	0.99 (0.81, 1.22)
High	11942	136	10.31	0.64 (0.51, 0.80)	0.71 (0.56, 0.88)
P value for trend				<0.001	0.003
10-year CHD Risk					
Low	29241	447	18.34	1	1
Moderate or High	613	52	102.58	5.59 (4.20, 7.45)	5.25 (3.92, 7.01)

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio

*Deaths per 10,000 person-years of follow-up adjusted for examination year

† Adjusted for examination year

‡ Further adjusted e-CRF for 10-year CHD risk or 10-year CHD risk for e-CRF

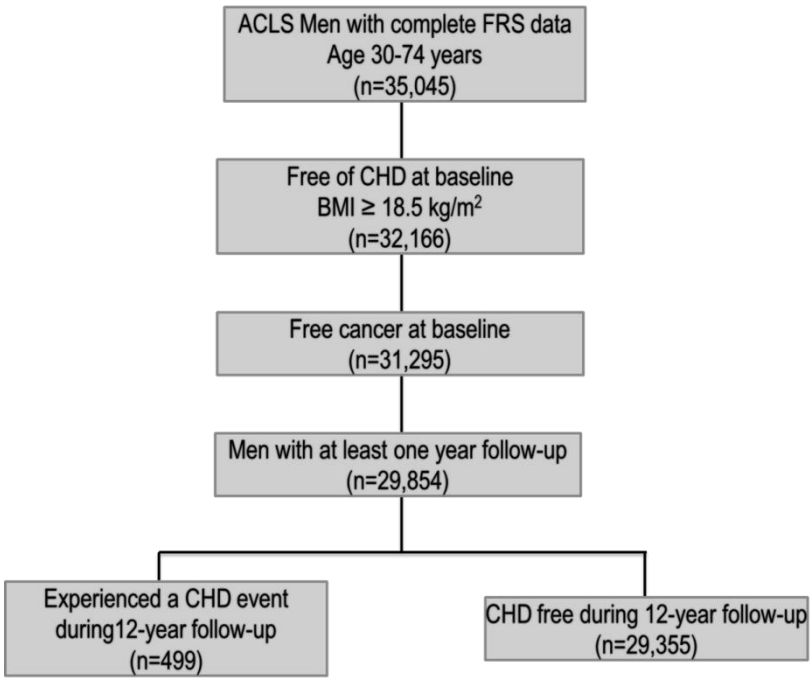


Figure 6.1. Inclusion criteria for the study population from the Aerobic Center Longitudinal Study (ACLS) inclusion criteria depicting final sample size and coronary heart disease (CHD) event frequency. Men with complete Framingham Risk Score (FRS) data, estimated cardiorespiratory fitness (e-CRF) data, and body mass index (BMI) $\geq$ 18.5 kg/m^2 were included in the analysis.

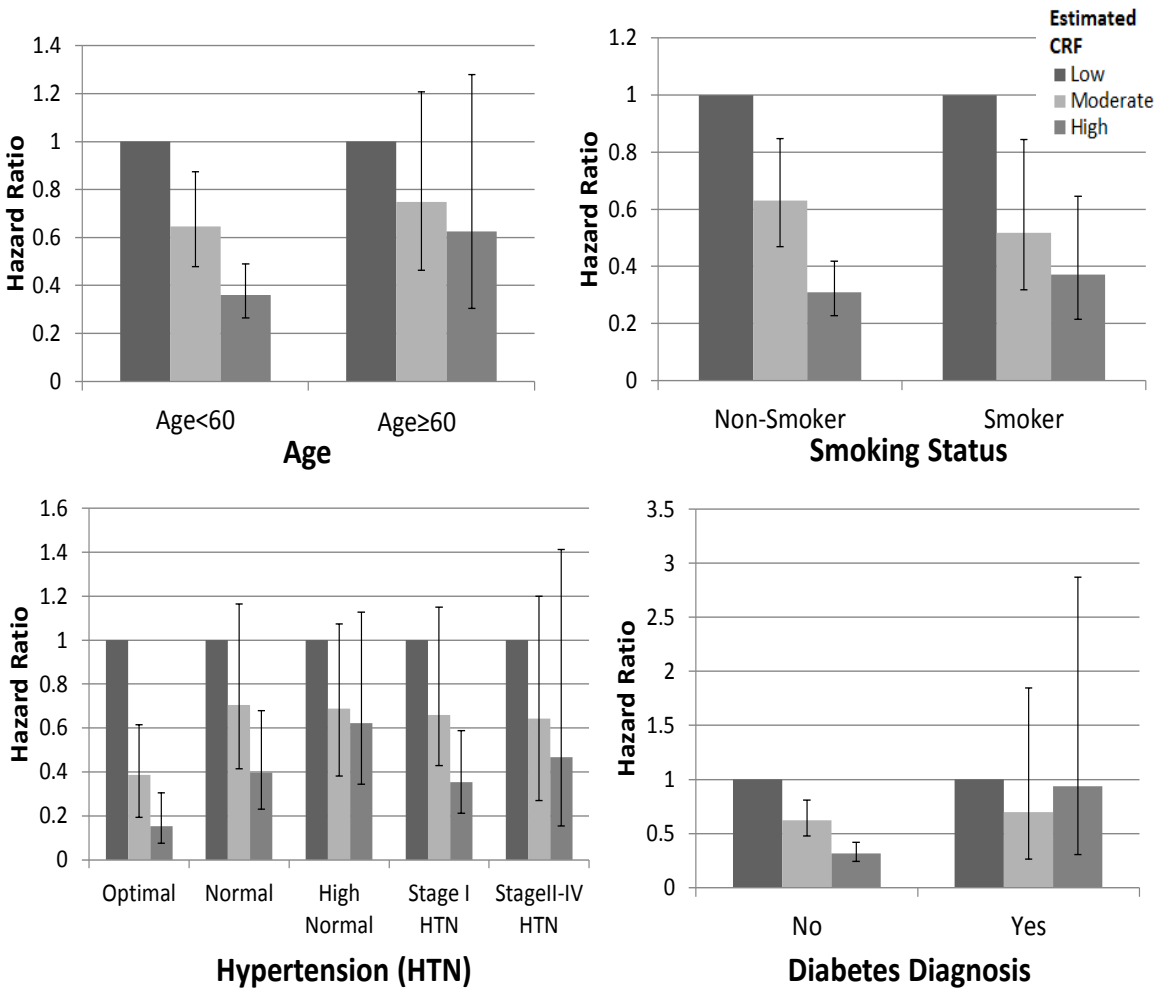


Figure 6.2. Multivariable adjusted hazard ratio and 95% confidence intervals for estimated cardiorespiratory fitness (e-CRF) and coronary heart disease (CHD) events among population subsets. Survival models are adjusted for baseline examination year.

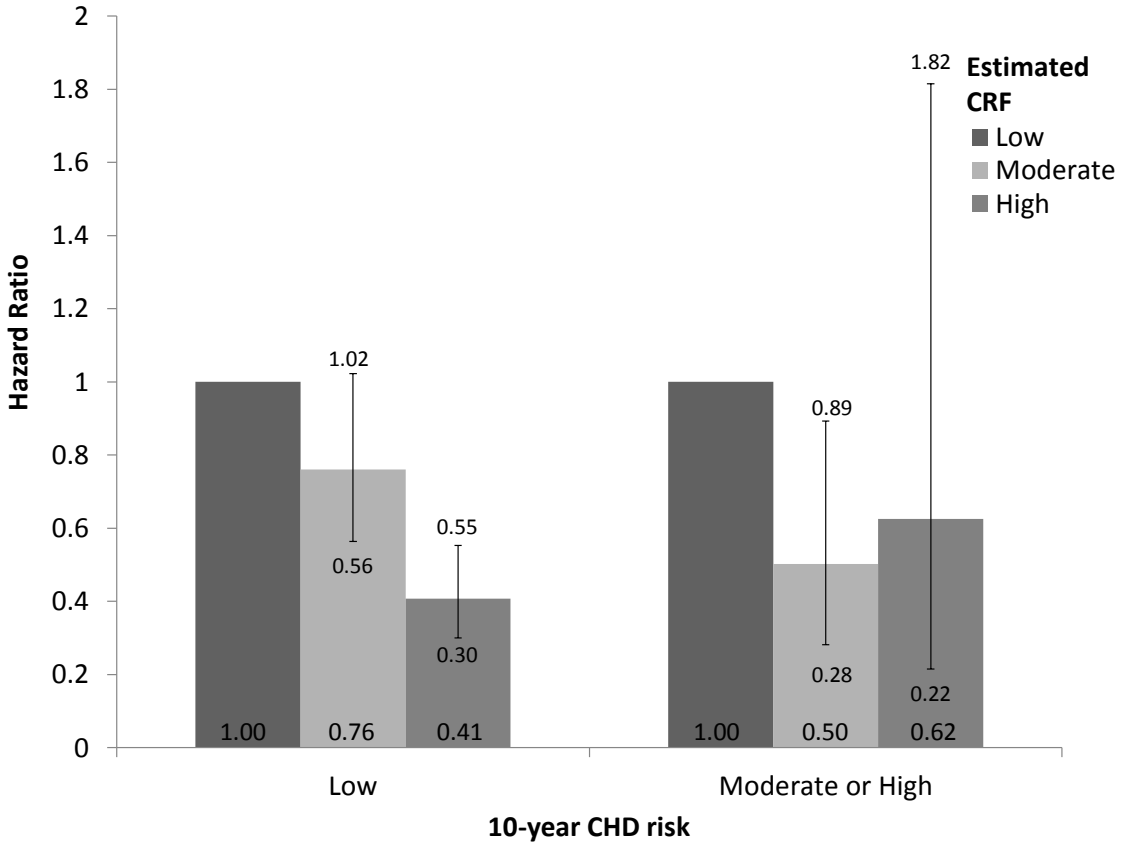
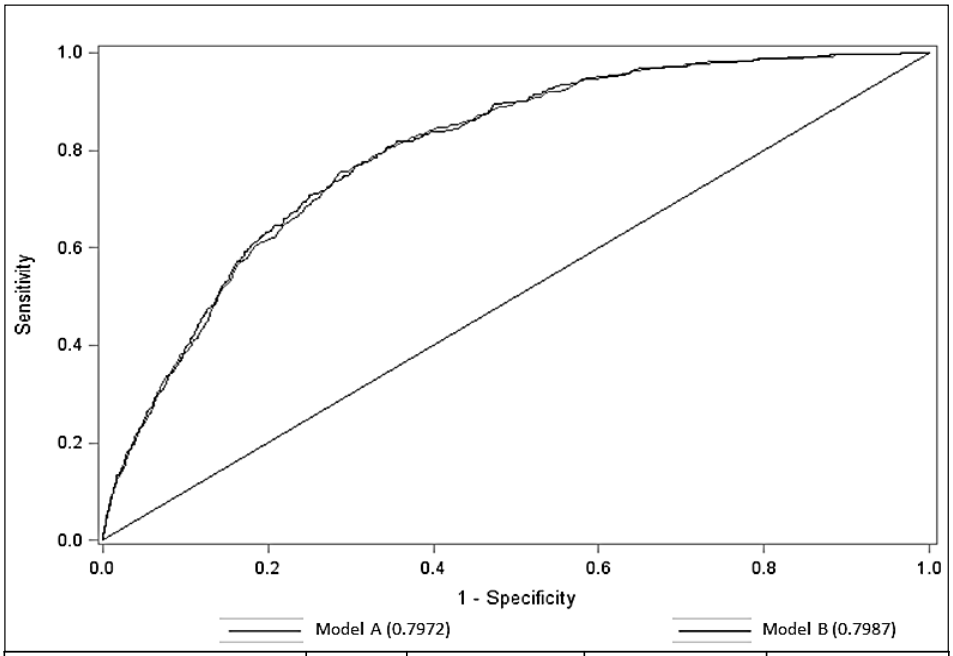


Figure 6.3. Adjusted survival analysis to determine the association between estimated cardiorespiratory fitness (e-CRF) and risk of CHD. Population was stratified by 'low' and 'moderate or high' 10-year Framingham Heart Study (FHS) predicted CHD risk to display the interaction between 10-year CHD risk and CRF.



Model	Area Under the Curve	95% Confidence Interval		ROC curve difference p-value	Predicted and Observed events p-value
A. Framingham Risk Score point summation	0.7972	0.7798	0.8146	0.9046	0.1313
B. Framingham Risk Score point summation and e-CRF	0.7987	0.7813	0.8161		

Figure 6.4. Receiver Operating Characteristic Curve comparing the predictive ability of the Framingham Risk Score (FRS) point summation (Model A) compared to the Framingham Risk Score point summation and estimated cardiorespiratory fitness (e-CRF) (Model B). Both models were applied to the ACLS cohort with a 12 year follow-up. The Hosmer-Lemeshow c-statistic is represent by the Area Under the Curve for Model A(c=0.7972; 95% CI 0.7798, 0.8146) and B (c=0.7987 95% CI 0.7813, 0.8161) with no significant difference (p=0.9046). The chi-square test for difference between predicted and observed events is not significantly different (p=0.1313).

CHAPTER VII

SUMMARY

Coronary heart disease (CHD) incidence has decreased worldwide in the past 30 years. [7,8] Age-adjusted CHD mortality has decreased in the U.S., [184] and self-reported prevalence in the U.S. has also decreased [185] from 2006-2010. Despite these statistics, CHD still remains one of the leading causes of death in the U.S. [186] The Framingham Risk Score (FRS) is an age-adjusted, sex-specific composite score that incorporates CHD risk factors such as hypertension, hypercholesterolemia, diabetes diagnosis, and smoking status. The FRS does not include cardiorespiratory fitness (CRF), a factor consistently shown to have a protective effect on CHD [45,46] and other adverse outcomes. [34,43,88,127,141]

The purpose of this research was to validate the FRS in the Aerobics Center Longitudinal Study (ACLS) cohort; update and improve the predictability of the FRS through the addition of CRF while resolving limitations in previous studies; and assess the predictability of non-exercise estimated CRF (e-CRF) and FRS on CHD.

PAPER 1: Framingham Risk Score applied to the Aerobic Center Longitudinal Study (ACLS)

Risk factor scores, have been developed to help clinicians quantify their patient's CHD risk, [18,23,113] and the FRS is the most commonly used. [24] Although the FRS has been validated in various populations, [6,26,175] most lacked congruency with FRS methodology or had small sample sizes. This paper aimed to improve upon recent literature by strictly applying the FRS to the large ACLS cohort. We hypothesized that the FRS would be significantly predictive of CHD events for men within the ACLS population.

Data collected from men (n=34,557) in the ACLS cohort were used to complete the multivariable survival analysis and determine the relationship between FRS variables and 10-year CHD risk. The FRS variables included age, systolic and diastolic blood pressure, total cholesterol, high density lipoprotein cholesterol (HDL-C), diabetes diagnosis, and smoking status. The analysis found that the FRS variables applied to the ACLS cohort had similar results compared to the original publication, [113] with a predictive statistic of 0.77 (95% CI 0.75, 0.79). This study further validates the FRS predictive ability of 10-year CHD risk although limitations still exist. To control for potential limitations, future research should focus on the expansion of the FRS to include other modifiable risk factors, such as CRF.

PAPER 2: Augment the Framingham Risk Score (FRS) applied to the Aerobic Center Longitudinal Study (ACLS) with the addition of Cardiorespiratory Fitness (CRF)

The FRS provides a sex-specific, age-adjusted risk score that accounts for systolic and diastolic blood pressure, total cholesterol, high density lipoprotein cholesterol, diabetes diagnosis, and smoking status. [25] Previous studies [29,30,104] have modified the FRS to include additional risk factors. None of these modifications involved the addition of cardiorespiratory fitness (CRF), a characteristic that has shown significant protective effects for all-cause mortality, [43,136] cancer-related mortality, [139] diabetes incidence, [34] CHD incidence [47] and mortality. [25,45,46] In this paper, we aimed to expand on previous literature by modifying FRS with CRF and hypothesized that CRF would improve the FRS predictive ability of CHD events for men within the ACLS population.

The ACLS cohort was utilized for this analysis and included men who completed a baseline examination between 1970 and 2003 (n=29,854). FRS was applied as a composite score to each participant and a binomial ('low' and 'moderate or high') 10-year CHD risk was determined. Multivariable Cox Regression analysis was used to determine the relationship between CRF, FRS, and CHD. The population also was stratified by 'low' and 'moderate or high' risk for CHD to test for interaction between CRF and FRS. The study concluded that men within the 'low' 10-year CHD risk strata and moderate (HR=0.92 95% CI 0.68, 1.25) or high (HR=0.62, 95% CI 0.45, 0.84) CRF had a lower probability of experiencing CHD compared with men in the same strata with

low CRF *(p-value <0.001).* CRF is a modifiable risk factor with a protective association with CHD. It may be advantageous for clinicians to evaluate a patient's CRF to provide a more accurate assessment of the 10-year risk for CHD.

PAPER 3: Determine the association between non-exercise estimated CRF (e-CRF) and CHD. Utilize e-CRF and FRS to predict the risk of CHD.

Determining a patient's risk for CHD early is important to primary prevention. The FRS was developed to assist physicians in completing this task. The FRS' predictive power has been consistent in various populations [26,27] and additions of various risk factors [29,30,106] but some physicians still believe the FRS does not provide additional clinical value [24]. CRF's significant predictive effects on CHD have also been well documented, however, until recently, CRF was not easily ascertained in a clinical setting [170]. Our aim for this study was to improve on the FRS and CRF limitations by analyzing non-exercise estimated CRF (e-CRF) with FRS to predict 10-year CHD.

Men (n=29,854) in the ACLS cohort who completed a baseline examination at the Cooper Clinic in Dallas, TX were included in the analysis. Crude and adjusted Cox Proportional Hazard Ratios were calculated for the association between estimated CRF (e-CRF), FRS, and CHD. The relationship between e-CRF and CHD was also analyzed in subsets of the population based on age, smoking status, hypertension, and diabetes diagnosis. To test for interaction between e-CRF and FRS, a survival analysis between e-CRF and CHD was conducted on a population stratified by 'low' and 'moderate or high'

10-year CHD risk. Our main finding from these analyses was that among men with 'moderate or high' risk for CHD, men with moderate e-CRF were 50% (HR=0.50; 95% CI 0.28, 0.89) less likely to experience a CHD incident compared to men with low e-CRF. A secondary finding was that the significant protective effect e-CRF has on CHD among population subsets. Among current smokers, men with moderate e-CRF (HR=0.52; 95% CI 0.32, 0.84) or high CRF (HR=0.37; 95% CI 0.22, 0.65) had a smaller probability of a CHD event compared to current smokers with low e-CRF. This study provides additional clinical value to the FRS by augmenting the traditional risk score with e-CRF.

OVERALL DISCUSSION AND FINDING

CHD is one of the leading causes of death in the U.S. and early establishment of CHD risk is important for primary and secondary prevention. The FRS encompasses some of CHD's major risk factors, except CRF is not included. A recent study provided researchers and clinicians with a tool to determine a patient's non-exercise estimated CRF through a 5-item scale. The series of papers presented in this dissertation provide the evidence needed to establish a more comprehensive and clinically feasible CHD risk prediction tool. This research concludes that the FRS was consistently predictive of 10-year CHD events. FRS's effect is improved through the addition of CRF to provide a more clinically accurate prediction of individual 10-year CHD risk. Clinicians may want to consider capturing their patients' medical history, CHD risk factors, and their e-CRF so they can take advantage of CRF's improved prediction of CHD. This comprehensive

approach can help physicians predict adverse events for their patients while also counseling them on how to improve their overall health through improvement of CRF.

FUTURE DIRECTIONS AND RESEARCH

There are several research ideas that stem from the presented conclusions. To further the presented results in each of the three papers, the analysis should be replicated for females. FRS [104] and CRF [42,85] have both been shown to have significant associations with CHD and other outcomes but the combined association with FRS and CRF should be assessed with the CHD outcome in women. To improve the external validity of our findings, the association between FRS, CRF, and CHD will need to be investigated in women.

Future studies may want to replicate these FRS analyses using D'Agostino et al's [176] 2008 version, which focuses on cardiovascular disease (CVD) as an outcome which encompasses CHD diagnosis, as well as stroke and coronary artery disease. Although CHD comprises the majority of CVD diagnoses, utilizing a CVD risk score may provide a prediction with broader implications but may be potentially less accurate.

Furthermore, e-CRF relationship with other adverse outcomes should be explored. Since Jurca et al [170] published the non-exercise e-CRF scale, the scale has been validated [191] and applied to selective populations such as older adults [192]. The measurement of e-CRF may provide significant interpretations for both research and clinical settings. Future clinical research should focus on capturing e-CRF to analyze effects on short and long-term outcomes. CRF's ability to be modified through exercise [47,137] and CRF's effect on

CHD risk factors such as glycemic control an cholesterol make e-CRF a very useful measure for the clinical setting.

CONCLUSION

This dissertation involved implementing sophisticated, predictive modeling to determine the association between CRF, FRS, and CHD. The statistical analyses were based on a subset of data from ACLS, a large cohort derived from the patients of the Cooper Clinic in Dallas, TX. The information and interpretations gained from this research provide further comprehension of FRS and CRF as well as suggestions for new clinical protocols for physicians to consider. We stress the importance of a comprehensive medical approach while balancing the burden placed on the physician and patient. We believe that e-CRF is an accurate assessment tool for CHD independent of, and jointly with FRS, and should be implemented in the clinical setting.

This dissertation process was a valuable experience that enhanced my appreciation of academia and clinical research. My dissertation challenged me academically to apply and interpret statistical methodology I had not previously learned. The receiving operating characteristic (ROC) curve helps determine the predictability of a model on the outcome of interest and was applied to each of the three manuscripts. I had to go beyond the simple application of the ROC curve and determine if this analytical method was appropriate for the data by examining the ROC curve's strengths and limitations. Fortunately, academia recognizes the necessity for collaboration to generate and test research hypothesis. The collaboration characteristic of academia made learning

a new statistical method easier because it enabled me to consult with other researchers and gain their perspective on this method and the best approaches.

Collaborating can also save time and provide motivation to complete a project. When I initiated my dissertation and began to formulate my scope and specific aims, I did not fully appreciate the limiting ability of data or other student's work-in-progress. After review of the published literature and months developing potential aims, I drafted and discussed a miniature proposal with my chair and co-chair. This collaboration helped me refine my specific aims, determine the potential variables that were available for analysis, and learn about the ongoing projects my peers were investigating in the ACLS cohort. Without this collaboration, I might have spent a few more months developing hypotheses that could not be investigated in ACLS or that another researcher was already developing.

Throughout my time spent obtaining my doctoral degree, I began my transition from an epidemiology student to a career as a junior epidemiologist. Part of this transition encompassed enhanced partnership with physicians and medical staff. My involvement with clinical research has forced me to acknowledge limitations such as imperfect data and limited sample size while capitalizing on the strength of the data. The enhanced appreciation for clinical research while still working with a large, prospective cohort provided me the opportunity to engage in the full spectrum of study designs. With encouragement from my dissertation committee and my clinical research colleagues, I have begun developing research projects to apply the knowledge and research experience that I gained during my dissertation with ongoing or new clinical research ideas.

This dissertation process has served as a hands-on learning experience that enhanced my epidemiological and statistical knowledge, improved my analysis and research skills, and enabled me to bridge my past research interests and experience with new opportunities. I hope to continue my work with both the University of South Carolina and my clinical research team to help integrate estimated cardiorespiratory fitness in a clinical setting and show clinicians the value of this metric.

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APPENDIX A

EVIDENCE OF PERMISSION TO PUBLISH AND PRINT CHAPTER IV Factors Related to Coronary Heart Disease Risk in Men: Validation of the Framingham Risk Score

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