CARDIORESPIRATORY FITNESS VERSUS PHYSICAL ACTIVITY AS PREDICTORS OF ALL-CAUSE MORTALITY IN MEN

By
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A thesis submitted to the School of Kinesiology and Health Studies in conformity with the requirements for the Degree of Master of Science

Queen’s University
Kingston, Ontario, Canada
August, 2017

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Abstract

BACKGROUND: Physical activity (PA) is a behaviour, defined as any bodily movement that increases energy expenditure above resting levels, while cardiorespiratory fitness (CRF) is a physiologic trait that reflects the ability of the respiratory, circulatory, and musculoskeletal systems to deliver and utilize oxygen. Although both CRF and PA are inversely associated with mortality risk, whether they are associated independent of each other is unclear.

METHODS: CRF was assessed by a maximal exercise test and PA was measured by self-report in 8171 male veterans. The predictive power of CRF and PA, along with clinical variables, was assessed for all-cause mortality during a mean (±SD) follow-up period of 8.7 (4.4) years during which there were 1349 deaths.

RESULTS: CRF was associated with mortality after adjusting for traditional risk factors commonly measured in clinical practice, and remained a strong predictor of mortality after further adjusting for PA (hazard ratio [HR], 0.85; 95% confidence interval [CI], 0.83 –0.87). PA was a significant predictor of mortality after controlling for clinical variables, however the association was eliminated after further adjusting for CRF (HR, 0.98; 95% CI, 0.88 – 1.10). In CRF stratified analysis, being active (≥150 min/week) was not associated with mortality within the unfit or fit categories (p>0.4). However, in PA stratified analysis, subjects categorized as fit (≥7 METS) had a lower risk of mortality regardless of PA status (p<0.001).

CONCLUSION: In adult men, PA was associated with mortality above and beyond established risk factors, but not CRF. Conversely, CRF remained a strong predictor of mortality, independent of PA status and established risk factors.
Statement of co-authorship and thesis contributions

The co-investigators for this study are Dr. Robert Ross, Dr. Jonathan Myers (Veterans Affairs Palo Alto Health Care System and Stanford University School of Medicine), Dr. Peter Kokkinos (Veterans Affairs Medical Center, Washington, DC, and Georgetown University School of Medicine), and Dr. Baruch Vainshelboim (Veterans Affairs Palo Alto Health Care System and Stanford University School of Medicine).

This thesis is a secondary analysis of the Veterans Exercise Testing Study (VETS), an ongoing prospective longitudinal study established to explore the role of clinical and lifestyle factors in the development of adverse health outcomes. Beginning in 1983, the data has been collected by the physicians and staff at the Veterans Affairs Medical Centre in Palo Alto, CA, and Washington, DC. We would like to thank the patients, staff, and physicians at the Veterans Affairs Medical Center in Palo Alto, CA, and Washington, DC, for making this research possible.

In July of 2016, I travelled to Stanford University to meet and collaborate with Dr. Jonathan Myers and Dr. Baruch Vainshelboim. Dr. Myers has been performing research in regard to exercise testing and training for over 20 years, and is currently the coordinator for the Palo Alto Veteran Affairs Health Care System Cardiology Exercise Laboratory in Palo Alto, CA. I was able to learn from Dr. Myers about the VETS and about the field of epidemiology in general. While in Palo Alto, Dr. Vainshelboim helped me with the statistical methods used in the current study. Upon my return to Kingston, I was uniquely responsible for performing all analyses presented in this report. Dr. Ross and I designed the study and are primarily responsible for interpretation of the data. I am entirely responsible for drafting of the manuscript and all authors contributed to critical revision of the manuscript.
Acknowledgements

This experience would not have been the same without the support of my professors, mentors, family, and friends. First and foremost, thank you sincerely Dr. Ross for all of your guidance and support over the last two years. You have a knack for inspiring motivation in others, for challenging your students to think about things in new ways, and for being really, really understanding. Thank you for the opportunities that you made available to me. I know that I will carry the skills and knowledge that I have learned into my next endeavors in medical school in the fall, and as a clinician in the future!

To all of the staff members of the Ross Lab (John, Melinda, Ronnie, Tammy, Steph, and Paula), and to all of the SKHS staff, thank you for always being a friendly face in the building. Paula, a special thank you for all of your stats chats! Trish and Josie, you make my day every time I pop into the SKHS office! And Angie, a very special thank you for always going above and beyond for us (like the time you drove me all the way to the FedEx centre to make sure my application package got in the mail on time!).

My fellow “Ross lab” graduate students, I don’t know where to start. I can’t imagine spending every day in the same room with anyone else! I am grateful for the friendships we made, and the tremendous help from all of you along the way. I have learned something from each of you. Britt, you have been my partner in crime. I’m excited for our many adventures yet to come as we begin our next chapters. Nic, you don’t have a mean bone in your body and you have a heart the size of Manitoba! Louise, you’re always willing to lend a hand and your positivity brightens the lab. Andrea, I can’t begin to tell you how much I look up to you, and how much you’ve helped me over the past 2 years. You are utterly hilarious and I am so grateful for our friendship.

Thank you to Dr. Jonathan Myers and Dr. Baruch Vainshelboim for your hospitality during my stay in Palo Alto, and to Dr. Peter Kokkinos for all of your time and effort on this project. It has been a pleasure working with all of you.
To my family, thank you for all of your love and unwavering support. Mom and Dad, thank you for the life chats, always encouraging me to pursue my dreams, and filling my freezer with home-cooked meals. Talia, Lauren, and Sean, I am grateful that I got to spend so much time with all of you at Queen’s over the last 6 years. There’s nothing like family!

To all of my friends I’ve met at Queen’s along the way (special shout-out to “HGOG”), it has been an absolute blast! And to Khalid, I could not have done this without your continued support through all of the highs and lows. You have a “joie de vivre” that keeps me smiling ear-to-ear every single day!

Taryn Davidson

July 24, 2017
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List of abbreviations

PA, physical activity
CRF, cardiorespiratory fitness
CVD, cardiovascular disease
CHD, coronary heart disease
MET, metabolic equivalent
PAR, population-attributable risk
\( \text{VO}_2 \), oxygen consumption
NRI, net reclassification improvement
HR, heart rate
EE, energy expenditure
BMI, body mass index
HTN, hypertension
BP, blood pressure
WC, waist circumference
HR, hazard ratio
SED, time spent sedentary
CAD, coronary artery disease
SES, socioeconomic status
ACLS, Aerobics Center Longitudinal Study
ROC curve, receiver operating characteristic curve
VETS, Veterans Exercise Testing Study
Chapter 1. General Introduction

Since the seminal observations of Dr. Jeremy Morris in 1953 and Dr. Ralph Paffenbarger in 1970 first demonstrating a link between occupational physical activity (PA) and risk of major cardiovascular disease (CVD) events, numerous investigations have confirmed and extended these observations in both men and women, in relatively healthy individuals, and in individuals with chronic disease. It is well established that PA is strongly associated with several cancers, CVD, CVD-mortality, and mortality from all-cause, and these associations remain after controlling for traditional risk factors including obesity, blood pressure, and smoking status [1].

Initial observations demonstrating an association with adverse health outcomes were subsequently reinforced by evaluation of serial measures of PA, showing a significant inverse relationship between improvements in PA and mortality risk [2].

More recently, similar relationships have been reported for cardiorespiratory fitness (CRF) [3]. Like PA, the relationship between CRF and health risk is characterized by an inverse dose-response relationship in that higher levels of CRF are associated with incremental reductions in health risk [4]. CRF remains a potent predictor of health risk beyond traditional risk factors that are commonly measured in clinical practice, and examination of the association between changes in CRF and risk of CVD and all-cause mortality supports a causal relationship between CRF and health outcomes [5].

Risk assessment has been instrumental in characterizing the strong, independent relationship between PA and CRF with mortality risk, and identifying PA as an important lifestyle target for the prevention of chronic disease. The prognostic utility of PA and CRF has been further amplified by investigations which demonstrate that PA and CRF significantly improve classification of mortality risk when added to a standard risk assessment model, such as the Framingham Risk Score [6]. Efforts to characterize the PA-mortality curve over the last 5 decades have led to congruent national and international PA guidelines recommending that people of all ages engage in regular PA to promote and maintain health, and more recently,
several researchers and health organizations such as the American Heart Association have advocated for the measurement of CRF in clinical practice to improve patient risk management [4, 7].

PA is a behaviour, defined as any bodily movement that increases energy expenditure above resting levels, while CRF is a physiologic trait that reflects the ability of the respiratory, circulatory, and musculoskeletal systems to deliver and utilize oxygen. Although PA is a major determinant of CRF, PA and CRF are influenced by several factors including genetics, sex, age, environmental factors, and disease state [1, 8]. In fact, when examined cross-sectionally, the association between PA and CRF is modest at best, with variance explained values ranging from 1 to 36% [9, 10]. That PA and CRF are strong predictors of health outcomes, but are modestly associated with each other, suggests that PA and CRF may act to some degree through distinct mechanisms.

Although several studies have simultaneously examined the relative contributions of CRF and PA to mortality risk [10-14], whether PA and CRF predict mortality risk independent from each other remains unclear. There is consensus that CRF remains a potent predictor of mortality after controlling for PA [10-14], however prior studies present conflicting findings regarding the independent effect of PA on mortality. While three studies suggest that PA remains a significant predictor of mortality after controlling for CRF [10, 11, 13], two studies reported that PA is no longer associated with mortality after controlling for CRF [12, 14].

Upon careful review of prior studies, we identified a limitation that may partially explain discrepant findings. Several studies used stratified analysis to examine the relationship between PA and mortality independent of CRF. The objective of stratification being to control for the possible confounding effects of CRF by producing strata within which CRF does not vary substantially. However, examining the PA-mortality association within CRF strata does not guarantee that the confounding effects of CRF are entirely removed. It is possible that the CRF levels in the active groups were substantially higher than CRF in the inactive groups. Were this
true, any observed effect that was attributed to PA may be explained by naive differences in CRF.

Failure to account for differences in CRF across PA groups may have biased interpretations of the direct effect of PA on mortality risk. To address this issue, the current project aimed to examine the relative contributions of PA and CRF to mortality risk after carefully matching inactive and active subjects on CRF. This would rigorously fix CRF in order to examine the independent contribution of PA to mortality risk.

The findings of our study may help resolve inconsistencies in the literature regarding the independent associations of PA and CRF with mortality risk. As evidence continues to accumulate on the prognostic utility of PA and CRF in the healthcare setting, determining whether PA and CRF are independently linked to a significant burden of mortality will be of direct clinical importance. First, defining the relative contributions of PA and CRF to mortality risk may help to clarify the pathways by which PA and CRF affect health. Additionally, drawing attention to a potential limitation in prior study designs, and the importance of considering confounding in stratified analysis, may affect future investigations examining this question.
Chapter 2. Review of literature

2.1 The economic and health burden of physical inactivity and low cardiorespiratory fitness

The development of modern society and advancements in technology have facilitated the transition from a lifestyle that requires physical exertion and puts high demands on the human cardiovascular and musculoskeletal systems, to an environment that is explicitly designed to eradicate physical labor [15]. This notion is reflected in the observation that high income countries have more than double the prevalence of physical inactivity compared to low income countries. The prevalence of physical inactivity in high income countries is 41% and 48% in men and women, respectfully, while that in low income countries is 18% and 21% [16]. In Canada, corresponding values are much higher, perhaps due to objective measures of PA. Evaluation of accelerometry data from the Canadian Health Measures Survey reveals that around 85% of Canadian adults do not meet the recommended 150 min of moderate-to-vigorous PA performed in bouts lasting 10 min or more [17]. Indeed, the prevalence of physical inactivity in Canada is higher than for all other modifiable cardiovascular disease risk factors, including hypertension, smoking, obesity, alcohol consumption, and diabetes [18].

Concomitant with the transition to a less energetically costly way of life has been a rise in the prevalence of chronic diseases such as CVD, cancer, chronic respiratory diseases, and diabetes. Deaths due to non-communicable diseases represent a growing public health concern in virtually all modern, industrialized nations [16, 19]. In 2012, non-communicable diseases were responsible for 68% of all deaths, and continue to be the leading cause of death worldwide as populations grow and age [20]. The increasing prevalence of various non-communicable diseases is a considerable financial burden. If changes are not made, the global cumulative economic cost associated with diabetes, CVD, respiratory diseases, and cancer between 2011-2025 has been estimated to be a staggering US$ 7 trillion [21]. The prevention and treatment of chronic diseases is of vital importance in Canada and around the world, from both a public health and economic standpoint.
2.2 Risk factors for morbidity and mortality

Several modifiable risk factors contribute to increases in the incidence of death from non-communicable diseases in developed nations, including a sedentary lifestyle, diet, smoking, PA patterns, and poor CRF [15, 22]. Insight regarding the importance of PA as a behavior for maintaining health dates back more than 2000 years, and over the past five decades a large body of epidemiological and clinical evidence has amassed that recognizes PA as potent prognostic indicator of health risk. Fueled by increasing prevalence of obesity, diabetes, and chronic diseases around the globe, mounting attention is being given to the role of PA in improving quality of life and preventing disease and premature mortality.

In 1995, the Centers for Disease Control and Prevention jointly with the American College of Sports Medicine published national recommendations on the amount and type of PA needed to reduce risk of chronic diseases and premature mortality. These guidelines were closely followed by the Report of the US Surgeon General in 1996 and similar recommendations have been promoted by other countries and by the World Health Organization [23, 24]. The guidelines provide a clear public health message and encourage increased participation in PA, recommending that adults accumulate at least 150 minutes of moderate-to-vigorous intensity PA per week. Today, the World Health Organization considers insufficient PA to be one of the 10 leading risk factors for global mortality [19].

CRF has been recognized as an important risk factor itself for non-communicable diseases, including CVD and cancer mortality. In fact, CRF has been recognized as a stronger predictor of mortality than several traditional risk factors such as hypertension, smoking, obesity, hyperlipidemia, and diabetes [25]. Even small increments in CRF (1 metabolic equivalent [MET]) are associated with relatively large improvements in survival (approximately 15 – 19% reduction in mortality risk) [4, 26]. Although there is currently no criterion-based CRF cut points or thresholds that would define low, moderate, and high CRF, there is general consensus that 5
METs is a good threshold to identify those adults at increased risk of morbidity and mortality across age, sex, and race [4]. The American Heart Association recently released a statement that outlines the importance of CRF in the prevention and treatment of CVD, and calls for the recognition of CRF as a vital sign that should be routinely measured in clinical practice [4, 27].

2.3 Physical activity

PA is a behaviour, defined as bodily movements that are produced by skeletal muscles and require energy expenditure above resting levels [28]. PA is typically characterized by the frequency, intensity, duration, energy expenditure or amount, and type of activity involved. Frequency indicates the number of sessions of PA within a given time period. There are different means of classifying intensity of PA. Absolute intensity of PA refers to the energy cost per minute of the activity, commonly expressed as ml/kg/min of oxygen consumed or METs. Whereas relative intensity takes the physiologic capacity or CRF level of the individual into account, and is often expressed as a percent of an individual’s VO$_2$max, as a percent of their measured or estimated maximal heart rate, or as a subjective rating of perceived exertion.

Duration is a measure that indicates the time spent performing PA in a given session. Duration can be combined with information on frequency to determine the total number of minutes of PA accumulated. The total amount of PA an individual performs, or the total amount of energy expedited during PA, is a function of the intensity, duration, and frequency of PA. Lastly, type of activity or modality refers to the nature of the activity, often defined as aerobic, resistance, or flexibility activities. Current PA guidelines for adults aged 16 – 64 years recommend a balance of aerobic and resistance activity; it is recommended that adults achieve at least 150 minutes of moderate or higher intensity aerobic PA per week, as well as muscle and bone strengthening activities at least 2 days per week [23].
2.3.1 PA, morbidity and mortality

Since Hippocrates first advised of the importance of PA to health and longevity over 2000 years ago, the evidence that PA is important in the prevention and treatment of chronic conditions and premature mortality has continued to accumulate [29]. In 1843, Dr. William Guy was one of the first to objectively assess the benefits of PA. After contrasting the mortality rates for sedentary workers and physically active workers, he concluded that “strong exercise is favourable to health” [30].

A century later, Dr. Jeremiah Morris published a seminal paper that examined a large cohort (n= 31,000 men) of London transport workers [31, 32]. The principal observation was that sedentary bus drivers had higher rates of cardiovascular mortality compared to their active peers, the bus conductors. These findings were later reproduced when Morris et al. examined the associations among active postmen compared with sedentary government workers and telephone operators. Postmen who, like conductors, were active during the work day, seemed to be protected against coronary heart disease (CHD) as compared to less active government workers. In 1966, Morris et al. pursued their investigation further by examining the association between PA and other risk factors for CHD. They reported that the prevalence of CVD, hypertension, and blood lipids were significantly reduced in active conductors when compared with sedentary drivers. Dr. Morris’ work using classical epidemiological analyses to examine the association between PA and chronic diseases earned him the title “Father of Physical Activity Epidemiology”, and ushered in the age of large-scale prospective observational studies examining the impact of PA in the prevention and treatment of chronic diseases.

The influential work by the Morris group was followed by the investigations of Dr. Ralph Paffenbarger, who identified PA as a powerful independent predictor of mortality in a group of San Francisco longshoremen [33]. With advances in technology, modern working conditions soon reduced the energy cost of most jobs to the point where the categorization of PA based on profession became impractical. Epidemiologists continued to examine the relationship between
PA and major cardiovascular events and all-cause mortality in large populations using questionnaires. For example, Paffenbarger et al. further examined the relationship between PA and mortality using a detailed questionnaire in a large cohort of male Harvard alumni. The Harvard Alumni Study followed over 36,500 men and is one of the most well-controlled and widely cited studies on the relationship between PA and mortality. In an early report published in 1986, Paffenbarger et al. demonstrated that PA decreased mortality risk in a dose-response fashion across all age groups studied, and the association remained after adjusting for traditional risk factors such as familial history of CVD, obesity, smoking, hypertension, and diabetes [34].

The benefits of PA extend across a wide range of other health outcomes, including CVD [35, 36], some cancers [37-40], stroke [41, 42], diabetes [43, 44], hypertension [45-47], cognitive function [48, 49], mental health [50], and frailty [1]. In addition, level of PA remains a potent predictor of risk across various clinical populations. A large number of epidemiological studies have paralleled and extended the observations of early investigations in a myriad of other populations, including women [51], ethnically diverse participants [52-54], broad age classes [55-57], and patients with chronic disease. Cardiac rehabilitation exercise training programs provide striking evidence of the benefits of PA in patients with CVD. In a meta-analysis of 22 trials, patients who were enrolled in a cardiac rehabilitation program after experiencing a major cardiovascular event demonstrated reductions in CVD and overall mortality of 25% and 20%, respectively [58]. Therefore, adoption of regular PA is associated with better prognosis even amongst individuals who are at high-risk of a major adverse cardiovascular event.

2.3.2 Characterization of the PA-mortality curve

Several reviews and meta-analyses have been conducted to examine the relationship between PA and mortality risk. Authors consistently report a dose-response relationship between PA and all-cause mortality in both sexes and across all ages groups, in that increasing
activity is associated with significantly lower risk of CVD and all-cause mortality [18]. The relationship between PA and mortality appears to be independent of common risk factors that are measured in clinical practice such as age, smoking, hypertension, and BMI, suggesting that PA assessment provides information on mortality risk that is not captured by traditional risk factors [59].

The evidence demonstrating that approximately 30 minutes of moderate-intensity PA most days of the week is associated with significant reductions in all-cause and CVD-mortality, colon and breast cancer, and diabetes is clear [34, 38, 44, 60]. And greater health benefits occur with higher intensities and/or volumes of PA [59]. On the basis of these observations, most PA guidelines around the world recommend the adoption of 150 minutes of moderate-intensity PA per week. The evidence is consistent, indicating that meeting consensus guidelines renders at least a 20 – 30% reduced risk of premature mortality compared to not meeting the guidelines [24].

Although different ways of measuring and categorizing PA makes it is difficult to synthesize data across studies and precisely quantify the shape of the PA-mortality curve, there is emerging evidence that less PA than the recommended 150 minutes a week may be protective against cardiovascular events. Compared to their sedentary peers, engaging in some PA, even if less than that recommended worldwide, has demonstrated to be associated with reduced risk of all-cause mortality amongst Taiwanese men and women [61], American men and women aged 50-70 years [62], and in pooled data from 6 prospective cohorts from the Unites States and Europe [63]. Low amounts of PA have also been associated with substantially lower risk of chronic disease in a large group of postmenopausal women [64-66]. Amongst those who are sedentary, even modest improvements in PA are likely to have considerable health benefits. Further investigation is required to accurately identify the minimum amount of PA that associated with reduced mortality risk.
2.3.3 Population-attributable risk estimates

Population-attributable risk (PAR) estimates provide an indication of the impact of a given risk factor within a specific population. PAR is the proportion of events (i.e. deaths) in the population that are due to exposure to the risk factor. In practical terms, the PAR characterizes the proportion of events that would be avoided if exposure to the risk factor were completely eliminated. Published estimates of the percent reduction in the number of deaths due to physical inactivity range from 23%-46% in investigations that have usually assumed two PA categories (i.e. inactive and active) [67]. Several investigators have examined the PAR estimates for various components of PA. In the Harvard Alumni study, not engaging in moderate-vigorous PA was associated with a PAR of 12%, whereas not walking 9 miles/week was associated with a PAR of 9.7% and climbing less than 20 flights of stairs/week was associated with a PAR of 8.8%. Notably, in the same cohort, estimates of attributes risk from cigarette smoking and elevated BMI were 11.3% and 6.3%, respectively [2]. Comparison of the PAR for physical inactivity with that of smoking and BMI provides evidence that the level of risk attributable to physical inactivity is similar to that of traditional risk factors that are measured in clinical practice. Physical inactivity therefore constitutes a major public health concern.

2.3.5 Serial changes in PA and mortality risk

In observational studies with one assessment of PA at baseline, it is difficult to eliminate the possible influence of subclinical disease and/or other intrinsic factors since subjects may have had undiagnosed disease at baseline that caused both sedentary habits and premature mortality. Studies that examine the association of changes in PA (for example, at least two serial measures of PA) provide a stronger test for a causal relationship between PA and mortality risk.

A report by Paffenbarger et al. demonstrated that men who adopted or maintained moderate-to-vigorous sports activity (> 4.5 METs) had a 23% and 29% lower risk of all-cause
mortality, respectively, compared to men who did not engage in moderate-vigorous activity at both PA assessments after adjustment for changes in age, smoking, hypertension, and BMI. These findings are in agreement with analyses of the association between changes in PA and risk of death from CHD, and similar findings have been reported in women [68]. Important to note, the associations remain in men and women > 75 years old [2, 68].

Evaluation of the association between change in PA with mortality risk reaffirm the validity of a direct association between PA and health risk. The observations suggest that serial measures of PA may provide a more optimal approach for stratifying patients according to risk for all-cause mortality compared to a single, baseline PA assessment.

2.3.4 Reclassification with the addition of PA to traditional risk factors

Risk assessment has been an important element in identifying PA as a strong predictor of CVD and all-cause mortality, and identifying PA as a target for therapeutic lifestyle interventions. Efforts to characterize the PA-mortality curve over the last 5 decades are reflected in current national and international guidelines recommending that adults participate in at least 150 minutes of moderate-intensity PA per week. However, the strong independent relationship between PA and mortality does not necessarily translate into direct improvements in patient risk stratification in the clinical setting. In clinical practice, relative risk estimates can be difficult to interpret. Instead, risk prediction algorithms are used to identify individuals with high risk for developing future adverse health outcomes such as CVD and early mortality. Therefore, the American Heart Association recently advised that original association studies be followed by a thorough assessment of the prognostic utility of novel risk factors using statistical analyses such as net reclassification improvement (NRI) [69].

Few studies have examined whether the addition of PA to a standard risk prediction algorithm improves classification of risk for mortality (Table 1). In a large cohort (n= 6962) of male US Veterans, Myers et al. reported that the addition PA significantly improved
reclassification of risk for mortality by 10.2% for individuals who had an event (all-cause mortality) and by 12.6% for individuals who did not when added to a risk prediction model (NRI=0.228, p<.001) [6]. Of particular interest, in this study PA was assessed using a simple, binary query regarding participation in guideline PA (i.e. meeting guideline PA or not). These preliminary observations suggest that PA has the potential to improve patient management. The findings reported by Myers et al. reinforce the diagnostic utility of PA, and provide incentive for clinicians to measure PA status and prescribe PA in clinical setting in order to improve risk assessment.
Table 1. Net reclassification improvement by addition of PA

<table>
<thead>
<tr>
<th>Reference</th>
<th>PA assessment</th>
<th>Baseline risk factors</th>
<th>Outcome</th>
<th>Sample</th>
<th>Event NRI (%)</th>
<th>Non-event NRI (%)</th>
<th>Overall NRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang et al 2015</td>
<td>PA questionnaire</td>
<td>Framingham risk variables†</td>
<td>All-cause mortality</td>
<td>1288 men &amp; women</td>
<td>64.6</td>
<td>-31.9</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CVD mortality</td>
<td>1288 men &amp; women</td>
<td>64.1</td>
<td>-32.0</td>
<td>0.32</td>
</tr>
<tr>
<td>Myers et al 2015</td>
<td>PA questionnaire</td>
<td>Age, BMI, HTN, hyperlipidemia, CVD, smoking, diabetes</td>
<td>All-cause mortality</td>
<td>6962 men</td>
<td>10.2</td>
<td>12.6</td>
<td>0.23</td>
</tr>
</tbody>
</table>

† Framingham risk variables: age, sex, race, systolic blood pressure, medications, body mass index, smoking, diabetes mellitus, cholesterol levels, coronary artery disease, creatinine level, peripheral artery disease

BMI, body mass index; HTN, hypertension; CVD, cardiovascular disease; NRI, net reclassification index; PA, physical activity
2.3.6 Summary

Physical inactivity has been consistently associated with increased risk of premature mortality and morbidity, including CVD, cancer, and diabetes. The association between PA and health risk is characterized by an inverse, dose-response relationship that is largely independent of other risk factors that are measured in clinical practice. The investigations reviewed underscore the strength of the relationship between PA and health outcomes.

Preliminary evidence suggests that PA provides incremental predictive information beyond standard risk assessment models, such as the Framingham Risk Score. Additional evidence demonstrating that insertion of PA into established risk engines is required to firmly establish that routine measurement of PA in clinical settings improves patient management.

2.3.7 Assessment of PA

A summary of the techniques commonly used for PA assessment are described in Table 2. In the context of epidemiological research, PA is generally assessed subjectively by means of questionnaires and activity logs. Self-report PA assessment tools have been used for nearly 50 years, and have been instrumental in building our current understanding of the relationship between PA and health [70]. The tools that are employed to measure PA are diverse in their level of complexity, the period surveyed, and in the type of information assessed. Dependent on the goal of PA assessment, questionnaires typically evaluate some component of energy expenditure (i.e. the frequency, duration, intensity, or total amount of PA performed).

Questionnaires range from detailed, extensive forms that may require up to an hour to complete, to global questionnaires that may only categorize subjects as either “active” or “inactive” based on their response to a simple query. “Active” generally refers to individuals who meet the minimum amount of PA recommended by current PA guidelines, whereas “inactive” translates to those who do not meet PA recommendations. Comparison of simple, single-item
questions with more detailed question sets reveal moderate correlations, with values that range from 0.14 – 0.41 [71]. Notably, simpler questionnaires receive some of the highest coefficients of reliability and validity, likely because subjects may become bored completing lengthy questionnaires and detailed questionnaires often require considerable interpretation. A list of validated single-item and short PA tools are identified in Table 3. Across studies, single-item and short questionnaires have generally demonstrated moderate correlations with longer questionnaires that have previously been validated and, similar to other self-report assessment tools, single-item and short questionnaires have relatively weaker correlations with accelerometers (Table 3).

Regardless of the questionnaire employed, the data acquired from self-reported PA will have limited reliability and validity compared to objective measures of PA (doubly-labelled water, accelerometers, pedometers, heart rate monitors etc.) [72]. Responses are depended on subject recall and are therefore restricted by the limitations of human memory. Secondly, whether deliberate or not, subjects may be influenced by social desirability. As such, subjective reporting may lead to either over or underestimating PA [72]. Imprecise classification of subjects would tend to reduce the magnitude of the effect of PA on health. This notion is supported by the observation that objectively measured PA is more strongly related to mortality than self-reported PA [73].
Table 2. Advantages and disadvantages of techniques used for PA assessment

<table>
<thead>
<tr>
<th></th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Self-reported Questionnaires</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global questionnaire</td>
<td>Simplicity (minimal info required to classify subjects), ease of administration</td>
<td>Difficulty in evaluating dose-response relationships and capturing all components of PA</td>
</tr>
<tr>
<td>Short-term recall questionnaire</td>
<td>Establish dose-response relationship, measure several dimensions of PA (i.e. frequency, intensity, duration)</td>
<td>Difficulty averaging frequencies and durations of past PA behaviour, and difficulty with recall of detailed PA info</td>
</tr>
<tr>
<td>Quantitative history recall questionnaire</td>
<td>Evaluate relationship between chronic PA and health, establish dose-response relationship</td>
<td>Difficulty with recall of PA info from past year or lifetime</td>
</tr>
<tr>
<td><strong>Objective measures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accelerometer</td>
<td>Provide detailed info (i.e. frequency, duration, pattern, and intensity of PA over days, weeks etc.), minimal invasiveness, detect postural transitions</td>
<td>Difficulty evaluating sedentary, light-intensity activities, and non-ambulatory activities, relatively expensive</td>
</tr>
<tr>
<td>Pedometer</td>
<td>Quantify ambulatory activities, easily understood metric (steps), relatively low cost, provide real-time behavioural feedback and motivation</td>
<td>Inability to monitor non-ambulatory activities, posture, and EE</td>
</tr>
<tr>
<td>HR monitor</td>
<td>Monitor non-ambulatory activities that are not captured by pedometers and accelerometers</td>
<td>HR-EE relationship not as strong during light-intensity PA, need to account for influence of BP lowering medication, potential discomfort when worn for long periods of time, relatively expensive</td>
</tr>
<tr>
<td>Doubly labelled water</td>
<td>Validation of other PA measurements, standard protocol allows direct comparisons between different labs</td>
<td>High cost and subject burden (impractical for large scale studies), unable to establish modality,</td>
</tr>
</tbody>
</table>

*adapted from Ainsworth et al. 2015 [70]. PA, physical activity; HR, heart rate; EE, energy expenditure
Table 3. Summary of short and single-item PA assessment tools*

<table>
<thead>
<tr>
<th>Source (Year)</th>
<th>Single-item or short PA measure</th>
<th>Reliability</th>
<th>Validity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scott et al. [74]</td>
<td>Single-item measure</td>
<td>ICC=0.75</td>
<td>Accelerometer: VO₂; r=0.44</td>
</tr>
<tr>
<td>Eaton et al. [75]</td>
<td>“In the past month, how often on the average do you do continuous vigorous exercise for 20 min or more? Would you say it was &lt;once a week, 1 or 2 times a week, 3 or more times a week, or not at all&gt;?”</td>
<td></td>
<td>VO₂: r=0.13-0.19</td>
</tr>
<tr>
<td>Milton et al. [76]</td>
<td>Single-item measure</td>
<td>r=0.72-0.82</td>
<td>Accelerometer: r=0.53</td>
</tr>
<tr>
<td>Iwai et al. [77]</td>
<td>Average weekly time spent engaging in sports or physical exercise? Average time per day spent walking indoors or outside? Frequency of engagement in sports or physical exercise. “over the past year or 2”?</td>
<td>kappa=0.25-0.56</td>
<td>Interview data: r=0.43–0.60</td>
</tr>
<tr>
<td>Jackson et al. [78]</td>
<td>Single-response option chosen from 5 descriptors of PA. Responses are based on usual behaviour and the length of time that respondents have maintained their current level of PA.</td>
<td>r=0.81</td>
<td>VO₂: r=0.57</td>
</tr>
<tr>
<td>Kohl et al. [79]</td>
<td>“How many times a week do you engage in vigorous PA long enough to work up a sweat?”</td>
<td></td>
<td>VO₂: r=0.51</td>
</tr>
<tr>
<td>Li et al. [80]</td>
<td>Single-response rating of usual PA using a 5-point Likert scale ranging from highly active to inactive, based on “usual PA”</td>
<td>r=0.88</td>
<td>Detailed questionnaire: r=0.66</td>
</tr>
<tr>
<td>Macera et al. [81]</td>
<td>“In the past month, other than your regular job, did you do any PA or exercises such as running, calisthenics, golf, gardening, or walking for exercise?”</td>
<td></td>
<td>Detailed questionnaire: 5% of patients misclassified</td>
</tr>
<tr>
<td>Rose et al. [82]</td>
<td>“As a rule, do you do at least half an hour of moderate or vigorous exercise (such as walking or a sport) on five or more days of the week?”</td>
<td></td>
<td>Detailed questionnaire: kappa=0.56</td>
</tr>
<tr>
<td>Siconolfi et al. [83]</td>
<td>“At least once a week do you engage in any regular PA similar to brisk walking, jogging, bicycling, etc., long enough to work up a sweat?” If the answer is yes, “How many times per week?”</td>
<td>Paffenbarger PA questionnaire: r=0.57</td>
<td>VO₂: r=0.46</td>
</tr>
<tr>
<td>Washburn et al. [84]</td>
<td>“At least once a week, do you engage in any regular activity long enough to work up a sweat (e.g., brisk walking, jogging, bicycling, construction work, etc.)? If yes, how many hours per week do you engage in these activities?”</td>
<td>Paffenbarger PA questionnaire: r=0.39</td>
<td></td>
</tr>
<tr>
<td>Smith et al. [85]</td>
<td>The number of bouts of vigorous-intensity PA that were &gt;20 min in duration and bouts of walking or moderate-intensity activity that were &gt;30 min in a usual week</td>
<td>r=0.42-0.61</td>
<td>Accelerometer: r=0.36-0.39, kappa=18.2</td>
</tr>
<tr>
<td>Marshall et al. [86]</td>
<td>Two-item question, assessing frequency and duration of vigorous-intensity PA, and frequency and duration of moderate-intensity PA (including walking). Time frame is “usual week”</td>
<td></td>
<td>Detailed questionnaire: 0.45-0.58, kappa=46.7</td>
</tr>
</tbody>
</table>

*adapted from Milton et al. 2010 [76]. VO₂, oxygen consumption; PA, physical activity
2.4 Cardiorespiratory Fitness

The concept of maximal oxygen consumption or CRF was initially described in 1923 by Hill and Lupton, two physiologists who were the first to demonstrate that an upper limit exists in a human’s capacity to deliver oxygen to working muscles [87]. CRF is a physiologic trait that is defined as the maximal oxygen uptake attained during aerobic exercise that cannot be increased despite further increase in exercise workload. Compared to other traditional risk factors, CRF is unique in providing an indication of the integrated function of numerous bodily systems. It quantifies the ability of the respiratory and cardiovascular system to transport oxygen to working muscles, and of the muscles’ ability to utilize oxygen at the level of the mitochondria to perform work. In other words, it is a reflection of the physiological health of the respiratory and cardiovascular systems [4].

2.4.1 CRF, morbidity and mortality

Over the last two decades, measures of CRF have proven to be important in the prognosis of CVD, several cancers, and all-cause and CVD mortality in both men and women and across all age groups [4]. In 1989, Dr. Steven Blair published a seminal report using data from the Aerobics Center Longitudinal Study in which CRF was assessed objectively using a maximal treadmill exercise test in >13,000 asymptomatic subjects who were followed prospectively for mortality [3]. In both men and women, CRF was inversely associated with mortality due to all causes, CVD, and cancer, and these trends remained after adjustment for several established risk factors. The findings from the Aerobics Center Longitudinal Study closely followed an earlier report published in 1988 from the Lipid Research Clinics Mortality Follow-up study [88], in which exercise time on the treadmill during a treadmill exercise test measured in 4276 men was associated significantly with mortality from all-causes, CVD, and
CHD after controlling for conventional risk factors in both asymptomatic men and men with existing CVD.

Since these early studies, findings from research groups around the world support an inverse and independent association between CRF and overall mortality risk [4, 89]. CRF consistently provides information on mortality risk independent of traditional cardiovascular risk factors, and CRF has demonstrated to outperform several common risk factors such as smoking status, hypertension, cholesterol, and diabetes [90]. CRF also appears to be a stronger predictor of morbidity and mortality than PA. In a review of 16 PA and 7 CRF studies, Williams et al. reported that the risk reduction associated with higher CRF levels was twice as great as that for PA [9]. It is crucial to appreciate, however, that the superiority of CRF may be explained by elevated measurement error associated with self-reported assessment of PA compared to objective measures of CRF [18].

While the majority of studies have been performed in men, there is mounting evidence that the protective effects of CRF remain regardless of sex [3, 91-93], age [94-96], race [97], documented cardiovascular disease [90, 98], major risk factors, and comorbid conditions, including obesity, diabetes, hypertension, and lipid abnormalities [99-106]. The association between CRF and mortality has also been confirmed amongst clinical populations, including patients undergoing surgical interventions [107, 108] and patients referred for exercise testing for clinical reasons (VETS [90], Cleveland Clinic [109], Mayo Clinic [110, 111], and Toronto Rehabilitation Institute [112, 113]). CRF has also shown to be an important risk factor for other clinical endpoints, including CVD mortality [3, 88, 114, 115], cancer mortality [3, 116-120], and incidence of CHD [121], myocardial infarction [122], stroke [123, 124], and sudden cardiac death [125].

Several meta-analyses have demonstrated a strong inverse relationship between CRF and hard outcomes [9, 89, 126, 127]. In 2009, Kodama et al. were the first to highlight the strength of the association between CRF and both CVD and all-cause mortality in a meta-
analysis. This review selected 33 studies, comprising 102,980 participants with 6910 deaths [89]. Kodama et al. confirmed previous findings, demonstrating a dose-response relationship between CRF and both all-cause and CVD-mortality. The observations remained after controlling for numerous established risk factors including age, sex, smoking, coronary risk factors, abnormal exercise electrocardiogram, follow-up period, instrument for assessing CRF, and exercise testing method. Notably, each 1-MET increment in CRF was associated with a 13% decrement in risk of all-cause mortality and 15% reduction in risk of CVD mortality.

2.4.2 Characterization of the CRF-mortality curve

A consistent finding among studies that have characterized the CRF-mortality curve is that the greatest health benefit is observed at the lower end of the CRF spectrum, with diminishing returns associated with higher CRF at the upper end of the spectrum [4]. When subjects are categorized according to quartiles or quintiles, more than half of the reduction in risk of mortality occurs between the least fit group (which generally translates to <5 METS) and the next least fit group (approximately 5 – 7 METS) [4]. Therefore, particularly high CRF levels are not necessary to provide significant health benefits. That small differences in CRF are associated with a substantial reduction in risk of mortality has important public health implications. Achieving rather modest improvements in CRF is likely attainable by regular involvement in moderate-intensity PA (i.e. meeting the PA guidelines), and consequently, may be associated with considerable reductions in risk of morbidity and mortality [1].

There are highly congruent national and international guidelines for PA, however currently consensus regarding a precise clinical categorization of CRF has not been achieved. It is widely accepted that individuals with a CRF level <5 METs have a particularly high risk for mortality [4]. Thereafter, higher CRF levels are accompanied by incremental reductions in risk, with CRF levels >8 to 10 METs associated with protection [4]. Important to note, the CRF-
mortality association remains after adjusting for the strong influence of age on CRF, and after considering sex, BMI, and various cardiovascular risk factors. On the basis of these observations, various thresholds for CRF have been suggested by different groups of researchers and organizations with the aim of identifying high-risk individuals [4, 128], and a recent study defined age-specific CRF cutoffs to identify increased mortality risk in a large group of men who were referred for exercise testing for clinical reasons [96]. Still, there exists a need for widely accepted CRF reference values to allow accurate interpretation of CRF values across diverse populations [129].

2.4.3 Population-attributable risk estimates

As with PA, the relative importance of CRF as a risk factor for mortality is highlighted from a population-disease-burden perspective by estimating the PAR of CRF and other risk factors. In the ACLS cohort, after taking both the strength of the association between CRF and mortality and the prevalence of low CRF into account, low CRF accounted for approximately 16% of all deaths in both men and women. With the exception of hypertension in men, low CRF in this cohort accounted for more deaths than other established risk factors that were examined, including obesity, smoking, high cholesterol, and diabetes [130]. In addition, in a later study in a large group (n= 18,102) of male US veterans (age, 25-92 years), 32% of deaths were attributable to low CRF. PAR estimates provide compelling evidence that the implementation of strategies to promote an active lifestyle, with the aim of improving CRF, has the potential to have profound consequences from a publish health perspective.

2.4.5 Serial changes in CRF and mortality risk

The majority of studies examining the relationship between CRF and mortality have been limited to a single baseline assessment of CRF with subsequent mortality follow-up.
Examination of the association between changes in CRF and mortality allows investigators to consider whether confounding variables, such as genetic factors or underlying disease, are a significant cause of the observed relationship between CRF and mortality. In 1995 Blair et al. examined changes in CRF and all-cause mortality in 9777 men who had two exercise assessments over an average period of 4.9 years between examinations. Men who were unfit at both visits had the highest risk of all-cause and CVD mortalities, men who were fit at both visits had the lowest risk, and men who improved their CRF between examinations had a 44% reduction in mortality risk relative to men who were unfit at both examinations [5]. In fact, each minute increase in maximal treadmill time between examinations was associated with a 7.9% decrease in the risk of mortality and researchers reported a similar pattern in all age groups that were examined. Important to note, in multivariate analysis that considered favourable changes in BMI, systolic blood pressure, cholesterol, smoking, and CRF between the first and subsequent examination, a favourable change in CRF was the only significant predictor of all-cause mortality [5].

These findings were reproduced in the same cohort when reanalyzed with a comparatively larger sample (n= 14,345), over a wider age range (20 to 100 years at baseline) and over a longer follow-up time (11.4 years) [26]. Every 1-MET improvement in CRF was associated with a 15% and 19% reduction in risk of all-cause and CVD mortality, respectively [26]. To note, BMI change was not significantly associated with CVD or all-cause mortality after controlling for change in CRF. These findings are strikingly similar to those reported in a Norwegian study (n=1428) [131], and those reported by Kokkinos and colleagues in a group of older men who were referred for exercise testing for clinical reasons (n=867) [94].

These observations provide a unique opportunity for inference regarding the relationship between CRF and mortality that is not available from studies that are limited to a single baseline measurement. Improving CRF or simply preventing CRF loss, likely through increases in PA, is important for longevity, and the benefits of improving CRF are observed irrespective of changes
BMI and even at an advanced age. Furthermore, the finding that improvements in CRF are associated with a significant reduction in risk of mortality compared with men who do not improve their CRF between subsequent examinations provides evidence that the hereditary component of CRF is not solely responsible for the observed association between CRF and mortality.

2.4.4 Reclassification with the addition of CRF to traditional risk factors

As previously discussed regarding PA, examination of NRI offers insight into the extent to which CRF provides clinically meaningful prognostic information beyond traditional risk factors [69]. Several investigations have reported that the addition of CRF to standard risk markers significantly improves both 10 and 25-year NRI [6, 132-135]. A summary of investigations that have examined reclassification of mortality risk by the addition of CRF are presented in Table 4. NRI values for the addition of CRF to a common set of baseline risk factors range from 0.12 – 0.31 and from 0.35 – 0.44 for CVD and all-cause mortality, respectively (Table 4). Published NRI values provide impetus for incorporating CRF into statistical models in clinical practice to optimize patient risk assessment for CVD and all-cause mortality. Future research should continue to determine the contribution of CRF to traditional risk factors across diverse populations, and focus on identifying thresholds for NRI that represent a clinically meaningful improvement in risk classification (i.e. whether an overall NRI of 0.12 improves predicted risk sufficiently versus an NRI of 0.44).

Of particular interest, another study examined whether traditional risk factors improve risk stratification when added to estimated CRF, instead of assessing the incremental contribution of CRF to a standard risk assessment algorithm [136]. The estimated CRF algorithm demonstrated good ability to discriminate risk of CVD mortality (Harrell’s C statistic 0.848, 95% CI [0.836-0.861] and 0.878, [0.862-0.894] for men and women, respectively), and the addition of conventional risk factors to estimated CRF did not considerably improve
classification of risk. The findings support the notion that determining CRF by an estimated CRF algorithm provides a valid indication of future health status. Estimated CRF may be a practical method of predicting long-term CVD risk in clinical practice to help manage patients’ health risk.
**Table 4. Net reclassification improvement by addition of CRF***

<table>
<thead>
<tr>
<th>Reference</th>
<th>CRF assessment</th>
<th>Baseline risk factors</th>
<th>Outcome</th>
<th>Sample</th>
<th>Event NRI (%)</th>
<th>Non-event NRI (%)</th>
<th>Overall NRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gupta et al</td>
<td>Maximal treadmill test</td>
<td>Sex, age, BP, diabetes, cholesterol, smoking</td>
<td>CVD-mortality</td>
<td>43,041 men</td>
<td>11.3</td>
<td>0.8</td>
<td>0.12</td>
</tr>
<tr>
<td>2011</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stamatakis et al</td>
<td>Non-exercise CRF algorithm</td>
<td>Sex, age, BMI, resting HR, PA</td>
<td>CVD-mortality</td>
<td>14,650 men</td>
<td>25.6</td>
<td>1.6</td>
<td>0.27</td>
</tr>
<tr>
<td>2012</td>
<td></td>
<td></td>
<td></td>
<td>17,669 women</td>
<td>20.2</td>
<td>0.8</td>
<td>0.21</td>
</tr>
<tr>
<td>Artero et al</td>
<td>Maximal treadmill test</td>
<td>Sex, age, BMI, WC, resting HR, PA</td>
<td>CVD-mortality</td>
<td>34,211 men</td>
<td>12.7</td>
<td>-0.4</td>
<td>0.12</td>
</tr>
<tr>
<td>2014</td>
<td></td>
<td></td>
<td></td>
<td>9145 women</td>
<td>20.8</td>
<td>-1.0</td>
<td>0.20</td>
</tr>
<tr>
<td>Myers et al</td>
<td>Maximal treadmill test</td>
<td>Age, BMI, HTN, hyperlipidemia, CVD, smoking, diabetes</td>
<td>All-cause mortality</td>
<td>6962 men</td>
<td>25.8</td>
<td>17.6</td>
<td>0.44</td>
</tr>
<tr>
<td>2015</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holtermann et al</td>
<td>Self-reported CRF</td>
<td>Age, sex, smoking, BMI, BP, medication, diabetes, cholesterol, education, income, alcohol, PA</td>
<td>All-cause mortality</td>
<td>8936 men &amp; women</td>
<td>-20.6</td>
<td>46.0</td>
<td>0.25</td>
</tr>
<tr>
<td>2015</td>
<td></td>
<td></td>
<td></td>
<td>8936 men &amp; women</td>
<td>-25.3</td>
<td>55.8</td>
<td>0.31</td>
</tr>
</tbody>
</table>

*adapted from Ross et al. 2016 [4]. BP, blood pressure; CVD, cardiovascular disease; BMI, body mass index; HR, heart rate; PA, physical activity; WC, waist circumference; HTN, hypertension; CRF, cardiorespiratory fitness; NRI, net reclassification index
2.4.6 Summary

Extensive evidence demonstrates an inverse association between CRF and morbidity and mortality. There is consistency across studies that examined men and women, different age groups, and in patients with comorbidities and/or chronic disease. Like PA, the relationship is characterized by an inverse gradient across CRF groups for various health outcomes.

Because most CRF-mortality studies are observational in nature, evaluation of change in CRF and mortality risk is one criterion used to infer a cause-and-effect relation between CRF and mortality. At least four investigations have reported on the relationship of change in CRF from one CRF assessment to a second CRF assessment, with subsequent follow-up for mortality. Findings from serial measures of CRF parallel those from studies with only one CRF measure at baseline. These observations further underscore the value of CRF as a risk marker and suggest that in clinical practice, routine evaluation of CRF may provide more comprehensive prognostic information than can be obtained from a single CRF measure.

More recently, several studies have used novel metrics such as NRI to assess the incremental value of CRF beyond standard risk assessment models (i.e. the Framingham Risk Score). Whether CRF was measured objectively using an exercise test or estimated using a non-exercise algorithm, the addition of CRF to a standard risk assessment model significantly improved reclassification of risk for CVD and all-cause mortality. Indeed, CRF has the potential to complement common risk factors in risk prediction, thereby providing clinically meaningful information that would optimize patient management. The observations support the notion that CRF should be measured in clinical practice.

2.4.7 Assessment of CRF

CRF is typically assessed by a maximal or submaximal exercise test. The measurement of performance during an exercise test is expressed as oxygen uptake (ml/min or normalized for body weight to facilitate comparison between subjects, ml/kg/min) or in relation to basal
metabolic equivalents (METs). 1 MET, or 3.5 ml O₂/kg/min, is the oxygen consumption rate required to maintain life in the resting state. Directly measured maximal oxygen uptake is the most valid measure to evaluate functional cardiorespiratory capacity [137]. However, if ventilator expired gas analysis equipment is not available, maximal exercise capacity can be estimated using a standardized equation based on the speed, grade, and duration achieved during a maximal or submaximal treadmill test, or the peak workload attained during a maximal or submaximal cycle ergometer test. Traditionally, VO₂ max refers to a VO₂ plateau despite an increase in workload during an exercise test. In the event that an individual does not attain a VO₂ plateau, the test is a measure of VO₂ peak rather than VO₂ max [137].

In the healthcare setting, patients are generally referred for exercise testing either for assessment of suspected coronary artery disease or for clearance to participate in exercise or activities of daily living post myocardial-infarction [138]. In these circumstances, a symptom-limited maximal exercise test is often employed. During a symptom-limited maximal test, the test is terminated if the patient develops a significant symptom. Generally, the parameters that are monitored include the patient's appearance, breathing rate, heart rate, blood pressure, perceived exertion, and electrocardiogram response. In the absence of symptoms or other clinical indications for stopping the test, subjects are encouraged to exercise until volitional fatigue. It has been established that following this protocol, if the patient's electrocardiogram and blood pressure are normal, little risk is posed for the patient [138].

Several different protocols are used to measure CRF. Comparison between treadmill and cycle ergometer protocols reveal that maximal oxygen uptake values are 10 – 20% greater using a treadmill protocol. Among cycle protocols themselves or among standard treadmill protocols, no major differences are observed in maximal oxygen uptake, maximal heart rate, or blood pressure [139, 140]. Standard treadmill protocols were developed and named after major researchers in exercise physiology, such as the Balke [141], Bruce [142], and Ellestad [143] tests. Over time, the Bruce protocol has come to be most prominent in the clinical setting to
assess aerobic function. A survey revealed that the Bruce protocol was used by 82% of 71 cardiology divisions within the US Veterans Health Care system, and a survey of 1375 laboratories in North America reported that 65.5% of those performing exercise testing used the Bruce protocol [144, 145]. Consequently, distinctive advantages to using the Bruce protocol include clinician experience in delivering this approach and extensive data accumulation that supports the notion that one’s performance on the Bruce protocol is a strong predictor of morbidity and mortality.

It is assumed that the accuracy of predicted oxygen uptake from treadmill speed, grade, and time applies to the entire population examined. However, the Bruce protocol and other standardized exercise tests that involve large and sometimes rapid jumps in workload between stages are often too aggressive for some participants, especially those with documented heart disease and/or limited physiological capacity [139]. Tests with large work-rate increments result in lower sensitivity for detecting coronary artery disease [146] and have a tendency to overestimate oxygen uptake [139, 147], likely because patients with documented heart disease have reduced oxygen kinetics throughout exercise compared with normal subjects [147]. Ramp protocols, wherein treadmill speed and grade increase gradually every minute, offer a means of overcoming the limitations of standard incremental protocols [138].

One type of ramp test, the individualized ramp protocol, uses a computer program to personalize ramp rates based on an individual’s estimated maximum CRF with the aim of achieving an optimal test duration of approximately 9 – 10 minutes. Tests that are individualized to last 10 minutes are capable of producing the highest values for oxygen uptake [138, 148]. Intuitively, a test that elicits a higher oxygen uptake likely represents a truer examination of one’s maximal cardiopulmonary function, rather than being influenced by peripheral muscle fatigue.

Comparison of the individualized ramp and Bruce treadmill protocols reveals only minor differences in directly measured maximal oxygen uptake. This finding is similar in asymptomatic
individuals and in those with established coronary artery disease or chronic heart failure [139]. However, there is evidence that suggests that protocols that employ smaller work increments, such as the ramp test, yield a more accurate prediction of maximal oxygen uptake when gas exchange equipment is unavailable. For example, the difference between measured and predicted maximal oxygen uptake is larger using the Bruce treadmill protocol compared to the individualized ramp protocol [139]. Therefore, although the Bruce protocol is an established method for estimating maximal oxygen uptake and does not produce marked differences in directly measured maximal oxygen uptake compared to ramp protocols, the error associated with predicting oxygen uptake from work load may be minimized by using an individualized ramp protocol.

Exercise testing can be a costly and time consuming procedure, which can be impractical for most health-care settings. Because of the wealth of important information that can be derived from CRF, it is encouraging that non-exercise testing methods prove to be a practical and less resource-demanding alternative for estimating CRF. They have showed consistent associations with CVD and all-cause mortality and, as mentioned above, they have demonstrated to improve reclassification of risk for mortality in both men and women [133].

2.5 Physical activity, cardiorespiratory fitness, and mortality

2.5.1 The relationship between PA and CRF

It is well established that increases in PA of moderate or higher intensity are associated with concomitant improvements in CRF in most people [1, 8, 149]. Increasing PA has been recommended to increase levels of CRF by several organizations around the world, including the American College of Sports Medicine and the American Heart Association [7, 150]. Regular involvement in aerobic PA positively alters cardiac morphology and produces systemic vascular changes that lead to enhanced physiological function and improved capacity of muscle fibers to
extract oxygen. In particular, alterations of the left ventricle are thought to be of central importance for improvements in aerobic function [151]. Left ventricular dilation and left ventricular hypertrophy, often termed exercise-induced cardiac remodeling, lead to increases in cardiac output and are therefore accompanied by improved performance on a maximal exertion test. The relationship between cardiac output and maximal exertion is defined by the Fick equation:

\[ VO_2 = (\text{heart rate} \times \text{stroke volume}) \times [\text{arterio-venous}]O_2\text{difference} \]

\[ = CO \times [\text{arterio-venous}]O_2\text{difference} \]

Although PA is a major determinant of CRF, there is a complex interplay between PA, a behaviour, and CRF, a physiological attribute. PA and CRF are influenced by multiple factors, including inherent factors (i.e. genetics and sex) and acquired factors (i.e. disease state, age, and environmental factors) [152]. There is ample evidence that intrinsic CRF (i.e. untrained or baseline CRF), measured by assessing CRF in those who have had a life history of being sedentary, has a considerable genetic component. After controlling for age, sex, BMI, and body composition, approximately 50% of the variance in CRF is attributable to heritable factors. In addition, Bouchard et al. posit that the adaptation in CRF in response to a standardized training program varies between individuals and is also determined by a substantial genetic component, on the order of 45 to 50% [153, 154]. Despite being prescribed a fixed exercise dose, VO\textsubscript{2}max responses range from almost no gain, termed “poor” or “non-responders”, up to 100% increases in CRF [155, 156].

These observations suggest that there may be a substantial fraction of inactive adults who maintain a relatively high CRF despite not engaging in regular PA and similarly, there may be a large portion of physically active individuals who may not be characterized as highly fit. In fact, when examined cross-sectionally, the association between CRF and PA is modest, with variances ranging from 1 to 36% [10, 157]. This notion challenges the dogma that CRF is a surrogate measure of recent PA patterns. That PA and CRF are strong predictors of future
health outcomes but are moderately associated with each other suggests that PA and CRF may be independent in relation to mortality risk.

2.5.2 Putative mechanisms that may explain the link between PA and mortality, independent of CRF

Because PA affects the cells and tissues of virtually every organ system in the body in many different ways, several mechanisms may explain the link between routine PA and reduced risk of chronic diseases and premature mortality [158]. In the context of chronic adaptations that are brought about by regular PA, beneficial effects include favorable alterations in body composition [159], blood lipid profiles [160], glucose homeostasis [161], insulin sensitivity [162], coronary blood flow [163], endothelial function [164], blood pressure [165], systemic inflammation [166], and blood coagulation [167]. Regular PA is also associated with enhanced psychological well-being, indicated by reduced anxiety and depression [168], which is important for prevention and management of many chronic diseases. Whether changes in these intermediary risk factors are independent of CRF is not fully understood. Like all physiologic traits, CRF level has a substantial genetic (i.e. intrinsic) component. The extent to which inherent factors, such as intrinsic CRF and genetics, influence the response to PA, and thereby determine the subsequent physiological benefits associated with PA requires further investigation.

There is some evidence that PA is significantly associated with several risk factors for cardiovascular and metabolic disease independent of measured CRF. In cross-sectional investigations, PA is associated with waist circumference [169, 170], fasting glucose [169, 171], HDL-cholesterol and triglyceride levels [169-171], blood pressure [171], insulin [170, 171], and clustered metabolic risk [169, 171] after controlling for common confounding factors and CRF. Similarly, prospective analysis of the relationship between baseline PA and CRF levels with subsequent follow-up demonstrates a strong, inverse association between PA and the
metabolic syndrome independent of CRF. Whereas, CRF was not a predictor of the metabolic syndrome after adjusting for PA [172, 173]. These variables are established risk factors for morbidity and mortality. By favorably modifying these risk factors it is expected that increases in regular PA will have implications for metabolic disease risk reduction. The observations provide evidence that the benefits of PA may not be solely attributed to accompanying improvements in CRF.

Beyond these changes in established cardiovascular risk factors, the molecular mechanisms that explain the protective effects of PA are multifactorial and not fully understood. However, the protective effects of PA are not fully explained by that which would be predicted based on changes in traditional risk factors [174]. Further research is required to appreciate how increases in PA translate to better health. In response, a recent initiative, the National Institute of Health Common Fund’s Molecular Transducers of PA in Humans program, was launched to help identify the key molecules that are responsible for adaptations to PA and to further our understanding of the mechanisms that underlie the causal link between PA and health risk [175].

2.5.3 Putative mechanisms that may explain the link between CRF and mortality, independent of PA

The relationship reported between CRF and various risk factors and health outcomes is well-documented, including CVD and all-cause mortality, the metabolic syndrome, diabetes, obesity, triglycerides, and blood pressure [4, 176]. However, the causal link between CRF, which is a reflection of the capacity of the human circulatory and respiratory systems to supply oxygen to skeletal muscles during sustained exercise, and one’s metabolic status is not intuitively clear and remains mechanistically unresolved.

The relationship between CRF and morbidity and mortality described in humans is also observed in rodents. Rats bred for either low or high CRF have allowed for deeper mechanistic
exploration of the association between CRF and health and longevity [177, 178]. Compared to rats that were bred for high intrinsic CRF, rats bred for low intrinsic CRF have reduced metabolic control in the heart, mitochondrial regeneration, antioxidant status, insulin-stimulated glucose transport, insulin signal transduction, and skeletal muscle oxidative enzyme capacity [179-182]. Furthermore, in rats kept sedentary all their life, those bred for low intrinsic CRF had a shorter life span (28% - 45% shorter) compared to those bred for high intrinsic CRF. The rate of death in the low-fit rats was almost 6 times greater than for the high-fit rats [178].

Observations in animal models provide support for the notion that one’s baseline or intrinsic CRF may be a reflection of one’s inherited capacity for energy metabolism and may underlie cardiovascular and metabolic disease risk [178-181]. Further research is required in humans to understand whether the protective effect of CRF simply reflect the association between regular PA with health, or whether intrinsic CRF is a marker of a genetically endowed stronger cardiovascular system.

2.5.4 Summary

Although PA is a major determinant of CRF, PA and CRF are influenced by several factors and the association between PA and CRF is modest. Therefore, it is conceivable that PA and CRF are related to health and longevity through distinct mechanisms. However, the interplay between PA, CRF, and risk of all-cause mortality is not fully understood. Although further investigation is required, research from animal studies and evaluation of the relationship between PA and CRF with cardiometabolic risk factors provide insight into the possible pathways by which PA and CRF might independently affect mortality risk.
2.6 PA vs CRF as predictors of mortality

2.6.1 Current evidence

As evidence continues to amass on the importance of PA and CRF as risk factors for morbidity and mortality, defining their relative contributions to mortality risk will provide clinically relevant information. There is ongoing debate as to whether the effect of PA on mortality is largely mediated by CRF or whether one’s habitual PA patterns determine one’s CRF and, consequently, its inverse association with morbidity and mortality. Although several studies have simultaneously examined PA, CRF, and mortality, consensus regarding the relative contributions of PA and CRF to mortality risk remain unclear [10-14]. While current knowledge suggests that CRF remains a predictor of mortality after controlling for PA [10-14], whether PA remains a predictor of mortality beyond CRF remains uncertain. Three studies reported that PA remains a significant predictor of mortality independent of CRF [10, 11, 13], whereas two studies reported that PA is not associated with mortality after controlling for CRF [12, 14] (Table 5 and 6).
Table 5. Studies that reported that PA and CRF are independent in relation to all-cause mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Men; Women (n)</th>
<th>Age [range] or (\bar{x}) (SD)</th>
<th>Method of measurement</th>
<th>Covariates</th>
<th>HR for mortality by PA and by CRF(^\dagger)</th>
<th>HR for mortality by PA in CRF stratified analysis(^\ddagger)</th>
<th>HR for mortality by CRF in PA stratified analysis(^\ddagger)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myers 2004 [10]</td>
<td>842; 0</td>
<td>59 (11)</td>
<td>PA Questionnaire (lifetime adulthood EE)</td>
<td>CRF Max treadmill test</td>
<td>Unfit Active</td>
<td>Active Unfit</td>
<td>Active Unfit</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Age, CVD, smoking, BP, CAD, diabetes, obesity, hypercholesterolemia</td>
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<td></td>
<td></td>
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<td></td>
<td>CRF Very low: 1.0 Low: 0.59* (0.52-0.68) Moderate: 0.46* (0.39-0.55) High: 0.28* (0.23-0.34)</td>
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<td>PA Sedentary: 1.0 Low: 0.63 (0.36-1.10) Moderate: 0.42* (0.23-0.78) High: 0.38* (0.19-0.73)</td>
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<tr>
<td>Celis-Morale 2016 [13]</td>
<td>31,414; 36,288</td>
<td>57 (8.1)</td>
<td>PA Questionnaire (last 7-days recall)</td>
<td>CRF Submax cycle ergometer test</td>
<td>Low CRF PA: 1.13* (1.02-1.26)</td>
<td>Moderate CRF PA: 1.11* (1.01-1.22)</td>
<td>High CRF PA: 1.03 (0.91-1.16)</td>
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<tr>
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<td>Age, sex, ethnicity, SES, BMI, smoking, SED, alcohol, depression, stroke, angina, heart attack, BP, cancer, diabetes</td>
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<td>CRF: 1.11* (1.03-1.20)</td>
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<tr>
<td>Edwards &amp; Loprinz 2016 [11]</td>
<td>1131; 1164</td>
<td>[20-85]</td>
<td>PA Accelerometer</td>
<td>Income-to-poverty ratio, medication, race, sex, SED</td>
<td>CRF Unfit: 1.0 Fit: 0.20* (0.09-0.43)</td>
<td>PA Inactive: 1.0 Active: 0.35* (0.15-0.82)</td>
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<td></td>
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<td></td>
<td>CRF Algorithm to estimate CRF</td>
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</tbody>
</table>

\(^\dagger\) Adjusted for covariates. \(^\ddagger\) Adjusted for covariates and CRF for PA or PA for CRF. HR, hazard ratio; CRF, cardiorespiratory fitness; PA, physical activity; EE, energy expenditure; SED, time spent sedentary; CVD, cardiovascular disease; CAD, coronary artery disease; SES, socioeconomic status; BMI, body mass index; BP, blood pressure. *\(p <0.05\)
Table 6. Studies that reported that PA is no longer associated with all-cause mortality after controlling for CRF

<table>
<thead>
<tr>
<th>Study</th>
<th>Men; Women (n)</th>
<th>Age [range]</th>
<th>Method of measurement</th>
<th>Covariates</th>
<th>HR for mortality by PA and by CRF †</th>
<th>HR for mortality by PA in CRF stratified analysis ‡</th>
<th>HR for mortality by CRF in PA stratified analysis ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blair, 2001 [14]</td>
<td>26,764; 8755</td>
<td>[20-90]</td>
<td>PA Questionnaire (PA during the last 3 months)</td>
<td>BMI, smoking, alcohol, parental CVD, age, sex</td>
<td>CRF:</td>
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<td></td>
<td></td>
<td>Unfit: 1.0</td>
<td>Fit: 0.50*</td>
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<td></td>
<td>High-Fit: 0.30*</td>
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<td></td>
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<td>PA: not significantly associated</td>
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<td></td>
<td></td>
<td>Unfit: 1.0</td>
<td>Inactive: 1.0 (0.54-0.72)</td>
<td>Inactive: 1.0 (0.53-0.71)</td>
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<td></td>
<td>Fit: 0.62* (0.54-0.72)</td>
<td>Active: 0.90 (0.56-1.45)</td>
<td>Active: 0.61* (0.53-0.71)</td>
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<td>PA Inactive: 1.0</td>
<td>Fit: 0.96 (0.85-1.09)</td>
<td>Fit: 0.64 (0.39-1.04)</td>
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<td>Active: 1.05 (0.92-1.19)</td>
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<td></td>
<td></td>
<td></td>
<td>CRF Max treadmill test</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>WOMEN CRF:</td>
<td>WOMEN Unfit: 1.0</td>
<td>WOMEN Inactive Unfit: 1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unfit: 1.0</td>
<td>Inactive: 1.0 (0.29-2.44)</td>
<td>Inactive: 1.0 (0.45-0.89)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Fit: 0.62* (0.44-0.86)</td>
<td>Active: 0.85 (0.29-2.44)</td>
<td>Active: 0.63* (0.45-0.89)</td>
</tr>
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<td></td>
<td>PA Inactive: 1.0</td>
<td>Fit: 0.92 (0.65-1.29)</td>
<td>Fit: 0.49 (0.16-1.46)</td>
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<td></td>
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<td></td>
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<td></td>
<td>Active: 0.95 (0.68-1.33)</td>
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</tbody>
</table>

† Adjusted for covariates. ‡ Adjusted for covariates and CRF for PA or PA for CRF. HR, hazard ratio; CRF, cardiorespiratory fitness; PA, physical activity; CVD, cardiovascular disease; BMI, body mass index; BP, blood pressure. *p <0.05
2.6.2 Possible explanations for conflicting findings

2.6.2.1 Differences in the composition of the various cohorts

Inspection of the observations reported in Tables 5 and 6 reveals that discrepancy regarding the independent effect of PA on mortality is not likely explained by age, sex, or BMI, as the composition of the cohorts that report an independent association between PA and mortality are not materially different from those that report no association after controlling for CRF. With the exception of the study by Edwards and Loprinzi [183], all studies controlled for age, sex, smoking, and a measure of obesity, either by stratification, including the variable in multivariate analysis, or examining the associations separately in men and women. Notably, Edwards and Loprinsi did not control for age, BMI, and smoking status in multivariate analysis since these parameters were used in the algorithm that was derived to estimate CRF [183].

2.6.2.2 Measures of PA and CRF

It is possible that discrepant findings regarding the independent effect of PA on mortality are a reflection of the measurement method used to assess PA in prior studies. While CRF was measured objectively using an exercise test, the majority of the evidence examining the relationship between PA and mortality has been based on subjective, self-report questionnaires. Despite their extensive use in the literature for nearly 50 years, PA questionnaires display limited reliability and validity and fail to capture all components of PA. For example, questionnaires are often limited in their ability to account for energy expended through low-intensity activities of daily living such as household chores, walking, and standing. In addition, subjects may be influenced by social desirability bias and recall bias. Reliability estimates for self-report PA questionnaires generally show acceptable to good reliability. However, for the majority of PA questionnaires, validity correlation coefficients are generally poor to moderate. In a systematic review of the reliability and validity characteristics of 96 existing questionnaires, the
median validity correlations between objective measures of PA (i.e. doubly labelled water, pedometers or accelerometers) and self-reported PA ranged from 0.30 – 0.46 [70, 72, 184, 185]. Therefore, in studies that simultaneously examined objectively measured CRF and self-reported PA, it is possible that misclassification of PA rates may have underestimated the effect of PA on mortality, and hindered the ability to accurately contrast the roles of CRF and PA in the prevention of premature mortality. Additional study using objective measures of PA are required to further evaluate the relationship between PA, CRF, and mortality risk.

2.6.2.3 Limitation in the analytical approach used

Discrepant findings regarding whether PA predicts mortality independent of CRF may be partially explained by the analytical approach used in prior studies. Several studies used stratified analysis to evaluate the PA-mortality association within CRF strata [10, 12, 13]. The objective of stratification is to control for any confounding effects of CRF by producing strata within which CRF does not vary substantially. However, the characteristic attribute of a confounder is that it is associated with the primary variable of interest (PA). Thus, it is possible that CRF values varied within strata in relation to PA status. In other words, CRF values in the active groups could be substantially higher compared to CRF values in the inactive groups. Were this true, the attenuation of mortality risk in the physically active groups would be explained by CRF (i.e. residual confounding). Failure to account for differences in CRF across PA groups may have biased interpretations of the direct effect of PA on mortality risk.

2.7 Summary

The interplay between PA, CRF, and health risk is complex and not fully understood. A few recent studies have attempted to disentangle these complexities, however, studies report
discrepant findings. Whether PA and CRF predict mortality risk independent of each other remains unclear and warrants further investigation.

We proposed that discrepant findings in prior studies may be explain by 1) differences in our ability to accurately measure PA and CRF, since PA was mainly self-reported and CRF was predominantly based on objective measures, and/or 2) a limitation in the analytical approach used to examine the interaction of PA and CRF.

We appreciate the limitation of self-report PA in contrast to objective measurements, however we are unable to address this limitation. Important to note, although self-reported PA is not an ideal criterion, the ability to assess detailed activity information in a large cohort makes self-reported PA the most suitable PA assessment tool for the purposes of epidemiological research. It is well established that PA, albeit based on self-report, is a strong predictor of numerous health outcomes and the addition of PA to a traditional risk assessment model significantly improves reclassification of risk for all-cause mortality [6]. It is encouraging that a single PA query has the potential to complement traditional risk factors in risk assessment and could be employed in minutes in a healthcare setting. Although we are unable to address the limitation of self-reported PA in the current analysis, whether self-reported PA predicts mortality beyond measured CRF is of direct clinical importance.

We will aim to address the second limitation that was noted above. In stratified analysis, it is possible that CRF in the active groups was comparatively higher than CRF in the inactive groups. In response, the aim of the current study is to evaluate the relative contributions of PA and CRF to mortality risk after taking careful steps to control for confounding by matching inactive and active groups on CRF. This would fix CRF across PA groups in order to rigorously examine the PA-mortality association independent of CRF. Defining the association between PA and CRF with mortality after carefully controlling for traditional risk factors and PA for CRF or CRF for PA would help improve our understanding of the biologic nature of the relationship between these risk factors and adverse health outcomes.
Chapter 3. Cardiorespiratory fitness versus physical activity as predictors of all-cause mortality in men
3.1 Abstract

BACKGROUND: Physical activity (PA) is a behaviour, defined as any bodily movement that increases energy expenditure above resting levels, while cardiorespiratory fitness (CRF) is a physiologic trait that reflects the ability of the respiratory, circulatory, and musculoskeletal systems to deliver and utilize oxygen. Although both CRF and PA are inversely associated with mortality risk, whether they are associated independent of each other is unclear.

METHODS: CRF was assessed by a maximal exercise test and PA was measured by self-report in 8171 male veterans. The predictive power of CRF and PA, along with clinical variables, was assessed for all-cause mortality during a mean (±SD) follow-up period of 8.7 (4.4) years during which there were 1349 deaths.

RESULTS: CRF was associated with mortality after adjusting for traditional risk factors commonly measured in clinical practice, and remained a strong predictor of mortality after further adjusting for PA (hazard ratio [HR], 0.85; 95% confidence interval [CI], 0.83 –0.87). PA was a significant predictor of mortality after controlling for clinical variables, however the association was eliminated after further adjusting for CRF (HR, 0.98; 95% CI, 0.88 – 1.10). In CRF stratified analysis, being active (≥150 min/week) was not associated with mortality within the unfit or fit categories (p>0.4). However, in PA stratified analysis, subjects categorized as fit (≥7 METS) had a lower risk of mortality regardless of PA status (p<0.001).

CONCLUSION: In adult men, PA was associated with mortality above and beyond established risk factors, but not CRF. Conversely, CRF remained a strong predictor of mortality, independent of PA status and established risk factors.
3.2 Introduction

The association between physical activity (PA) and cardiorespiratory fitness (CRF) with morbidity and mortality is established, with authors reporting a negative, dose-response gradient for both CRF and PA [1, 4]. Although increases in PA are associated with concomitant increases in CRF [1, 8, 149], the association is modest with explained variance ranging from 1 to 36% [9, 10]. These findings suggest that PA and CRF may affect mortality through distinctly different mechanisms.

The findings of previous studies that have simultaneously examined the independent associations between CRF, PA, and all-cause mortality [10-14] are inconsistent. While there is consensus that CRF remains a predictor of mortality after controlling for PA [10-14], whether PA remains a strong predictor of mortality beyond CRF remains uncertain. Three studies suggest that PA remains a significant predictor of mortality after controlling for CRF [10, 11, 13], whereas two studies have reported that PA is not associated with mortality after controlling for CRF [12, 14].

Discrepant findings regarding the independent effect of PA on mortality may be partially explained by a failure to account for potential differences in CRF between the inactive and active groups. Consequently, it is possible that CRF values in the active groups were substantially higher than those in the inactive groups. Were this true, it would lead to an inaccurate estimate of the independent effect of PA on mortality. In categorical analyses, this limitation can only be overcome through carefully matching inactive and active groups on CRF.

In this study, we examined the independent and combined effects of CRF and PA in a large sample of men from the Veterans Exercise Testing Study (VETS). To overcome prior limitations, we matched inactive and active groups on CRF. We hypothesized that the reduction in risk attributed to being active would be diminished after carefully controlling for CRF, whereas CRF would remain a strong predictor of mortality beyond currently measured risk factors and PA.
3.3 Methods

3.3.1 Study population

The VETS is an ongoing prospective longitudinal study established in 1983 to explore the role of clinical and lifestyle factors in the development of adverse health outcomes. The VETS study population includes male and female veteran subjects referred for exercise testing for clinical reasons by their respective healthcare providers. The current analysis was restricted to men for which we had a measurement of CRF and PA (n= 8171) who attended the Veterans Affairs Medical Centre in Palo Alto, CA, or Washington, DC. All participants gave written consent before a symptom-limited exercise tolerance test and the study was approved by the Internal Review Board at each institution. Participants with less than one month of follow-up were excluded. All demographic, clinical, and medication information was obtained from participants' computerized medical records at the time of the exercise test, including information regarding hypertension, hypercholesterolemia, diabetes and smoking status. Cardiovascular disease (CVD) was defined as those individuals with a history of myocardial infarction, coronary artery disease, heart failure, or peripheral vascular disease.

3.3.2 Exercise testing

Exercise capacity was assessed using a standard Bruce protocol (Washington, DC) and an individualized ramp protocol (Palo Alto, CA) [139]. Peak exercise time (minutes) was used to estimate exercise capacity (METs), employing a commonly used equation for the Bruce protocol and utilizing the American College of Sports Medicine equation for the individualized ramp protocol [186, 187]. The majority of subjects (80%) were assessed using the individualized ramp protocol in Palo Alto, CA. To explore the interaction of PA and CRF, participants were dichotomized as Fit or Unfit based on peak METS achieved: Unfit was defined as < 7 METS while Fit was defined as ≥ 7 METS. Although there is no consensus on a CRF level that provides clinically relevant health benefits, evaluation of the optimal MET level threshold for risk
of mortality in male veterans using receiver operating characteristic curve (ROC curve) analysis revealed an optimal threshold for increased risk of mortality of 7 METS [97]. Patients with a CRF level of approximately 7 METS or greater have substantially lower rates of all-cause mortality compared to those who achieve < 7 METS [97, 128].

3.3.3 Physical activity

Participants’ involvement in regular physical activity at a moderate or higher intensity was assessed using a simple, dichotomous questionnaire administered by a healthcare professional. Prior to the exercise test, participants were asked, "At least three times a week, do you engage in some form of regular activity such as brisk walking, jogging, bicycling, or swimming, long enough to work up a sweat, get your heart thumping, or become short of breath?". This standard has been equated to meeting the minimal criteria that have been recommended for physical activity, 150 minutes of moderate or higher intensity PA per week [188]. Based on their response, participants were categorized as active (meeting 150 min/wk) or inactive (not meeting 150 min/wk). This simple question that identifies those meeting PA guidelines has been associated with all-cause mortality after controlling for common risk factors in prior literature, and has demonstrated to significantly improve reclassification of risk for mortality when added to a traditional risk assessment algorithm [6].

3.3.4 Follow-up

The primary outcome was all-cause mortality. The Beneficiary Identification and Records Locator System (BIRLS) Death File and Social Security Death Indices (SSDI) were used to collect information about the veterans' vital status. Name and social security number were used to match all patients to their record. BIRLS death reporting is relatively complete, and the addition of SSDI death reporting further improves researchers’ ability to establish vital status [189].
3.3.5 Statistical analysis

Cox proportional hazards models were constructed to depict hazard ratios (HRs) and 95% confidence intervals (CIs) for CRF (as a continuous variable and unfit (<7 METs) vs fit (>7 METs)) and PA (active (≥150 min/wk) vs inactive (<150 min/wk)). The reference groups comprised individuals who were categorized as unfit or inactive. In all fully adjusted models the covariates were: age (years), BMI (kg/m²), smoking status, history of stroke, use of medications, and presence or absence of hypertension, diabetes, hypercholesterolemia, family history of risk factors, and CVD (model 1). To examine whether CRF and PA predicted mortality independent of each other, we further controlled PA for CRF, and CRF for PA (model 2).

To assess the interaction of PA, CRF, and mortality, subjects were cross-classified according to CRF and PA. Subjects were first dichotomized into fit and unfit groups, defined using a CRF threshold of 7 METS. Within the fit and unfit groups, active individuals and inactive individuals were matched, one-to-one, on the following parameters (± tolerance range): METS (± 0.5), age (± 2.0), and BMI (± 2.0) using a case-control matching method. This created four combined PA and CRF groups: unfit-inactive, unfit-active, fit-inactive, and fit-active. Cox proportional hazard models were used to estimate the relative risks and 95% confidence intervals for all-cause mortality for these four groups, controlling for clinical variables listed above. All statistical tests were two-sided and p<0.05 was considered statistically significant. Analyses were performed using SPSS (version 24).

There was a significant association between CRF and PA ($\chi^2(1) = 175.99$, p<.001), however the strength of association was weak (phi value= 0.147, p<.001). There were no significant interactions between PA and CRF on all-cause mortality using an interaction term in the Cox regression model. We further examined the association between CRF and mortality after controlling for the possible interaction effects of age by including the interaction term in a multivariate model. When CRF was examined as a continuous variable the interaction term was significant, although the magnitude of the effect was negligible (HR 0.998, 95% CI 0.996-1.0).
When CRF was considered as a dichotomous variable using a CRF threshold of either 5 or 7 METs, no significant interactions were found.

3.4 Results

Baseline characteristics of the entire cohort and for subjects categorized by PA within CRF strata are presented in Table 1. There were 1349 deaths during a mean ± SD follow-up period of 8.7 ± 4.4 years. Subjects ranged in age from 20 to 89 years (mean 58.3 years, SD 11.4). Decedents were older, had a lower BMI, were less fit, less physically active, and had a less favorable risk profile compared to survivors.
Table 1. Descriptive statistics for the entire cohort and for Inactive and Active subjects within CRF strata

<table>
<thead>
<tr>
<th></th>
<th>Entire Cohort</th>
<th>Fit</th>
<th>Inactive</th>
<th>Unfit</th>
<th>Active</th>
<th>Inactive</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>8171</td>
<td>1988</td>
<td>1988</td>
<td>880</td>
<td>880</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.3 ± 11.4</td>
<td>56.0 ± 9.8</td>
<td>55.9 ± 9.8</td>
<td>64.9 ± 10.0</td>
<td>64.9 ± 9.9</td>
<td></td>
</tr>
<tr>
<td>Follow-up (years)</td>
<td>8.7 ± 4.4</td>
<td>9.1 ± 4.2</td>
<td>8.9 ± 4.5*</td>
<td>9.1 ± 4.5</td>
<td>9.3 ± 4.6</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>176.4 ± 8.2</td>
<td>176.4 ± 7.8</td>
<td>176.7 ± 8.0</td>
<td>175.7 ± 7.9</td>
<td>176.1 ± 7.8</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>91.1 ± 18.4</td>
<td>90.2 ± 16.2</td>
<td>90.5 ± 16.4</td>
<td>88.6 ± 16.6</td>
<td>89.2 ± 16.5</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.3 ± 5.8</td>
<td>28.9 ± 4.6</td>
<td>28.9 ± 4.6</td>
<td>28.7 ± 4.8</td>
<td>28.7 ± 4.8</td>
<td></td>
</tr>
<tr>
<td>CRF (METs)</td>
<td>8.5 ± 3.3</td>
<td>9.9 ± 2.1</td>
<td>9.8 ± 2.1</td>
<td>5.0 ± 1.2</td>
<td>4.9 ± 1.2</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>1409 (17.2)</td>
<td>271 (13.6)</td>
<td>357 (18.0)*</td>
<td>171 (19.4)</td>
<td>208 (23.6)†</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>4529 (55.4)</td>
<td>1009 (50.8)</td>
<td>1042 (52.4)</td>
<td>565 (64.2)</td>
<td>553 (62.8)</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>2585 (31.6)</td>
<td>639 (32.1)</td>
<td>666 (33.5)</td>
<td>235 (26.7)</td>
<td>216 (24.5)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>4528 (55.4)</td>
<td>1176 (59.2)</td>
<td>992 (49.9)*</td>
<td>619 (70.3)</td>
<td>626 (71.1)</td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td>4707 (57.6)</td>
<td>1051 (52.9)</td>
<td>1107 (55.7)</td>
<td>569 (64.7)</td>
<td>555 (63.1)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>20 (0.2)</td>
<td>1 (0.1)</td>
<td>4 (0.2)</td>
<td>4 (0.5)</td>
<td>3 (0.3)</td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>1178 (14.4)</td>
<td>240 (12.1)</td>
<td>214 (10.8)</td>
<td>232 (26.4)</td>
<td>229 (26.0)</td>
<td></td>
</tr>
<tr>
<td>Family History</td>
<td>1799 (22.0)</td>
<td>445 (22.4)</td>
<td>490 (24.6)</td>
<td>193 (21.9)</td>
<td>205 (23.3)</td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>1349 (16.5)</td>
<td>191 (9.6)</td>
<td>208 (10.5)</td>
<td>292 (33.2)</td>
<td>310 (35.2)</td>
<td></td>
</tr>
<tr>
<td>PA (active)</td>
<td>3945 (48.3)</td>
<td>1998 (100)</td>
<td>0 (0)*</td>
<td>880 (100)</td>
<td>0 (0)†</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or n (%). Fit-Active subjects were matched (1:1) with Fit-Inactive subjects for BMI, age and CRF. Unfit-Active subjects were matched (1:1) with Unfit-Inactive subjects for BMI, age and CRF. Medications assessed include statins, ACE, beta-blockers, calcium blockers, ACE, and diuretics. CVD defined as individuals with a history of CAD, CHD, CAB, PTCA/PCI, or MI. For continuous variables, a t-test was applied to determine if the combined PA and CRF groups differed. For categorical variables, differences between groups were assessed using a chi-squared test. METS, metabolic equivalents. *Fit-Inactive different than Fit-Active (p<0.05); †Unfit-Inactive different than Unfit-Active (p<0.05).
To examine whether PA and CRF were associated with all-cause mortality independent of clinical risk factors, we determined the relative risk of mortality for CRF (as a continuous variable) and PA (active, $\geq 150$ min/wk) vs inactive (<150 min/wk)) \textit{(Table 2)}. PA and CRF were inversely related with mortality. Each 1-MET increment in CRF was associated with a 15% reduction in mortality risk after adjusting for clinical risk factors ($p<0.001$), while being active was associated with a 17% reduction in risk ($p=0.001$).

To assess the association between PA (inactive vs active) and CRF (unfit vs fit, and as a continuous variable) with mortality independent of each other, PA and CRF were included in the same multivariable model \textit{(Table 2)}. CRF was associated with a 15% reduction in mortality risk after adjusting for clinical variables and PA ($p<0.001$). Conversely, PA did not remain a significant predictor of mortality after controlling for CRF ($p=0.59$).
Table 2. Hazard ratios for mortality risk according to CRF and PA

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>HR</td>
</tr>
<tr>
<td>CRF (continuous)</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>Unfit</td>
<td>2615</td>
<td>1.0</td>
</tr>
<tr>
<td>Fit</td>
<td>5556</td>
<td>0.48</td>
</tr>
<tr>
<td>CRF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unfit</td>
<td>8171</td>
<td>0.85</td>
</tr>
<tr>
<td>Fit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive</td>
<td>4226</td>
<td>1.0</td>
</tr>
<tr>
<td>Active</td>
<td>3945</td>
<td>0.83</td>
</tr>
</tbody>
</table>

**Model 1** adjusted for age, BMI, smoking status, history of stroke, use of medications, and presence or absence of hypertension, diabetes, hypercholesterolemia, CVD, and family history of risk factors.

**Model 2** adjusted for variables in Model 1 and further adjusted CRF (continuous variable) for PA, and PA for CRF.

CRF, cardiorespiratory fitness; PA, physical activity; HR, hazard ratio; CI, confidence interval.
We further examined whether the association between PA and mortality varied by CRF status, analyzing separately those subjects categorized as unfit (<7 METS) and fit (≥7 METS). Within the unfit and fit groups, inactive subjects were matched, 1:1, with active subjects on CRF to ensure that CRF did not differ considerably between PA groups (Table 3 and Figure 1). Within both the unfit (<7 METS) and fit (≥7 METS) categories, being active consistent with consensus guidelines (≥150 min/week) did not reduce the risk of all-cause mortality compared to inactive participants (HRs and [95% CIs] were 0.99 [0.85-1.16] and 0.93 [0.76 – 1.13] for unfit and fit groups, respectively). When the same analysis was performed without carefully matching inactive and active subjects on CRF (Figures 2 and 3), the hazard ratio for risk of all-cause mortality for active subjects within the fit category approached significance (HR 0.85 [95% CI, 0.73-1.02]). Further analysis using a CRF threshold of 5 METS revealed that PA was a significant predictor of mortality within the fit group (HR 0.84 [95% CI, 0.74-0.97]). After ensuring that the CRF values in the inactive and active groups were matched, PA was no longer associated with mortality (HRs and [95% CIs] were 0.93 [0.76-1.13] and 0.90 [0.77-1.05] using a CRF threshold of 7 and 5 METS, respectively).

To determine whether the association between CRF and mortality differed by PA status, we examined the effect of CRF separately in inactive (<150 min/wk) and active groups (≥150 min/week) (Table 4 and Figure 1). Within both the inactive and active categories, being fit was associated with a significant reduction in risk of mortality compared to being unfit (p<0.05). Further, being fit was associated with a similar reduction in risk whether subjects were categorized as inactive or active (48% and 49% reduction, respectively).
<table>
<thead>
<tr>
<th>PA</th>
<th>N</th>
<th>(n)</th>
<th>CRF*</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>INACTIVE</td>
<td>880</td>
<td>310</td>
<td>4.9 ± 1.2</td>
<td>1.0</td>
<td>(referent)</td>
<td></td>
</tr>
<tr>
<td>ACTIVE</td>
<td>880</td>
<td>292</td>
<td>5.0 ± 1.2</td>
<td>0.99</td>
<td>0.85 – 1.16</td>
<td>0.92</td>
</tr>
</tbody>
</table>

**FIT**

<table>
<thead>
<tr>
<th>Deaths</th>
<th>N</th>
<th>(n)</th>
<th>CRF*</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988</td>
<td>208</td>
<td>9.8 ± 2.1</td>
<td>1.0</td>
<td>(referent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1988</td>
<td>191</td>
<td>9.9 ± 2.1</td>
<td>0.93</td>
<td>0.76 – 1.13</td>
<td>0.46</td>
<td></td>
</tr>
</tbody>
</table>

Within Unfit and Fit categories, Inactive and Active subjects were matched (1:1) for CRF, BMI, and age. Adjusted for smoking status, history of stroke, use of medications, and presence or absence of hypertension, diabetes, hypercholesterolemia, family history of risk factors and CVD. *CRF given in METS, presented as mean ± SD. CRF, cardiorespiratory fitness; METS, metabolic equivalents.
Table 4. Hazard ratios for mortality risk across CRF groups in PA stratified analysis

<table>
<thead>
<tr>
<th>CRF</th>
<th>INACTIVE</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>ACTIVE</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deaths</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>(n)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>CRF*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNFIT</td>
<td>880</td>
<td>310</td>
<td>4.9 ± 1.2</td>
<td>1.0</td>
<td>(referent)</td>
<td></td>
<td>880</td>
<td>292</td>
<td>5.0 ± 1.2</td>
<td>1.0</td>
<td>(referent)</td>
<td></td>
</tr>
<tr>
<td>FIT</td>
<td>1988</td>
<td>208</td>
<td>9.8 ± 2.1†</td>
<td>0.52</td>
<td>0.43 – 0.63</td>
<td>&lt;0.001</td>
<td>1988</td>
<td>191</td>
<td>9.9 ± 2.1†</td>
<td>0.51</td>
<td>0.42 – 0.63</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Within Unfit and Fit categories, Inactive and Active subjects were matched (1:1) for CRF, BMI, and age. Adjusted for smoking status, history of stroke, use of medications, and presence or absence of hypertension, diabetes, hypercholesterolemia, family history of risk factors, CVD, age and BMI. *CRF given in METS, presented as mean ± SD. †Mean CRF different than Unfit group (p<0.05). CRF, cardiorespiratory fitness; METS, metabolic equivalents.
Figure 1. Hazard ratios for mortality risk across PA groups within Fit and Unfit strata (Panel A) and across CRF groups within Active and Inactive strata (Panel B).

Panel A adjusted for smoking status, history of stroke, use of medications, and presence or absence of hypertension, diabetes, hypercholesterolemia, family history of risk factors and CVD.

Panel B adjusted for the same variables in Panel A with further adjustment age and BMI. Fit-Active subjects were matched (1:1) with Fit-Inactive subjects for CRF, age, and BMI. Unfit-Active subjects were matched (1:1) with Unfit-Inactive subjects for CRF, age, and BMI.

Group mean CRF value appears within each bar (MET, metabolic equivalents). *p<0.05 compared to referent group.
Figure 2. Hazard ratios for mortality risk for inactive and active subjects unmatched for CRF (Panel A) and matched for CRF (Panel B), examined separately within CRF strata using a CRF threshold of 7 METS.

Panel A and B adjusted for age, BMI, smoking status, history of stroke, use of medications, and presence or absence of hypertension, diabetes, hypercholesterolemia, family history of risk factors, and CVD.

Panel B, subjects categorized as Fit-Active were matched (1:1) with those categorized as Fit-Inactive for BMI, age and CRF, and Unfit-Active subjects were matched (1:1) with Unfit-Inactive subjects for BMI, age and CRF.

Group mean CRF value appears within each bar (MET, metabolic equivalents).
Figure 3. Hazard ratios for mortality risk for inactive and active subjects unmatched for CRF (Panel A) and matched for CRF (Panel B), examined separately within CRF strata using a CRF threshold of 5 METS.

Panels A and B adjusted for age, BMI, smoking status, history of stroke, use of medications, and presence or absence of hypertension, diabetes, hypercholesterolemia, family history of risk factors, and CVD.

Panel B, subjects categorized as Fit-Active were matched (1:1) with those categorized as Fit-Inactive for BMI, age and CRF, and Unfit-Active subjects were matched (1:1) with Unfit-Inactive subjects for BMI, age and CRF.

Group mean CRF value appears within each bar (MET, metabolic equivalents). *p<0.05 compared to inactive group
To account for the possibility that the higher mortality rates within the low CRF category were explained by subclinical disease, we performed the following analyses: (1) exclusion of subjects who died within the initial two years of follow-up, (2) exclusion of subjects with documented CVD, and (3) with both exclusions combined. Consistent with our original analysis, in all three circumstances, CRF remained a strong predictor of mortality after controlling for common risk factors and PA, whereas PA was associated with mortality after controlling for common risk factors but not CRF (Table 5).
Table 5. Adjusted hazard ratios for mortality risk according to CRF and PA with conditional exclusion of subjects

<table>
<thead>
<tr>
<th>Excluding deaths that occurred during the first 2 y of follow-up (n= 7940)</th>
<th>Excluding subjects with documented CVD* (n= 6980)</th>
<th>Excluding subjects who met both conditions (n= 6809)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1</strong></td>
<td><strong>Model 2</strong></td>
<td><strong>Model 1</strong></td>
</tr>
<tr>
<td>CRF</td>
<td>0.86 (0.84-0.88)</td>
<td>0.86 (0.84-0.88)</td>
</tr>
<tr>
<td>PA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INACTIVE</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>ACTIVE</td>
<td>0.86 (0.76-0.96)</td>
<td>1.001 (0.89-1.13)</td>
</tr>
</tbody>
</table>

**Model 1.** Adjusted for age, BMI, smoking status, history of stroke, use of medications, and presence or absence of hypertension, diabetes, hypercholesterolemia, CVD, and family history of risk factors.

**Model 2.** Adjusted all variables in model 1, and further adjusted PA for CRF or CRF for PA. *CVD defined as those with a history of angiographically documented coronary artery disease, myocardial infarction, coronary bypass surgery, coronary angioplasty, and history of a cerebrovascular accident.

Values in parentheses represent 95% Confidence intervals.
In case-control matching, less than 6000 men were included from the total sample of 8171, thus losing information on a considerable proportion of the sample. To address this issue, we used stratified analysis to examine the interaction of PA and CRF in the entire cohort (n=8171) after statistically controlling for CRF. Our findings were not markedly different from our analysis wherein subjects were matched on CRF (Appendix A, Table 1). In addition, to rule out the possibility that the protocol employed to measure CRF influenced the relationship between CRF, PA, and mortality, we examined the relative contributions of CRF and PA to mortality risk separately in subjects who completed the Bruce test and those who completed the ramp exercise test. We observed a similar pattern whether subjects completed the Bruce protocol in Washington, DC, or the ramp protocol in Palo Alto, CA, (Appendix A, Tables 3-4).

3.5 Discussion

The primary finding of this study is that PA was not associated with mortality when PA groups were carefully matched on CRF and established risk factors were considered. Conversely, CRF remained a strong predictor of mortality, independent of PA status and established CV risk factors. Notably, having a CRF of 7 METS or greater was associated with a similar reduction in risk (~50%) whether subjects were categorized as inactive or active. The current findings underscore the prognostic power of CRF, and support the notion that CRF should be measured in clinical practice to further improve risk prediction for adverse health outcomes[4].

Despite decades of investigation exploring the relationship between PA, CRF, and health outcomes[9], consensus regarding the relative contributions of each to mortality risk remains elusive[10-14]. The findings from the current analysis are in accord with observations from the Aerobics Center Longitudinal Study (ACLS). In the ACLS, CRF remained a strong predictor of mortality after adjusting for PA, whereas PA was not significantly associated with
mortality after adjusting for CRF[12, 14]. However, three studies provide evidence that PA and CRF are independent in relation to health outcomes[10, 11, 13].

We postulated that a failure to match inactive and active subjects on CRF biased estimations of the direct effect of PA on mortality. In other words, it was possible that the CRF value in the active groups was higher compared to the CRF within the inactive groups. This limitation is true for studies wherein researchers arbitrarily stratified CRF to evaluate the PA-mortality association within CRF strata. In fact, in our analysis in which subjects were not matched across PA groups we observed an attenuation of mortality risk in the active groups, likely attributed to a higher mean CRF compared to the inactive groups. Our findings provide strong evidence that CRF mediates the association between PA and mortality.

To minimize the possibility that the higher rates of mortality observed in the low CRF categories were a result of underlying disease, we excluded subjects with less than 2 years of follow-up and those with a history of CVD. In all circumstances, the association of CRF with mortality remained significant after further adjustment for PA, whereas the association of PA with mortality was no longer significant after controlling for CRF. To note, CRF was associated with a similar risk reduction compared to findings of the entire cohort. This analysis suggests reverse causality is unlikely and supports the validity of a direct association between CRF and all-cause mortality.

Although measurements of CRF using a maximal exercise test may be impractical in many clinical settings, it is noteworthy that non–exercise-based equations are readily available to conveniently estimate CRF[4, 133, 135, 136]. Non–exercise-based equations use variables commonly assessed in clinical settings and provide a rapid and inexpensive way of estimating CRF. It has also been shown that estimated CRF values predict long-term mortality, and that the risk reduction associated with estimated CRF is comparable the risk reduction associated with measured CRF[4].
Our findings, albeit based on self-reported PA, confirm a large body of evidence suggesting that PA explains mortality risk above and beyond traditional risk factors[1]. Clearly, PA captures information about mortality risk that is not captured by common risk factors. Indeed, meeting consensus PA guidelines (our ‘active’ group) was associated with a 17% reduction in mortality risk after adjusting for common risk factors. That PA can be assessed using a simple question suggests its implementation in clinical practice would not be difficult. The finding that PA did not remain a significant predictor of mortality after controlling for CRF may simply speak to the mechanisms by which PA exerts its effect on mortality since PA is the primary determinant of changes in CRF[58, 190, 191].

Our study has several limitations. Our findings are restricted to men, although findings in women are consistent with the current observations[12, 14], and we did not have information on subjects’ cause of death. In addition, the superiority of CRF in our analysis may be partially explained by our methodology used to determine PA levels. The simple, binary question employed to determine PA may be restricted by the inability to capture all dimensions of PA. In addition, the validity of self-reported measures of PA is questioned because they are not strongly associated with objective measures of PA[70]. This notion is underscored by the findings of numerous prospective studies reporting that objectively measured PA is inversely associated with several cardiometabolic risk factors independent of measured CRF[170-173]. Whether objective measures of PA would provide observations that suggest that PA predicts mortality independent of CRF awaits prospective evidence.

The principle strengths of the present study are the large sample size and the prospective assessment of mortality from all cause over an extended follow-up period. CRF was measured objectively using established methods that have been widely used in epidemiological studies. Lastly, we addressed a potential limitation in prior studies by carefully matching inactive and active subjects on CRF, separately within CRF strata. We reinforced our primary finding by including both CRF and PA in the same model which generated a more precise estimate of the
effect of PA or CRF, likely because reporting results separately by strata results in a smaller sample size in each individual stratum.

In summary, PA was not associated with mortality when PA groups were carefully matched on CRF and established risk factors were considered, Conversely, CRF did provide meaningful risk prediction information beyond common risk factors and PA. These findings reinforce the recommendation that CRF should be a routine measure in clinical settings.
Chapter 4. General discussion

The notion that PA and CRF act through partly distinct mechanisms is consistent with biological plausibility. However, whether PA and CRF predict morality risk independent of each other remains unclear. We identified a possible limitation in prior studies that may help explain discrepancies in prior literature. In response, a novel data analysis approach was used, in which subjects were matched on CRF across PA groups in order to isolate the independent contributions of PA and CRF to mortality risk. To summarize our main findings, meeting guideline PA was associated with a 17% reduction in risk compared to not meeting guideline PA after considering clinical characteristics and common risk factors. However, when PA groups were matched on CRF, PA was not associated with mortality risk. Conversely, CRF remained a potent predictor of mortality after adjusting for traditional risk factors and PA.

CRF is unique from traditional risk factors in that it captures information regarding one’s overall or general cardiovascular health status. This is reflected in the finding that CRF remains associated with mortality after controlling for common risk factors such as age, smoking, blood pressure, insulin sensitivity, triglycerides, obesity, and medication use. Of particular interest is the extent to which CRF predicts mortality risk even after adjusting for established risk factors. For example, in our analysis, the inclusion of traditional risk factors in multivariate analysis had minimal effect on the strength of the relationship between CRF and mortality (HR reduced from 0.84 [0.82-0.86] in age-adjusted analysis to 0.85 [0.83-0.87] after further controlling for BMI, smoking status, history of stroke, use of medications, and presence or absence of hypertension, diabetes, hypercholesterolemia, CVD, and family history of risk factors). In addition, adjusting for PA status had a negligible effect on the magnitude of the association between CRF and mortality. Our findings highlight the prognostic power of CRF, and support calls for routine assessment of CRF in clinical setting in order to optimize risk prediction.

Despite evidence of the strong, independent association of CRF with mortality, the importance of CRF is often overlooked in the conversation of mortality risk prediction in clinical
setting [4]. Our study parallels a large body of evidence that has shown that even a CRF level of 5 METs is associated with a lower risk of mortality compared to individuals who achieved <5 METs. This CRF level is achievable by most people by engaging in regular moderate-intensity PA, such as daily brisk walks. Therefore, one does not need to be highly fit to realize the health benefits of CRF.

The application of CRF would be facilitated with the development of standardized cutoffs for CRF that are associated with poor health outcomes. It is widely accepted that the CRF-mortality association is curvilinear in nature, with the largest reduction of risk occurring between the lowest and second lowest CRF categories. Based on these observation, several studies have suggested that a threshold for CRF exists at ~ 5 or 6 METs, however general consensus regarding a clinical definition of CRF has not been reached. In response, an independent group was formed to establish the Fitness Registry and the Importance of Exercise National Database (referred to as, “FRIEND”) with the aim of developing criterion-based CRF reference values in that could be used to interpret measured CRF in clinical setting [129]. It is encouraging that this database could provide CRF references to help clinicians identify and target unfit individuals who might benefit the most from PA counseling.

To note, our findings do not overlook the importance of regular PA. That PA does not predict risk beyond CRF in the current study may simple speak to the mechanisms by which PA affects mortality risk. It is well established that PA is the major determinant of changes in CRF. Therefore, if maintaining or improving CRF is the clinical goal, routine PA counseling should be a critical component of the therapeutic plan [192]. Furthermore, categorization of PA using our simple PA assessment tool has demonstrated to be a potent predictor of mortality independent of common risk factors, and it reclassifies risk when added to a traditional risk assessment model in prior studies [6]. Clearly, self-reported PA provides information regarding patient risk that is largely independent of the presence of other risk factors, and it appears that a simple PA query would demonstrate to be a useful tool in clinical practice that complements common risk
factors when measures of CRF are not available. It is noteworthy that the implementation of a simple yes/no query in clinical practice would not be difficult.

Findings from the National Health Interview Survey provide evidence that the percentage of American adults who currently meet the recommended amount of PA is 49% [193], and there are similar findings from self-reported data from the Canadian Community Health Survey in which 53.9% of people were at least moderately active [194]. These reports align with findings from the current analysis, in which approximately 48% of this cohort of US, male Veterans reported that they engaged in mod-vig activity at least 3 times per week. If the majority of Americans and Canadians are to realize the benefits of an active lifestyle this would require consideration of a multitude of variables, including patients’ motivational readiness, patients’ social support networks, an appreciation for the role that healthcare professionals play in PA counseling, various strategies for behavioural counselling, and the impact that environmental influences have. An environment that aims to reduce the barriers to involvement in regular PA likely requires collaboration between clinicians, public health agencies, and behavioral scientists and may require serious policy intervention [7]. We await a model that has the potential to be implemented in primary care and in the community to help individuals sustain PA behaviour long-term.

Several limitations were mentioned in our manuscript. Investigation of the independent contributions of CRF and PA to mortality risk requires an appreciation for the degree of measurement error associated with PA and CRF assessment. The superiority of CRF in the current analysis may simply reflect differences in our ability to accurately measure CRF and PA since CRF was measured objectively and PA was self-reported. Despite being a cost-effective and feasible approach, self-reported PA is subject to recall and social desirability bias [70]. Misclassification of PA rates may underestimate the effect of PA on mortality, and hinder the ability to accurately determine the independent role of PA in the prevention of premature mortality. Furthermore, our binary PA assessment tool may be restricted in its ability to capture
sporadic and low-intensity activities. Although low-intensity PA is likely insufficient to improve CRF for a substantial portion of the population, there is evidence that individuals who engage in PA that does not meet guideline PA have reduced risk of mortality compared to their sedentary peers [61]. Innovations in technology have led to the development of objective PA assessment tools, such as accelerometers, pedometers and HR monitors, that have transformed the study of PA. Examination of the relative contributions of PA and CRF to mortality risk using objectively measured PA and CRF warrants future investigation.

There are additional limitations that may limit interpretations from our data. CRF was based on one assessment and changes in participants’ CRF status over time were not available. It is possible that examination of changes in CRF, changes in PA, and mortality risk may help distinguish whether the observed reduction in risk associated with CRF is mainly explained by intrinsic (i.e. untrained/baseline CRF) or acquired CRF (i.e. one’s CRF obtained through regular PA). In addition, we did not have information on patients’ specific cause of death. Although the assessment of risk factors for all-cause mortality provides meaningful information in the context of the clinical environment, if only death from CVD or non-communicable diseases were considered it is likely that the magnitude of the association between CRF and PA with mortality would be appreciably higher. Lastly, information on patients’ income, social status, dietary habits, race, the severity of disease (i.e. hypertensive stage 1 versus stage 2), and the duration of therapy (i.e. onset of medication use) were not available.

Several strengths of our manuscript were highlighted. To discount the possibility that subclinical disease at baseline confounded our results by adversely affecting CRF or increasing risk of mortality (reverse causality), our manuscript included analyses that excluded subjects with documented CVD and those with less than 2 years of follow-up. We observed a similar trend and magnitude of risk reduction between these analyses compared to findings of the entire cohort. Therefore, although a substantial number of patients presented with risk factors
and/or CVD, the observations support the notion that our primary findings were unlikely to be biased by underlying disease.

In addition, while the homogeneity of the Veterans Health Administration patient population limits generalizability of our findings to women and other populations, it enabled a unique opportunity to analyze the relations of CRF, PA, and mortality while minimizing disparities in medical care due to patients’ financial status [195]; not surprisingly, the quality of medical care has been documented as an important risk factor for mortality [196]. Finally, the Veterans Health Administration’s electronic health records system permitted detailed recording of patients’ prior medical history, personal attributes, medication use, and comorbidities, allowing evaluation of these variables as possible confounders in our analysis.

As deaths due to chronic diseases such as CVD, cancer, chronic respiratory disease, and diabetes continue to increase worldwide [19], it is essential that clinicians have accurate tools to classify health risk. Precise identification of patients at the highest risk of disease and early mortality will allow targeted advice and treatment delivery. The research demonstrating the strong, inverse relationship between CRF with health and longevity is overwhelming, yet CRF is often overlooked in the conversation of risk prediction. With such a huge public health problem on the horizon it is encouraging that modifiable factors such as CRF are significant determinants of health. Decades of evidence point to the conclusion that CRF should be a routine measurement in the healthcare setting to improve risk prediction for CVD and all-cause mortality, and findings of the current project highlight the importance of CRF as a marker of risk for premature mortality. In order to translate this knowledge into clinical practice increased attention should be placed on strategies to help patients maintain or improve CRF and PA, and on finding practical and inexpensive ways of implementing routine evaluation of CRF and PA counselling in clinical practice. Given the influential nature of the patient-physician relationship, inclusion of CRF assessment and PA counseling in the healthcare setting may have profound effects on the prevention of chronic disease.
References


Appendix A: Supplemental tables

Table 1. Hazard ratios for mortality risk across PA groups in CRF stratified analysis (n=8171)

<table>
<thead>
<tr>
<th></th>
<th>CRF Unfit</th>
<th></th>
<th></th>
<th>CRF Fit</th>
<th></th>
<th></th>
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<tr>
<td></td>
<td>HR</td>
<td>(95% CIs)</td>
<td>p-value</td>
<td>HR</td>
<td>(95% CIs)</td>
<td>p-value</td>
</tr>
<tr>
<td>PA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive</td>
<td>1.0</td>
<td>(0.91-1.20)</td>
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<td>1.0</td>
<td>(0.76-1.09)</td>
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<td>Active</td>
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<td></td>
<td></td>
<td>0.91</td>
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<td></td>
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</tbody>
</table>

Adjusted for age, BMI, smoking status, history of stroke, use of medications, and presence or absence of hypertension, diabetes, hypercholesterolemia, CVD, family history of risk factors and CRF.

HR, hazard ratio; CI, confidence interval; PA, physical activity
Table 2. Age-specific mortality rates and cumulative incidence in 6489 men who attend the Medical Centre in Palo Alto, CA

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>No. of Deaths</th>
<th>n</th>
<th>Proportion (of total cohort)</th>
<th>Cumulative incidence per 1000 persons (%)</th>
<th>Time under observation (yr)</th>
<th>Mortality rate per 1000 person-years</th>
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</thead>
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<tr>
<td>&lt;50</td>
<td>132</td>
<td>1407</td>
<td>17.2</td>
<td>93.82</td>
<td>15870.94</td>
<td>8.32</td>
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<tr>
<td>50-60</td>
<td>198</td>
<td>2044</td>
<td>25.0</td>
<td>96.87</td>
<td>19649.68</td>
<td>10.08</td>
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<tr>
<td>60-70</td>
<td>435</td>
<td>1798</td>
<td>22.0</td>
<td>241.94</td>
<td>17339.29</td>
<td>25.09</td>
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<tr>
<td>&gt;70</td>
<td>536</td>
<td>1240</td>
<td>15.2</td>
<td>432.26</td>
<td>10581.55</td>
<td>50.65</td>
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<tr>
<td>Total</td>
<td>1301</td>
<td>6489</td>
<td>79.4</td>
<td>200.49</td>
<td>63441.46</td>
<td>20.51</td>
</tr>
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</table>

Table 3. Age-specific mortality rates and cumulative incidence in 1682 men who attend the Medical Centre in Washington, DC

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>No. of Deaths</th>
<th>n</th>
<th>Proportion (of total cohort)</th>
<th>Cumulative incidence per 1000 persons (%)</th>
<th>Time under observation (yr)</th>
<th>Mortality rate per 1000 person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>5</td>
<td>416</td>
<td>5.1</td>
<td>12.02</td>
<td>1946.43</td>
<td>2.57</td>
</tr>
<tr>
<td>50-60</td>
<td>18</td>
<td>571</td>
<td>7.0</td>
<td>31.52</td>
<td>2769.51</td>
<td>6.50</td>
</tr>
<tr>
<td>60-70</td>
<td>18</td>
<td>552</td>
<td>6.8</td>
<td>32.61</td>
<td>2574.25</td>
<td>6.99</td>
</tr>
<tr>
<td>&gt;70</td>
<td>7</td>
<td>143</td>
<td>1.8</td>
<td>48.95</td>
<td>678.21</td>
<td>10.32</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>1682</td>
<td>20.6</td>
<td>28.54</td>
<td>7968.4</td>
<td>6.02</td>
</tr>
</tbody>
</table>
Table 4. Hazard ratio for risk of mortality across PA and CRF, using data from Washington, DC (n= 1682, events= 48)

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th></th>
<th></th>
<th>Model 2</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CIs</td>
<td>p-value</td>
<td>HR</td>
<td>95% CIs</td>
<td>p-value</td>
</tr>
<tr>
<td>PA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive</td>
<td>1.0</td>
<td></td>
<td></td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>0.45</td>
<td>(0.21-0.97)</td>
<td>0.04</td>
<td>0.94</td>
<td>(0.41-2.15)</td>
<td>0.88</td>
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<tr>
<td>CRF</td>
<td>0.70</td>
<td>(0.61-0.80)</td>
<td>&lt;0.001</td>
<td>0.70</td>
<td>(0.61-0.81)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Model 1. Adjusted for age, BMI, smoking status, history of stroke, use of medications, and presence or absence of hypertension, diabetes, hypercholesterolemia, CVD, and family history of risk factors

Model 2. Adjusted for same risk factors in model 1 and further adjusted CRF for PA or PA for CRF

All subjects underwent exercise testing using the Bruce protocol. HR, hazard ratio; CI, confidence interval; PA, physical activity

Table 5. Hazard ratio for risk of mortality across PA and CRF, using data from Palo Alto, CA (n= 6489, events= 1301)

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th></th>
<th></th>
<th>Model 2</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CIs</td>
<td>p-value</td>
<td>HR</td>
<td>95% CIs</td>
<td>p-value</td>
</tr>
<tr>
<td>PA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive</td>
<td>1.0</td>
<td></td>
<td></td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>0.83</td>
<td>(0.75-0.93)</td>
<td>0.001</td>
<td>0.98</td>
<td>(0.88-1.10)</td>
<td>0.71</td>
</tr>
<tr>
<td>CRF</td>
<td>0.85</td>
<td>(0.83-0.87)</td>
<td>&lt;0.001</td>
<td>0.85</td>
<td>(0.83-0.87)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Model 1. Adjusted for age, BMI, smoking status, history of stroke, use of medications, and presence or absence of hypertension, diabetes, hypercholesterolemia, CVD, and family history of risk factors

Model 2. Adjusted for same risk factors in model 1 and further adjusted CRF for PA or PA for CRF

All subjects underwent exercise testing using the individualized ramp protocol. HR, hazard ratio; CI, confidence interval; PA, physical activity
Appendix B. Supplemental figures

Figure 1. Kaplan-Meier cumulative survival curves for unfit (<7 METs, dark survival curve) and fit (>7 METs, light survival curve) subjects

Figure 2. Kaplan-Meier cumulative survival curves for inactive (dark survival curve) and active (light survival curve) subjects
Appendix C. The Veterans Affairs Palo Alto Healthcare Centre consent form for the Veterans Exercise Testing Study.

What is this research about?

We are studying the role that short-term exercise (such as an exercise test) and regular exercise (such as regular physical activities) plays in the development of heart disease. We hope to learn if the amount of physical activities someone takes part in or how their heart functions during exercise can be used to determine whether they have or will develop heart disease in the future.

You were selected as a possible candidate for this study because your doctor has recommended that you have this test for a clinical reason. Although this test is being done for a clinical reason, the information obtained will also be used for research purposes.

What is expected of me? (Procedures)

If you decide to participate, you may be asked to do one or more of the following:

☐ Complete questionnaires assessing your physical activity, other health habits, and your capacity to perform daily activities

  The questions we will ask you pertain to your general health, including things such as how you are feeling, your ability to perform daily activities, your diet, and your ability to sleep. This will take about 15 minutes and involves no risk.

☐ Undergo an exercise test on a treadmill or bicycle

  The exercise test requires that you walk on a motor-driven treadmill or pedal a stationary bicycle for about 10 minutes. The difficulty (or resistance) will be increased during the test until you become tired (fatigued), experience shortness of breath or experience chest pain. During the test, you may be asked to breathe through a mask that will measure the amount of oxygen you exhale. You will be able to communicate with the doctor performing the test while wearing the mask. Your heart rate, electrocardiogram (a measure of your heart’s electrical activity), blood pressure, and symptoms will be monitored throughout the test.

  You can ask that the test be stopped at any time during the procedure, and we will stop the test if we think it is best for your health that it be stopped.

  Exercise testing is a routine and safe procedure. Although rare, serious complications such as a heart attack or death can occur (approximately 1 in 10,000 tests).

☐ Use the results from your exercise test
Your doctor has recommended that you have an exercise test as part of your clinical care. For this part of the study, we will use the results from the test in our research to find out more about how the test results are related to your future health. Your doctor or a technician will explain the exercise test and the risks of the test to you.

☐ Undergo an exercise test on a treadmill or bicycle with electrodes taped to your skin that will measure the hearts' electrical activity in order to obtain additional information on blood flow characteristics.

These electrodes will be in addition to the 10 electrodes you would normally have attached to your skin for the exercise test (for a total of 15 electrodes). They act much like sensing devices that are attached to certain places on the chest, and are barely noticeable since they are lightweight.

There are no risks to having additional electrodes attached to your skin, but there may be some minor discomfort to the areas where they are attached, such as redness or itching.

Because we are interested in how the test results are related to your future health, we will keep track of your future hospitalizations and any other medical problems that you may have. We will only be interested in this information if you are a Veteran. We may contact you to verify that our information is accurate and to ask some questions about your health status. You are free to decline to answer any questions when we contact you in the future.

While participating in this study, you should not take part in any other research project without approval from all of the investigators. This is to protect you from possible injury arising from such things as extra blood drawing, extra x-rays, interaction of research drugs, or similar hazards.

Will I benefit from the study?

There are some potential benefits to you by participating in this study. We will learn some information about your heart's function; if any abnormalities are detected, we can recommend therapies that may help to prevent further abnormalities. However, we cannot and do not guarantee or promise that you will receive any benefits from this study.

While participating in this study, you should not take part in any other research projects without approval from all of the investigators. This is to protect you from possible injury arising from such things as extra blood drawing, extra x-rays, interaction of research drugs, or similar hazards.
What are my alternatives to being in this study?

As an alternative to participating in this study, you may continue to receive routine management of your health care as determined by your physician.

How many subjects will be in this study?

Approximately 12,000 subjects will participate in this study.

Will I get paid?

You will not be paid for taking part in this study.

Will I have to pay anything?

There will be no costs to you for any of the treatment or testing done as part of this research study. However, medical care and services provided by the VA that are not part of this study (e.g., normal hospital and prescription expenses which are not part of the research study) may require co-payments if your VA-eligibility category requires co-payment for VA services.

Do I have to be in this study?

It is your choice alone whether or not to take part in this study. If you decide not to take part in the study there is no penalty and you will not lose any benefits that you may be entitled to receive.

If you decide to participate, you are free to withdraw your consent, including your authorization regarding the use and disclosure of your health information and to discontinue participation at any time without prejudice to you or effect on your medical care. If you decide to terminate your participation in this study, you should notify Dr. Froelicher at (650) 493-5000 ext. 64805.

If I decide to be in the study can I change my mind later and stop being in this study?

You can agree to be in the study now and then later change your mind and withdraw from the study without any penalty or loss of benefits that you may be entitled to receive. At the discretion of the principal investigator, subjects may be taken out of this study due to unanticipated circumstances.
Will information about me collected during the study be kept confidential?

We will protect the confidentiality of the information we collect about you in this study and we will only share information that identifies you with those listed in this document. We may publish the results of this study for others to read about, but you will not be identified in any articles about the study by name, social security number, address, telephone number, or any other direct personal identifier. Also, other federal agencies, such as the VA Office of Research Oversight and the VA Office of the Inspector General may have access to your information, as required.

Who can I talk to if I have questions about the research, problems related to the study or if I think I’ve been hurt by being a part of the study?

Appointment contact: Gay Wittenberg (650) 858-3932. If you need to change your appointment, please contact Gay Wittenberg at this number.

If you have any questions, concerns or complaints about this research study you should ask the Principal Investigator, Dr. Jonathan Myers at (650)-493-5000 X64661, or Dr. Victor Froelicher at (650)-493-5000 X64605. If you think you have experienced a research-related injury, call Dr. Jonathan Myers (650)-493-5000 X64661 at the Palo Alto VAHCS.

If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, and would like to speak with a person who is independent of the research, call the Stanford Institutional Review Board (IRB) at (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, MC 5579, Palo Alto, CA 94304.
Authorization to Use and Share Health Information For Research

HIPAA (Health Insurance Portability & Accountability Act) is a federal privacy law that protects the confidentiality of health information collected about you. The following sections explain how health information collected about you will be used by the investigators and who they may share your health information as part of this research.

How will my health information be used in this study?

As described above, health information about you will be used to study the role physical exercise plays in the development of heart disease.

What Personal Health Information Will Be Used or Shared?

The following health information about you will be used for this research:

- Medical history and physical examination records
- Diagnostic/Laboratory test results
- Survey/Questionnaire responses
- National electronic medical record through VA CAPRI/VistaWeb
- Medicare data

Who May Use or Share Your Health Information?

By signing this section of this document, you allow the following individuals and entities to obtain, use and share your health information for this research study:

- The Principal Investigator Jonathan Myers, PhD and members of the research team.
- Departments within the VA Health Care System responsible for the oversight, administration, or conduct of research.
- The Stanford University Administrative Panel on Human Subjects in Medical Research and other Stanford University Officials responsible for the oversight, administration, or conduct of research.
Others Who May Receive and Use Your Health Information

The investigators may share your health information with the following individuals or entities involved in this research study.

- The Office for Human Research Protections in the U.S. Department of Health and Human Services (the Federal office that oversees research)
- Other outside people or entities hired by the VA Palo Alto Health Care System to do certain work in support of the VA Health Care System

We will protect your health information as required by all laws, however health information shared with others may no longer be protected by Federal laws or regulations and might be shared by the parties above.

Agreeing to your health information to be use of your data in this study is your decision (voluntary). The VA may not condition treatment, payment, enrollment or eligibility for benefits based on signing this form. If you decide not to let the researchers use your health information as noted above you will not be able to take part in this study.

If I agree now, but later decide not to later?

Yes. You are free to take back your permission and stop being in the study. The investigators will not collect any more information about you after you take back your permission, but they can continue to use your information that was collected before you took back your permission.

Your request to take back your permission must be done in writing. Either give your written request to the investigator or send it by mail to:

Jonathan Myers, PhD
VA Palo Alto Health Care System
Cardiology 111C
3801 Miranda Ave Palo Alto, CA 94304
Does My Permission for the use my Personal Health Information Expire?

Yes. Your information cannot be used forever. Your permission related to the use and sharing of your health information expires when this research study is completed. Your authorization for the use and/or disclosure of your health information will expire on December 31, 2050.