The Effect of Exercise Training on Cardiovascular Mortality Risk

by

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PURPOSE: Clinicians use risk calculators in primary prevention to estimate CVD mortality. A potential limitation of available risk calculators are they generally estimate risk based on traditional risk factors, which is problematic since cardiorespiratory fitness (CRF)/physical activity are independent predictors of CVD. To address the limitations, Wickeramasinghe et al. developed a calculator to assess 30-year CVD risk that includes CRF as a variable, along with traditional risk factors, but few studies have evaluated the impact of aerobic training on this risk score. The purpose of the present study was to evaluate the effect of aerobic exercise training on 30-year CVD risk. METHODS: The study included adults with elevated CRP levels who were randomized to an aerobic exercise group or a control group. Baseline and follow-up data (age, total cholesterol, systolic blood pressure, diabetes, body mass index, fitness level, and smoking status) were entered into the Wickeramasinghe et al. [1] calculator to calculate 30-year CVD mortality risk. The aerobic exercise intervention lasted 4 months and individuals expended approximately 16 kcal/kg per week (KKW). The control group was asked to maintain their sedentary status over the course of the intervention. RESULTS: A significant reduction in 30-year CVD risk mortality was observed between the exercise and the control group following the intervention (-0.5[CI: -1.3,0.4] versus -2.0[CI: -2.9, -1.1]. There was a significant increase in

METs following the aerobic exercise intervention (p<.0001), but there was no significant changes in body mass index, total cholesterol, or systolic blood pressure. Also further, among those with high CVD risk a reduction in 30- year CVD mortality risk between the control group (-1.3[CI: -2.8, 0.26])and the exercise group (-3.5[CI:-5.5,-1.6]) following the exercise intervention approached significance. DISCUSSION: Results from the present study suggest that four months of aerobic exercise training resulted in a small reduction in estimated 30-year CVD mortality in a risk calculator that includes traditional risk factors and CRF. Future studies should investigate the relationship between CRF and estimated CVD mortality following a longer aerobic exercise intervention, in different study populations, and following different aerobic exercise programs.

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List of Abbreviations

Cardiovascular Disease (CVD)

American Heart Association (AHA)

Atherosclerotic cardiovascular disease (ASCVD)

Cardiorespiratory Fitness (CRF)

Inflammation and Exercise Study (INFLAME)

High- Density Lipoprotein (HDL)

Low- Density Lipoprotein (LDL)

Net Reclassification Improvement (NRI)

Integrated Discrimination Improvement (IDI)

Dual X-ray Absorptiometry (DXA)

Kcal/kg Per Week (KKW)

Analysis of Covariance (ANCOVA)

Chapter I: Introduction

Cardiovascular disease (CVD) is the leading cause of death in the United States for both men and women [2]. According to the American Heart Association (AHA), the rate of death from CVD is 235.5 per 100,000 individuals [2]. Risk assessment calculators are used to estimate CVD risk, and identify patients at moderate or high risk of developing CVD [3]. The calculators can also be beneficial to patients to help educate the individual on how the combination of risk factors affect overall CVD risk [3]. In 2013, the AHA released the pooled cohort equations which estimate sex and race specific 10-year risk of atherosclerotic cardiovascular disease (ASCVD) (nonfatal myocardial infarction, coronary heart disease, or death) based on a patient's history of CVD, age, total cholesterol, high- density lipoprotein cholesterol, untreated or treated systolic blood pressure diabetes mellitus, and current smoking status [4]. While risk calculators are useful in primary prevention, a major limitation of the pooled cohort equations and previous risk calculators [3] is that they do not incorporate a variable that represents physical activity, exercise or cardiorespiratory fitness (CRF) in their risk prediction.

The 2008 Federal physical activity guidelines recommends at least 150 minutes a week of moderate-intensity aerobic physical activity [5]. Recommendations of the 2008 Federal physical activity guidelines are based on epidemiological studies that have found that there is a relationship between physical activity and health [5]. A recent study, found that a 1 MET increase in CRF was associated with a 15 % reduction in CVD mortality [6]. Despite the current physical activity guidelines, current calculators do not have a physical activity or a CRF variable. Physical activity, exercise and CRF levels are likely important components in the prediction of CVD because as mentioned previously they are independent predictors of CVD [7, 8]. Importantly, these relationships are independent of traditional CVD risk factors included in available risk calculators such as lipids, blood pressure, and weight [3]. Therefore, the lack of an exercise or CRF variable could potentially lead to inaccurate estimation of CVD and may attenuate the estimated improvement of CVD risk from exercise. In addition, this is problematic especially when a clinician evaluates the change in CVD risk after aerobic exercise training because the changes are fully dependent on the changes in the calculators' risk factors, specifically blood pressure and cholesterol (if using the pooled cohort equations as an example). Studies have shown that aerobic exercise may reduce blood pressure, but changes in lipoprotein levels (e.g. total and LDL cholesterol) are inconsistent with aerobic exercise [9-14]. For example, if a patient begins an exercise-training program and the change in CVD risk is estimated using the pooled cohort equations, ASCVD risk would not decrease if the patient had no reductions in blood pressure and lipids, leading to inaccurate estimation of ASCVD risk. Thus, the addition of an exercise variable (such as CRF) within current risk calculators may increase the overall accuracy of estimating CVD mortality and more accurately determine the change in risk of CVD with exercise training.

To address the aforementioned limitations, Wickramasinghe et al. [1] developed a calculator that predicts 30-year cardiovascular mortality based on CRF and other traditional risk factors (age, blood pressure, blood lipid concentrations, diabetes mellitus, total cholesterol, and smoking status). The Wickramasinghe et al. [1] calculator was developed using data from the Cooper Center Longitudinal study and has overall good calibration in both men and women (men, 10.85 [p=0.286] and women, 6.7 [p=0.664]). Participants ranged in age from 20-90 years and were mostly Caucasian (n=16,533) [1]. The variables included in the Wickramasinghe et al. [1] calculator include age, systolic blood pressure, smoking, diabetes mellitus, total cholesterol, BMI, and CRF. At the present time, it has been unexplored to the extent which CVD mortality risk is modified by aerobic exercise training. The Wickramasinghe et al. [1] calculator addresses the limitations of previous calculators by including CRF as a variable in CVD risk assessment and therefore accounts for exercise habits. Understanding the extent to which aerobic exercise training modifies CVD risk mortality is beneficial to society because it will give the clinician the capability to inform patients about the overall effect of aerobic exercise training on CVD mortality, which may help encourage participants to begin and maintain exercise training habits.

The purpose of the present study was to determine the effect of exercise training on cardiovascular mortality risk as estimated by Wickramasinghe et al. [1] calculator using data. We will utilize data from the Inflammation and Exercise Study (INFLAME), which evaluated the effect of 4 months of aerobic exercise training on c-reactive protein (CRP) in adults [15]. Data from the INFLAME study will be entered into the Wickramasinghe et al. [1] calculator at baseline and follow-up to determine change in 30-year CVD mortality at after exercise training.

We hypothesized that 30-year CVD risk will decrease after implementing an aerobic exercise program in the group participating in aerobic exercise training. CRF should increase after aerobic exercise training and this may be one of the critical factors in the improvements in blood pressure [6, 8, 13, 14].

Limitations

Limitations of the study included participants that were mostly Caucasians, limiting the generalizability to specific populations. The exercise intervention lasted 4 months. If the exercise intervention lasted for a longer period of time greater reductions in 30-year CVD mortality may have been observed. Aerobic exercise training was also limited to the cycle ergometer or the treadmill.

Delimitations

Delimitations of the study included only observing effects of CVD risk reduction in sedentary adults with elevated CRP concentrations, with no past serious medical conditions, heart attack, stroke, diabetes, and no smoking history. The exercise sessions were also supervised for exercise adherence.

Key Terms

CVD: Group of disorders of the heart and blood that include coronary heart disease, cerebrovascular disease, peripheral artery disease, rheumatic heart disease, heart attack, stroke, and pulmonary embolism.

30-year CVD mortality: Estimated risk of death associated with a cardiovascular death in a 30-year span

Atherosclerotic cardiovascular disease (ASCVD): Nonfatal myocardial infarction, coronary heart disease or nonfatal stroke

Physical activity: Bodily movement that is produced by the contraction of skeletal muscle and that substantially increases energy expenditure.

Exercise: A type of physical activity that is defined as planned, structured, repetitive bodily movement done to improve or maintain on one or more component of physical fitness

CRF: Is a health- related component of physical fitness that related to the ability of the circulatory and the respiratory systems to supply fuel during sustained physical activity

Chapter II: Literature Review

Importance of Risk Calculators for Screening

Cardiovascular disease (CVD) is a group of disorders of the heart and blood that include coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, heart attack, stroke, and pulmonary embolism [2]. CVD is the leading cause of death in both men and women in the United States [2]. According to the American Heart Association, approximately 83.6 million Americans have 1 or more types of CVD, resulting in the rate of death to be 235.5 per 100,000 [2]. Modifiable risk factors that contribute to CVD mortality include hypertension, smoking, dyslipidemia, type 2 diabetes, and an inactive sedentary lifestyle [16].

Cardiovascular risk calculators allow clinicians to identify patients with moderate or high CVD risk and represent an important component of primary prevention [3]. For example, the Framingham risk score calculates an individual’s 10-year absolute risk of CVD based on the risk factors that include history of CVD, age, gender, diabetes, smoking, blood pressure, and blood lipid concentrations [17]. The American Heart Association pooled cohort equations estimate an individual’s 10-year risk of developing atherosclerotic cardiovascular disease (ASCVD) (risk of developing a first ASCVD event, defined as nonfatal myocardial infarction or coronary heart disease death or fatal or nonfatal stroke) based on age, total cholesterol, high- density lipoprotein cholesterol, untreated or treated systolic blood pressure, diabetes mellitus, and current smoking status [4]. Not only do these estimation tools provide a pathway for clinicians to formulate a prevention plan, but it also helps the clinician and the patient understand the complexity of their risk factors, and how the combination of risk factors affect overall CVD risk [3].

Lack of Assessment for Exercise in Risk Calculators

The Federal Physical Activity Guidelines recommends 150 minutes a week of moderate intensity aerobic physical activity or 75 minutes of vigorous aerobic physical activity at minimum for health benefits associated between physical activity and CVD [5]. Despite these recommendations, the available risk calculators fail to include a variable that represent physical activity habits within their algorithms. Importantly, both cardiorespiratory fitness (CRF) and physical activity are well-established independent predictors of CVD and are independent of traditional CVD risk factors lipids, blood pressure, and weight [18].

Therefore the exclusion of CRF in available risk calculators may lead to an inaccurate estimation of CVD mortality and may undervalue the improvement in CVD risk from exercise training. For example, if a patient engaged in a lifestyle modification program that included exercise training and the change in risk as estimated by the calculator would be fully dependent on the lipid and blood pressure changes (if using the pooled- cohort equations). Thus, the overall risk calculation will not reflect the reduction in CVD due to the potential increase in exercise or physical activity. If the risk estimation calculators used CRF as a variable a clinician could assess an individual’s risk before and after starting an exercise program to observe the decrease in CVD risk independent of other risk factors. This could be beneficial to the clinician because the estimation of CVD risk will be more accurate. Using CRF as an independent variable in risk estimation calculators could also be beneficial to patients, because it could educate the patients on the benefits of exercise training and the effects that exercise training has on decreasing CVD risk.

The variables in the risk assessment tools that may potentially be affected by exercise training currently in the available calculators include blood lipid concentrations, which include high-density lipoprotein (HDL) and low-density lipoprotein (LDL). Systolic blood pressure may also be affected by exercise training. Many studies have observed that exercise training do not have a major effect on plasma lipids, and changes that are observed are modest and are mainly due to weight loss [9-12]. For example a study by Desprès et al. [9] (n=13) observed no changes in triglycerides, HDL's, or total cholesterol after a 20-week aerobic training program on a bike. A study by Kraus et al. [10] (n=159) observed that there were no significant changes in total cholesterol or LDL cholesterol with exercise training, but there was a only a significant effect on HDL levels with the high amount high intensity group ($p < 0.0167$). At baseline the high-amount-high-intensity group HDL cholesterol was 44.3 +- 2.9 mg/dL and at the end of the study HDL cholesterol was 48.6 +- 3.3 mg/dL[10]. The study also revealed that a decrease in total cholesterol was due to decreases in caloric intake, while decreases in triglycerides were mainly due to higher baseline levels, and reduced total cholesterol is associated mainly with a reduction in body weight and caloric intake after exercise training[10]. During the cohort study at the Healthy Heart Program Prevention Clinic (n=248), Meikle et al. [12] observed that men did not have a significant reduction in their total and LDL cholesterol after exercise training (30 minutes of moderate physical activity a day), and they did not significantly increase their HDL cholesterol. The change in total cholesterol from the first to last visit was -1.29 +- 2.5 mg/dL, for LDL a change of -0.6 +- 1.3 mg/dL, and a change in HDL of only 0.1 +- 0.3 mg/dL [12]. The available literature [9-12] shows that exercise training has a minimal or modest effect on total, LDL, and HDL cholesterol changes are not associated with an increase in CRF.

It has long been known that exercise training improves blood pressure, but recently many studies have shown that improvements are moderate with systolic blood pressure decreasing by -2.4 to -5 mmHg and diastolic blood pressure decreasing by -4 to -1.7 mmHg [13, 14]. In a meta-analysis on the effect of exercise training on blood pressure, Whelton et al. [13] observed that in 44 out of 53 trials systolic blood pressure decreased, but it was only significant in 20 trials. Whelton et al. [13] also observed that diastolic blood pressure decreased in 42 out of 50 trials and was only statistically significant in 16 trials. The overall effect of aerobic exercise on systolic blood pressure was -3.84 mmHg (95% CI, -4.95 to -2.72 mmHg; $p < 0.001$) and diastolic blood pressure was -2.58 mmHg (95% CI, -3.35 to -1.81 mmHg; $p < 0.001$)[13]. In a meta-analysis of 72 trials Cornelissen et al. [14] observed that the exercise induced change in blood pressure averaged -3.3 mmHg (95% CI, -5.8 to -0.9) to -3.5 mmHg (95% CI, -5.2 to -1.9) ($p< 0.01$). The literature suggests that blood pressure may decrease slightly with exercise.

The studies mentioned above show that improvements in blood pressure and cholesterol are moderate with exercise training. Changes in blood pressure and cholesterol are dependent on individual variability. Improvement in cholesterol is also mainly due to weight loss and not exercise. This could be a limitation of risk assessment calculators. For example, a patient could start a lifestyle intervention program, such as exercise training, involving a baseline and post intervention clinical visit to assess CVD risk. At the post intervention clinical visit the patient's cholesterol or blood pressure did not change with exercise, resulting in the risk estimate to not reflect improvements of CVD risk because CRF and exercise are not independent variables in the risk assessment calculator. If calculators used CRF as an independent risk factor the risk of CVD would decrease at the post intervention clinical visit, despite the moderate changes in blood pressure and lipids.

Physical activity and cardiorespiratory fitness are independent predictors for CVD

Several epidemiological studies have shown that physical activity is an independent predictor for CVD [7, 8]. In a study in Finland (n= 32,677), Barengo et al. [7] observed that in men (n=15,853), ages 30-59, CVD risk decreased with moderate physical activity by 9% (95% CI, 0-18%) and with high physical activity by 17% (95 CI, 1-31%), when adjusted for age, body mass index, total cholesterol, education, smoking status, and physical activity. In the occupational, commuting, and leisure-time physical activity in relation to CVD study (n=26,643), Hu et al. [8] observed the risk of CVD among men and women with hypertension after adjusting for age, study year, education, alcohol consumption, smoking, body mass index, systolic blood pressure, total cholesterol, and use of antihypertensive drugs. The multivariate adjusted hazard ratios of CVD mortality for men with low, moderate, and high physical activity were 1.00, 0.84, and 0.73 ($p<.001$) [8]. The hazard ratios for women with low, moderate and physical activity were 1.00, 0.78, and 0.76 ($p<.001$) [8]. Men had a 36% lower multivariate-adjusted risk of CVD mortality and women had a 39% reduced CVD mortality [8]. Thus, risk assessment calculators could be overestimating CVD risk because physical activity is an independent predictor for CVD, even when the client has other risk factors, such as hypertension and dyslipidemia.

CRF is also a strong independent predictor for CVD [7, 8], and may represent a better assessment of physical activity status since it is not prone to misclassification, such as questionnaire determined physical activity. Artero et al. [19] (n= 43,356), observed that levels of CRF were inversely related to CVD mortality and non-fatal CVD events after adjusting for sex, age, body mass index, waist circumference, resting heart rate, physical activity level, and smoking status. The participants included men and women (21%) ages 20 to 84, who were followed up of a median of 14.5 years [19]. CRF (risk reduction per 1-MET) reduced CVD mortality in men by 17% [19]. CRF reduced non-fatal CVD events in women by 23% [19]. The CVD relative risk was reduced by 12.3% in men and 19.8 % in women[19]. Lee et al. [20] observed in the Aerobics Center Longitudinal Study (n=14, 345) that with every 1- Met improvement from the individual's last maximal treadmill test his/her risk of CVD mortality improved by 19%. Men who maintained fitness from baseline improved CVD mortality by 28% and men who improved fitness from baseline had a 44% less risk of CVD mortality, when adjusted for age, weight, fitness, blood pressure, fasting glucose, cholesterol levels, family history, current smoker and drinker. These studies [7, 8, 19] add to the fact that CRF should be added as an independent variable in the risk assessment calculators because CRF can decrease CVD risk even if other risk factors are present. If clinicians continue to use the current risk calculators then risk of CVD might be inaccurate because CRF is an independent factor and can reduce the risk of CVD.

Does Physical Activity or CRF Add to the Risk prediction?

Limited data is currently available evaluating whether adding either physical activity or CRF as an independent risk factor in the available risk calculators adds to its ability to predict cardiovascular or mortality outcomes. To our knowledge, several studies have evaluated the effect of physical activity or CRF on CVD mortality. Paytner et al. [21] (n=93676) observed how the combination of lifestyle-based and traditional risk factors influence CVD risk in postmenopausal woman ages, 50 to 79. The addition of lifestyle–based (healthy diet, recreational physical activity, moderate alcohol use, and low adiposity) and traditional risk factors in current CVD prediction models, such as the pooled cohort and Reynolds risk score, may influence improving CVD risk. Paynter et al. [21] concluded that a greater number of healthy risk factors decreased the risk of CVD (hazard ratio, 0.82; 95 % CI, 0.76-0.89) and after adjusting for components of the prediction models, having all five lifestyle factors resulted in a 20% lower risk of CVD. When adjusting for age and race, self-reported physical activity was the only lifestyle factor that remained independently associated with lower CVD risk. The addition of physical activity to the prediction models resulted in the change in the c statistic, categorical net reclassification improvement (NRI), and the integrated discrimination improvement (IDI) to be non-significant, but the continuous NRI was 0.14 (p=0.001). Even though traditional risk factors still predict the majority of CVD risk adding lifestyle factors to the prediction models improves the overall model performance, by improving the IDI and continuous NRI. However, the minimal improvement does not have an effect on classification into clinical absolute risk. Limitations of the study consisted of the measurements being self-reported potentially resulting in the estimation of physical activity being inaccurate. Future studies should determine if physical activity has a greater effect on risk classification or prediction of CVD mortality when physical activity is measured objectively, such as a pedometer.

In another study, Israel et al. [22] evaluated if the addition of an exercise capacity variable improves the ability of the Systematic Coronary Risk Evaluation Project (SCORE) estimation model ability to aid in 10-year CVD risk stratification in asymptomatic men and women (n=22,878), ages 47.4 ± 10.3 years. SCORE is used for CVD risk stratification in healthy adults and is based on traditional cardiovascular risk factors. Exercise capacity was measured using the Bruce treadmill protocol and was quantified in maximum METs achieved during the test. The SCORE risk estimation system was used to estimate 10- year CVD risk. The Kaplan-Meier survival analysis found a significant association between low fitness and an increased risk of mortality at 9 years in each of the SCORE groups ($p<0.001$). Individuals with a low SCORE combined with low fitness, have a 2.1 increased risk for all cause mortality, when compared to individuals with a low score, but high fitness ($p=0.016$). In addition, the authors added exercise capacity as an independent variable in the SCORE model. Israel et al. evaluated that this addition improved the risk prediction by approximately 57%, using the NRI approach.

In contrast, Gander et al. [23] (n= 29,854) evaluated the effect and association of CRF on the estimation of 10-year coronary heart disease (CHD) risk in men, estimated by the Framingham Risk Score. This was a secondary analysis using data from the Aerobics Center Longitudinal study. Inclusion criteria for the analysis included men, ages 30 to 74 years; individuals must have complete data for outcome and predictor variables, and were free from CVD or cancer diagnoses at baseline. In order to determine the individuals CRF, a Balke maximal exercise treadmill was used, and was quantified in maximal METs. During a 12-year follow up, there were 499 CHD events. It was found that the incidence of CHD with moderate or high risk was 37.6 per 10,000 person- years when compared to low 10–year CHD risk was 19.7 per 10,000. Men with high CRF have 33% lower risk of CHD than did men who had low CRF. Authors also found that men with low CRF, with moderate or high 10- year CHD risk were 6.5 times more likely to develop CHD than individuals with low risk. Following the sensitivity analysis Gander et al. [23] found that CRF had a significant protective effect on CHD, but did not add to the predictive power of the Framingham Risk Score for estimating 10-year CHD risk. In contrast, from the aforementioned studies it seems that physical activity or CRF aids in the prediction of CVD mortality in general, but there needs to be more research in the future with different SCORE models to determine the effect of fitness or physical activity on CVD mortality.

Wickramasinghe et al. [1] Calculator

To address the limitations of the available risk calculators, Wickramasinghe et al. [1] developed a sex specific 30-year risk prediction tool that includes CRF as a variable as well as the traditional risk factors using data from the Cooper Center Longitudinal study. The calculator also assesses CVD mortality at different time points in an individual's life that include 10, 20, and 30-year CVD risk. The participants used to develop the calculator ranged from 20 to 90 years of age and were mostly Caucasian (n= 16,533) [1]. The hazard ratios with 95% confidence interval in men and women are included in Table 1 [1]. Significant predictors of CVD in the calculator included age, systolic blood pressure, smoking, type 2 diabetes, total cholesterol, BMI, and CRF [1]. The new risk calculator has overall good calibration in both men and women (men ,10.85 [p=0.286] and women, 6.7 [p= 0.664]). The calculator also has overall good discrimination (C statistic: men: 0.81 [0.78-0.82]; women: 0.86 [0.81-0.91]) [1].

The new risk calculator by Wickramasinghe et al. [1] addresses the limitations of previous calculators by including CRF, which may represent exercise or physical activity habits. Adding CRF could be beneficial to clinicians to evaluate risk of CVD before and after exercise training. Using CRF as an independent variable in the calculator is also an advantage for clinicians because the new calculator can give a more accurate estimate on how the level of fitness decreases the risk for CVD. Comparing the effect of exercise training on CVD risk is important because physicians will be able to show their patients the importance of exercise training to decrease CVD mortality and estimate CVD mortality more accurately. To our knowledge, one study has compared the effect of exercise training on CVD risk objectively.

The Effects of Exercise training on CVD Risk

Recently, one study has evaluated the effect of exercise training on estimated CVD risk. Swift et al. [24] evaluated the effect of aerobic, resistance, or combination exercise training on 30- year CVD mortality risk in adults with type 2 diabetes. This study was a secondary analysis using data from the Health Benefits of Aerobic and Resistance Training in Individuals with Type 2 Diabetes study database. 30-year CVD mortality was estimated at baseline and follow up using the Wickramasinghe et al. [1] calculator. Swift et al. [24] found that aerobic or combination of aerobic and resistance training resulted in about a 3% reduction in 30- year CVD mortality. Additionally, the authors found using linear regression models that change in fitness was a major determinant in the reduction of CVD mortality. Approximately 27% of the change in fitness was due to CRF as opposed to other variables in the calculator. Change in systolic blood pressure was approximately 14%, total cholesterol 7%, BMI 1%, and diastolic blood pressure 1%.

Summary

According to the American Heart Association, CVD is the leading cause of death in the United States [2]. Clinicians using calculators, such as the Framingham Risk Score or the American Heart Association pooled cohort algorithms, estimate CVD risk by using traditional risk factors (age, gender, blood pressure, diabetes mellitus, cholesterol, and smoking status). Using the current calculators to predict CVD risk maybe a potential limitation because the algorithms do not use an exercise variable such as, CRF in the equation. CRF has been shown to have an independent effect on CVD risk in relation to other traditional risk factors. It would be beneficial to clinicians to use a calculator that uses traditional risk factors along with CRF as a variable because it will allow the clinician to observe the direct effect of exercise training on the improvement of CVD. It will also be beneficial to the patients because it will educate the patient on the importance of exercise in decreasing CVD risk. Recently, Wickramasinghe et al. [1] developed a calculator to assess 30- year CVD risk that includes CRF as a variable a long with traditional risk factors to address the limitations of the current calculators. However, there have been no studies that assess CVD risk after an exercise program using traditional risk factors along with CRF as a variable.

Chapter III: Methods

The purpose of the present study was to assess the effects of an exercise variable on 30-year cardiovascular mortality estimated by the Wickramasinghe et al. [1] calculator. Baseline and follow-up evaluation data from the Inflammation and Exercise (INFLAME) [15] study was entered into the Wickramasinghe et al. [1] calculator to estimate cardiovascular mortality and to assess cardiovascular risk improvement. We hypothesized that cardiovascular risk decreased after implementing an exercise intervention.

Subjects

The present study was a secondary analysis of the Inflammation and Exercise (INFLAME) study (n=162) [15, 25]. The INFLAME study's methodology and outcomes have been previously published and approved by the Institutional Review Board of the Cooper Institute [15, 25]. Prior to initiating the study, participants provided a written informed consent. Participants in the INFLAME study included healthy, sedentary (not exercising more than 20 minutes on 3 or more days a week) men and women between the ages of 30 and 75 with elevated CRP levels (≥ 2.0 mg/L but < 10.0 mg/L). The inclusion criteria of the INFLAME study also included a body mass index >18.5 kg/m^2 or < 40, fasting glucose < 126 mg/dL, a non smoker (has not smoked or chewed tobacco in the past 6 months), and not taking certain medications (statins, ace inhibitors, oral contraceptives, multi-vitamins, and anti-inflammatory drugs). Exclusion criteria included individuals on specific medications (hormonal replacement therapy, beta blocker, allergy shot, or systematic corticosteroids), significant cardiovascular disease or disorders, total cholesterol ≥ 240 mg/dL with LDL ≥190 mg/ dL or triglyceride levels > 300 mg/dL, and other significant medical conditions. Since this was a secondary analysis, individuals were also excluded (n=44) in the present if they did not complete the intervention, did not have all the variables needed to input in the Wickramasinghe et al. [1] calculator, and did not have adequate adherence (>90%).

Baseline and Follow- Up Evaluations

Screening measurements were taken to ensure participants met the INFLAME study's criteria [15, 25]. Participants fasted for 10 to 12 hours, did not drink alcohol or exercise for 24 hours, and did not take anti-inflammatory drugs for 48 hours prior to blood draws.

Resting blood pressure measurements were taken 20 minutes after heart rate variability measurements by a Colin STBP-780 automated BP unit (Colin Medical Instruments Corp., San Antonio, TX). Medical history (diabetes) and smoking status was determined by self-report questionnaires and glucose values. Weight was measured using a balance-beam scale and recorded to the nearest 0.1 kg. BMI was calculated by dividing the individual's weight in kilograms by the height in meters squared. Body composition was measured by a dual X-ray absorptiometry (DXA) scan using a Hologic Bone Densitometer (Hologic Inc., Bedford, MA). Waist circumference was measured at the level of the umbilicus and hip circumference was measured at the maximal girth of the hips. CRF was measured using a graded exercise test on a Lode Excalibur Sport Cycle Ergometer (Lode, BV, Groningen, Netherlands). Prior to the exercise test participants were fitted with a 12- lead ECG and blood pressure cuff. Heart rate and blood pressure were taken in the supine and standing position, as well 2 minutes after the participant was on the cycle ergometer. Both men and women performed the same cycle ergometer graded exercise protocol, but women initiated the test at 25 W and increased 25 W per stage, while men initiated the test at 35 W and progressed 35 W per stage. The stages lasted 2 minutes each and the last 30 seconds of each stage blood pressure, heart rate, and rating of perceived exertion was recorded. Pulmonary ventilation, oxygen consumption (VO^2) carbon dioxide production, and respiratory exchange ratio was measured every 15 seconds using a metabolic cart (Parvomedics True Max 2400 Metabolic Measurement Cart, alt Lake City, UT). The exercise test was terminated when the participant reached fatigue or exhaustion.

The plasma and serum samples were drawn at baseline and follow-up and stored in a -80 degree C freezer until analysis. Fasting blood lipids and lipoproteins (total cholesterol, HDL, and, LDL cholesterol) were measured by non-denaturing polyacrylamide gradient electrophoresis. At baseline and follow- up evaluation 20 ml of blood was drawn. All assessment measures were evaluated at baseline and follow- up.

CVD Risk Using the Wickramasinghe et al. [1] Risk Calculator

Baseline and follow-up data (age, sex, systolic blood pressure, total cholesterol, type 2 diabetes, BMI, fitness level, and smoking status) from the INFLAME study [15, 25] database was entered into the Wickramasinghe et al. [1] calculator to estimate 30-year cardiovascular mortality risk. The calibration of Wickramasinghe et al. [1] calculator in men is 10.85 (p=0.286) and in women is 6.7 (p=0.0664). The discrimination of the calculator in men is 0.81 [0.78-0.82] and in women is 0.86 [0.81- 0.91]. The calibration and discrimination of the calculator represents statistics, which reports how well the Wickramasinghe et al. [1] calculator predicts CVD mortality.

Intervention

After baseline assessments were measured, participants were randomized to an exercise group or a control group. The exercise group participated in supervised exercise sessions 3 to 5 times a week for four months. Individuals were prescribed to expend 16 kcal/kg per week (KKW). Exercise intensity was 60 -80 % of maximal oxygen consumption, which was determined at the baseline exercise test. Modes of exercise equipment used included the treadmill and cycle ergometer. Heart rate, blood pressure, rate of perceived exertion, mode, and speed/grade or watts were recoded each exercise session. The non-exercise control group was asked to maintain their sedentary status during the four-month intervention. Both the control and exercise groups wore a step counter to monitor physical activity throughout the day (the exercise group did not wear the pedometers during scheduled exercise sessions).

Statistical Analysis

The primary outcomes of this analysis were the change of CVD mortality risk after an exercise intervention. A student's t-test was used to compare the CVD mortality risk of the control and exercise group at baseline. Change in 30-year CVD mortality was analyzed using an analysis of covariance (ANCOVA) between the control and exercise group with baseline CVD morality risk entered as a covariate. Age and sex was not adjusted for in the analysis, since they are variables within the Wickramasinghe et al. calculator [1]. A post hoc analysis was performed utilizing a median split to analyze individuals with elevated 30-year CVD mortality. We defined elevated CVD mortality as greater than 10.2% (based on the median of the study sample). Results for the ANCOVA analyses are presented in adjusted least squared means with 95% confidence intervals. An alpha level of < 0.05 was the criterion for significance.

Chapter IV: Results

The control group had a mean (SD) age of 50.6 (11.5) years, a mean BMI of 32.1 (3.8) kg/m^2, with 5% African American and 66.2% female and baseline 30-year CVD risk was 18.1 (16.6). The exercise group had a mean age of 50.1 (9.3) years, a mean BMI of 30.9 (4.4) kg/m^2, with 5% African American and 80.4 % female and baseline 30-year CVD risk was 13.4 (13.3). The baseline descriptive characteristics of the control and exercise group are summarized in Table 2. No significant differences were observed between the control and the exercise group at baseline with the exception of baseline waist circumference (p=0.022), HDL (p=0.007), fasting glucose (p=0.037), and plasma insulin (p=0.021).

Table 3 presents the change in each CVD risk components in the Wickramasinghe et al.[1] calculator. There was a significant increase in METs following the exercise intervention (p<.0001), but there were no significant change in BMI, total cholesterol, or systolic blood pressure (all p>0.05).

Represented in Figure 1 is the change in 30-year CVD risk for control and exercise groups. Following the intervention, the exercise group (0.5[CI: -1.3, 0.4]) significantly reduced 30-year CVD risk mortality compared to the control group (- 2.0[CI: -2.9, -1.1]), p=0.018). Figure 2. represents the change in 30- year CVD risk for the control group and the exercise group among adults with high baseline CVD risk. The reduction in 30- year CVD mortality risk between the control group (-1.3[CI: -2.8, 0.26]) and the exercise group (-3.5[CI: -5.5, -1.6], p= 0.078) following the exercise intervention approached significance.

Discussion

The primary findings of the present study were: 1) Four months of aerobic exercise training resulted in a small reduction (~ 3%) in 30- year CVD mortality as estimated by the Wickramasinghe et al. [1] risk calculator which includes CRF as a variable and 2) The results did not differ substantially when we restricted the analysis to only individuals with high CVD mortality risk at baseline. This is the first study, to our knowledge, that has evaluated the effect of exercise training on estimated 30-year CVD mortality risk in sedentary, obese individuals, without type 2 diabetes.

The Wickramasinghe et al. [1] calculator is the first risk estimation calculator that includes CRF along with traditional risk factors to quantify 30–year CVD risk. CRF may be a needed variable within risk calculators as data from Kodama et al. [6] suggest that a 1 MET increase in CRF is associated with a 15% decrease in CVD mortality. Although the reduction of CVD mortality was only about 3% following aerobic exercise training, there would have been a minimal or possibly no reduction in CVD mortality if CRF were not a component within the calculator. In the present study, the only variable from the Wickramasinghe et al. [1] calculator that improved with exercise training was METs. Thus, no significant changes were observed for BMI, systolic blood pressure, or total cholesterol following aerobic exercise training. To our knowledge, only one other study has evaluated the effect of exercise training on estimated CVD mortality. Swift et al. [24] evaluated the effect of 9 months of aerobic, resistance or combination exercise training on 30-year CVD mortality in individuals with type 2 diabetes using the Wickramasinghe et al. calculator [1]. The authors observed that both aerobic or combination (combination of aerobic and resistance training) exercise training resulted in approximately a 3%

reduction in estimated 30-year CVD mortality [24], which is a similar magnitude compared to the results of the present study. Furthermore, when the variables within the calculator were entered into a linear regression model (e.g. change in CRF, BMI, type 2 diabetes, age, smoking status, and total cholesterol) that 27% of variance in the reduction of CVD mortality risk was explained by the change in CRF in in those who participated in aerobic training. Thus, it appears that exercise training reduces CVD mortality risk similarly in both sedentary and diabetic populations. It is possible that larger reductions in CVD risk may be possible in longer aerobic training interventions or in younger study populations.

Since exercise training appears to reduce CVD risk, the argument could be made that current risk calculators that do not include a variable for CRF/physical activity may be somewhat inaccurate. To our knowledge, there have been several studies,[21, 22] that have evaluated whether adding a physical activity or CRF component to available risk calculators improves the models calibration. Generally, the results from these studies suggest that CRF or physical activity does improve the models performance, however there is still the question on whether or not it improves risk stratification. Paytner et al. [21] evaluated how the addition of lifestyle-based risk factors added to traditional risk factors in current CVD prediction models, such as the pooled cohort and Reynolds risk in postmenopausal women within the Women's Health Initiative study. The authors [21] found that adding lifestyle based factors (healthy diet, recreational physical activity, moderate alcohol use, and low adiposity) improved the overall performance of the model estimating CVD risk. The addition of physical activity to the prediction model resulted in an improvement of the categorical net reclassification (NRI) and the continuous NRI was 0.14 (p=0.001). They also observed when adjusting for age and race, self-reported physical activity was the only lifestyle factor that remained independently associated with lower CVD risk. The addition of lifestyle factors, such as physical activity, to the prediction models improved model calibration, but it does not improve risk stratification. An important limitation of the study is that physical activity was obtained through a questionnaire and thus was self-reported. Recently, Israel et al. [22] evaluated if exercise capacity improves the ability of the Systematic Coronary Risk Evaluation Project (SCORE) estimation model ability to aid in cardiovascular mortality risk stratification in 22, 878 asymptomatic men and women The addition of CRF to the SCORE model improved risk stratification by 50% in low- risk populations[22]. However in contrast to these results, Gander et al. [23] found that that CRF did not add to the model performance of the Framingham Risk Score for estimating 10-year CHD risk.

The present study has several strengths, which included that the INFLAME study was a randomized controlled trial that was laboratory based. During the aerobic exercise intervention all of the participants exercise sessions were supervised. The exercise dose of 16 KKW was designed to be consistent public health recommendations for moderate to vigorous intensity physical activity [5]. The adults in the study exercised at an intensity of 60-80% of VO_2 max, which is significant enough for physiological changes associated with exercise training. Adherence of the exercise group was >90% and adults with low adherence levels were excluded. However, the study also had several limitations. Participants in the study were mostly Caucasian (65%), which could limit the generalizability to specific populations. The participants also alternated between two different exercise modalities: the treadmill and cycle ergometer. This could have potentially been a limitation because the participants were only tested on a cycle ergometer, which could have limited the potential change in VO_2 from training because they did not train on the cycle ergometer 100% of the time. Lastly, the duration of the exercise intervention was four months. If the aerobic exercise intervention lasted for a longer period of time, it is possible that larger reductions in 30-year CVD mortality may be observed.

CVD risk calculators are an important part of primary prevention and are useful in a clinical setting to estimate CVD mortality. The results of the present study suggest that there is a small reduction (3%) in estimated 30-year CVD mortality following 4 months of aerobic exercise training using a calculator that includes CRF as a variable. In addition, much of the risk reduction appeared to be mediated primarily through changes in CRF. Future studies should investigate the relationship between CRF and estimated CVD mortality following a longer aerobic exercise intervention, in different study populations, and different aerobic exercise program

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Tables and Figures

Table 1. Hazard Ratios with 95% Confidence Intervals for 30- year CVD Risk Mortality

Variables	Men	Women
Age (per 10 y)	2.2(2.06-2.38)	3.10(2.44-3.94)
SBP (per 20 mmHg)	1.40 (1.30-1.51)	1.17(0.94-1.46)
BMI (per 3 kg/m^2)	1.10(1.04-1.16)	1.18(1.01-1.37)
Diabetes mellitus (yes/no)	1.37(1.15-1.63)	2.02(0.97-4.18)
T. Cholesterol (per 40 mg/dl)	1.21(1.14-1.29)	1.08(0.87-1.34)
Smoking (yes/no)	1.38(1.20-1.60)	1.96(1.16-3.30)
METs (per SD)	0.84(0.82-0.88)	0.82(0.70-0.95)

SBP- Systolic Blood Pressure
BMI- Body Mass Index
T. Cholesterol- Total cholesterol
METs- Metabolic equivalents

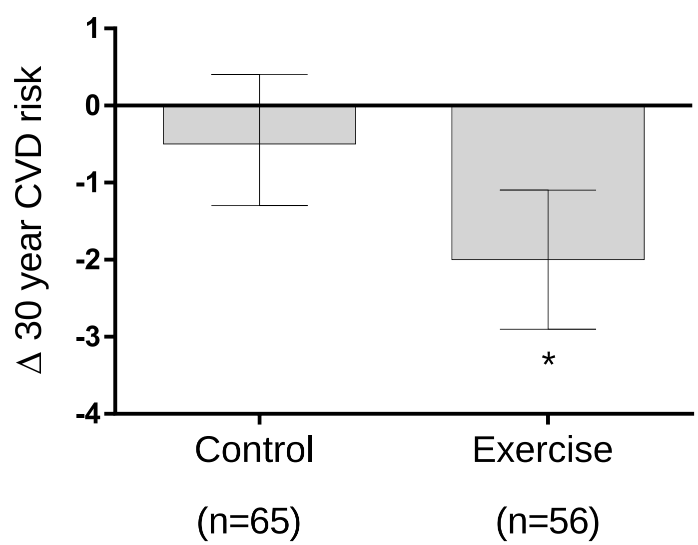
Table 2. Baseline characteristics for the control and exercise groups. Results presented as Mean (SD). * represents significance between groups, $p < 0.05$.

	Control (n= 65)	**Exercise** (n= 56)	**p**
Age (years)	50.6(11.5)	50.1(9.3)	0.803
BMI (kg/m^2)	32.1(3.8)	30.9(4.4)	0.108
Ethnicity African Americans (%), n	5.0(6)	5.0(6)	0.785
Sex Female (%), n	66.2(43)	80.4(45)	0.080
Systolic blood pressure (mmHg)	132.8(18.4)	129.5(19.9)	0.346
Diastolic blood pressure (mmHg)	80.3(10.2)	78.7(10.5)	0.398
Waist circumference (cm)	100.6(12.3)	95.4(12.5)	0.022*
High density lipoprotein (mg/dL)	51.6(11.7)	58.4 15.4)	0.007*
Triglycerides (mg/dL)	116.9(42.3)	112.3(42.2)	0.203
Fasting Glucose (pmol/L)	97.0(10.3)	93.1(9.7)	0.037*
Plasma Insulin (pmol/L	14.2(6.9)	11.4 (5.7)	0.021*
VO_2 (L/min)	1.7(0.6)	1.7(0.6)	0.834
VO_2 (ml·kg·min)	18.7(5.6)	19.7(5.5)	0.329
CVD Risk 30- years (pre)	18.1(16.6)	13.4(13.3)	0.082

Table 3. Change in mean for CVD risk calculator components. Results presented as Mean (+- 95% Confidence Interval). Represents significance between groups, $p < 0.05$.

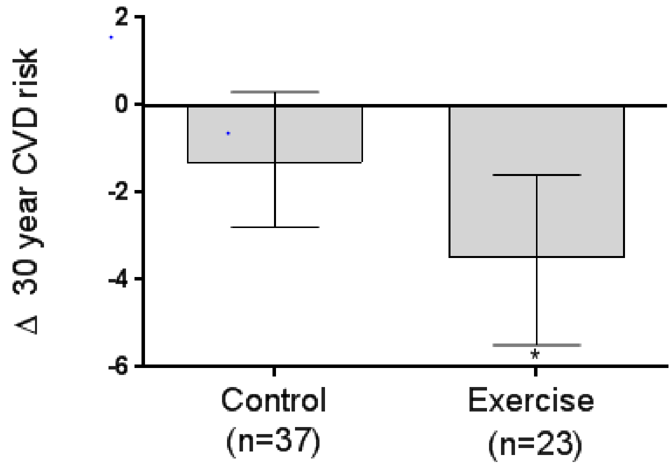
	Control	Exercise	p value
Δ METs	-.10 (-0.3, 0.1)	.80 (0.6, 1.0)	.0001*
Δ BMI	.09 (-0.2, 0.4)	-0.15 (-0.5, 0.2)	0.3396
Δ Total cholesterol	-2.27 (-7.2, 2.6)	2.77 (-2.5, 8.1)	0.1700
Δ Systolic blood pressure	-2.80 (-5.8, 0.2)	-5.81 (-9.1, -2.5)	0.1834

Figure 1. Change in 30- year CVD risk for control and exercise group.



* indicates significant difference compared to the control group

Figure 2. Change in 30-year CVD risk for control and exercise group above median CVD risk.



* indicates significant difference compared to the control group