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Article

Cardiorespiratory Fitness as a Risk Factor for Requiring Coronary Artery Bypass Grafting in a Veteran Population

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Abstract

Background: Regular physical activity is widely recommended to reduce the risk of coronary heart disease. Coronary artery bypass grafting is the gold standard treatment for severe multi-vessel coronary artery disease that has failed medical management. However, there is limited information on the relationship between cardiorespiratory fitness (CRF) and the likelihood of undergoing coronary bypass. This study aims to determine the association between CRF and the likelihood of requiring future coronary artery bypass in a US Veteran population. **Methods**: From a cohort of 740,075 United States Veterans who completed an exercise treadmill test between October 1, 1999, and September 3, 2020, with no evidence of cardiovascular disease, we identified 14,860 individuals who underwent a bypass more than six months after their fitness assessment. To assess the association between CRF and the risk of coronary bypass, we divided participants into CRF quintiles based on peak workload achieved: Least-fit: 4.7 ± 1.5 metabolic equivalents (METs) (n = 141,893); Low-fit: 7.2 ± 0.9 METs (n = 181,550), Moderate-fit: 8.5 ± 1.3 METs (n = 142,895), Fit: 10.5 ± 1.0 METs (n = 192,061) and High-fit: 13.5 ± 1.8 METs (n = 81,676). Cox proportional hazard models were used to calculate the risk of bypass across fitness categories. The models were adjusted for age, body mass index, race, cardiovascular medications, and cardiovascular risk factors. **Results**: The association between cardiorespiratory fitness and coronary artery bypass was inverse, independent, and graded. For every 1-MET increase in exercise capacity the risk of surgery was 10% lower (HR = 0.90; 95% CI: 0.89–0.91; $p < 0.001$). Comparisons across CRF quintiles revealed that the risk for surgery was lower by 29% in the Low-fit group (HR = 0.71; 95% CI: 0.68–0.74; $p < 0.001$), 37% in the Moderate-fit group (HR = 0.63; 95% CI: 0.60–0.66; $p < 0.001$), 47% in the Fit group (HR = 0.53; 95% CI: 0.54–0.60; $p < 0.001$), and 53% in the High-fit group (HR = 0.47; 95% CI: 0.43–0.50; $p < 0.001$). **Conclusions**: Our findings support a graded, inverse relationship between CRF and the likelihood of undergoing future coronary bypass surgery. A moderate CRF level, achievable by most older individuals engaging in age-appropriate physical activity, was associated with a 40% lower likelihood of undergoing future coronary bypass.

Keywords

cardiorespiratory fitness; coronary artery bypass grafting; exercise testing; coronary artery disease; cardiothoracic surgery

Introduction

Coronary artery disease (CAD) continues to be a leading cause of death and disability globally [1]. Within the United States, Veterans are at an exceptionally high risk for developing heart disease compared to non-Veteran populations [2]. Despite optimal medical therapy, many patients still experience severe CAD that requires coronary artery bypass grafting (CABG), which remains the gold standard for severe or multivessel CAD after medical therapy [3]. Over the past decades, there have been significant developments in the medical management of CAD, including optimization and the use of percutaneous coronary interventions (PCI) as an alternative intervention for severe disease. Both improved prevention and therapeutic options for CAD have contributed to an overall decrease in the rate of CABG and increased comorbidity burden at the time of surgery in both Veteran and civilian populations [3,4]. While the literature identifies many modifiable CAD risk factors for CABG, the impact of cardiorespiratory fitness (CRF) as a contributing risk factor has not been well studied.

Cardiorespiratory fitness (CRF) is defined as the capacity of the cardiorespiratory system to meet the oxygen demand of the exercising muscles during prolonged physical activity.

It is assessed objectively using a standardized exercise treadmill test (ETT) and expressed in metabolic equivalents (METs). One MET is equivalent to 3.5 mL of O_2 per kg of body weight (American College of Sports Medicine) [5]. A plethora of evidence supports an inverse and graded association between CRF and health outcomes, independent of comorbidities [6–9].

However, CRF is still commonly omitted from national Cardiology and Cardiothoracic Surgery disease prevention guidelines and risk calculators [10,11]. Higher fitness has been recognized to have a preventative impact on cardiovascular disease (CVD), but there is no standard therapeutic recommendation on how to practically measure or advise patients regarding fitness [10,12,13]. Since 1992, the American Heart Association (AHA) has classified physical inactivity as a "primary risk factor" for CVD [13]. In 2010, the Department of Health and Human Services described a suggested number of minutes of exercise as a preventative health behavior recommendation [12]. Physical activity contributes to but is not solely responsible for, fitness. DeFina *et al*. [11] summarize the impacts of environmental, genetic, and physiologic determinants on CRF beyond minutes of structured exercise. CRF was addressed in a 2016 Scientific Statement by the American Heart Association, along with the recommendation for using one of thirteen non-exercise CRF estimation calculators during annual adult physicals [12]. However, the same article also acknowledges that these subjective measurements are flawed and are not an appropriate replacement for an objectively measured CRF level. Therapeutic recommendations to optimize one's fitness remain challenging within the cardiology literature; however, CRF, as a modifiable risk factor, should be more regularly included in cardiothoracic surgery research.

Myers' response to the omission of CRF in the AHA's 2013 guidelines criticizes the tendency of guidelines to focus only on modifying risk factors for interventions such as revascularization [10]. However, considering that CABG is an intervention for severe CVD that has failed earlier medical management, there is a notable absence of literature regarding the impact of such a significant CAD risk factor on the rate of surgical revascularization. Smith *et al*. [14] evaluated the impact of preoperative (measured <90 days preoperatively) CRF on short-term outcomes after CABG within the Beaumont Health System, noting significantly higher operative and 30-day mortality among patients with low preoperative CRF (<5 METs). While this study demonstrates the potential association between CRF and postoperative mortality, the link between CRF and the need for CABG has not been evaluated. Our study aims to investigate the relationship between CRF and the rate of CABG within a United States Veteran population.

Materials and Methods

Population and Demographics

The Exercise Testing Health Outcomes Study (ETHOS) is a prospectively maintained database of exercise tolerance tests (ETTs) completed at Veterans Affairs Medical Centers (VAMC) across the United States from October 1, 1999 until September 3, 2020. During this study period, 822,995 Veterans underwent ETTs following standard the Bruce protocol. A total of 82,920 Veterans were excluded according to criteria described in our previous work [15]. Briefly, we excluded individuals with evidence of overt cardiovascular disease during or prior to the ETT. We also excluded those less than thirty years of age, those unable to complete the ETT, those with METs less than 2.0 or METs calculated to be beyond physiologic parameters, body mass index (BMI) <18.5 kg/m^2, or those missing either BMI data or METs results. To account for individuals with overt CVD at the time of the ETT and minimize reverse causality, we excluded those with overt evidence of CVD, including those who underwent prior PCI or were diagnosed with a myocardial infarction (MI) or congestive heart failure (CHF) within six months of the ETT. In addition, 10,220 patients who underwent a CABG before the date of the ETT were also excluded from the study sample. After these exclusions, the cohort consisted of 740,075 Veterans. Cardiac medications included aspirin, β-blockers, calcium channel blockers, diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and other antihypertensive medications. Hypoglycemic medications included insulin as well as metformin and sulfonylureas.

MET Extraction

We randomly selected 3000 samples of physician clinical notes on exercise capacity from the dataset and identified METs manually. This annotated dataset was further preprocessed and then used to train the Natural Language Processing models. In the preprocessing phase, we removed special characters ($, &, etc.) and restricted the note to 30 characters before and after the words METs or MET. These words were then replaced with a special character to identify their location within the notes. spaCy software (https://spacy.io/) was then used to convert the resulting string into word tokens and then into a vector of numbers. The corresponding labels were created such that "1" meant that the corresponding token contained the MET value and "0" if it did not. We used a two-layer convolutional neural network using the Tensorflow software

Table 1. Demographic and clinical characteristics according to CRF cohort.

Variables	Least Fit (n = 141,893)	Low-Fit (n = 181,550)	Mod-Fit (n = 142,895)	Fit (n = 192,061)	High-Fit (n = 81,676)	*p* value
Age, years	62.4 ± 9.8	60.9 ± 9.7	63.4 ± 10.2	60.4 ± 8.6	58.2 ± 10.1	0.000
METs	4.7 ± 1.5	7.2 ± 0.9	8.5 ± 1.3	10.5 ± 1.0	13.5 ± 1.8	0.000
BMI	30.5 ± 5.8	30.1 ± 5.0	29.5 ± 4.3	29.1 ± 4.0	28.1 ± 3.6	0.000
AFib	9213 (8.5)	6772 (3.7)	4996 (3.5)	4754 (2.5)	1667 (2.0)	0.000
MACVE	59,476 (41.9)	55,932 (30.8)	40,922 (28.6)	45,007 (23.4)	14,445 (17.7)	0.000
DM	43,982 (31.0)	44,189 (24.3)	29,056 (20.3)	29,859 (15.5)	6962 (8.5)	0.000
HTN	94,904 (66.9)	105,134 (57.9)	76,975 (53.9)	90,743 (47.2)	29,367 (36.0)	0.000
Smoking	4390 (30.4)	47,245 (26.0)	28,969 (20.3)	40,704 (21.2)	13,633 (16.7)	0.000
Stroke	1716 (1.2)	1344 (0.7)	991 (0.6)	879 (0.5)	240 (0.3)	0.000
Statins	100,565 (70.9)	119,101 (65.6)	88,755 (62.1)	112,004 (58.3)	40,210 (49.2)	0.000
CKD	9209 (6.5)	6981 (3.8)	4981 (3.5)	4517 (2.4)	1262 (1.5)	0.000
Cardiac Rx	100,286 (70.7)	111,923 (61.6)	81,344 (56.9)	96,614 (50.3)	31,047 (38.0)	0.000
Hypo-glycemics	38,189 (26.9)	38,490 (21.2)	24,219 (16.9)	25,079 (13.1)	5319 (6.5)	0.000

CRF, cardiorespiratory fitness; METs, Metabolic equivalents; BMI, Body Mass Index; AFib, Atrial Fibrillation; MACVE, Major Adverse Cardiovascular Event; DM, Diabetes Mellitus; HTN, Hypertension; CKD, Chronic Kidney Disease; Rx, Medication.

Table 2. Variables associated with the rate of undergoing CABG.

Variables	HR	95% CI	*p* value
Age (per 1 year)	1.01	1.00–1.01	0.000
BMI (per unit)	0.98	0.98–0.99	0.000
AFib	1.25	1.21–1.37	0.000
MACVE	2.34	2.26–2.43	0.000
DM	1.30	1.24–1.38	0.000
HTN	1.35	1.29–1.42	0.000
CKD	2.00	1.90–2.11	0.000
Statins	0.87	0.84–0.90	0.000

CABG, coronary artery bypass grafting; BMI, Body Mass Index; AFib, Atrial Fibrillation; MACVE, Major Cardiovascular Event; DM, Diabetes Mellitus; HTN, Hypertension; CKD, Chronic Kidney Disease.

(https://www.tensorflow.org/?hl=zh-cn) library to predict the probable location of METs in the note. The model was trained over 100 epochs. Once METs were extracted, the MET data were randomly and manually checked for errors. The model accuracy on the test dataset was 97%.

CRF Categories

Exercise capacity was determined for each participant during a single ETT performed at VA medical centers throughout the United States. Peak MET levels were calculated for each participant by standardized equations based on treadmill speed and grade [16]. We then stratified the cohort into five age groups (30–49, 50–59, 60–69, 70–79, and 80–95 years). Next, we established five CRF categories (quintiles) within each age group using methods described in our previous work [17]. We identified the age- and gender-specific MET level corresponding to the 20th, 40th, 60th, and 80th percentiles within their respective age category and stratified the cohort accordingly. The respective percentiles were then combined to form the following CRF categories: Least-fit, Low-fit, Moderately-fit, Fit, and Highest-fit.

Statistical Analysis

Follow-up time was calculated from the exercise test date to the date of coronary bypass, to the death date for decedents, or to September 30, 2021, for survivors and those who did not undergo bypass surgery. Continuous variables were reported as mean ± standard deviation and categorical variables were expressed as relative frequencies with percentages. Comparisons between categorical variables were evaluated by chi-square test and continuous variables were assessed with one-way Analysis of variance (ANOVA) tests. Cox proportional hazard models were used to calculate the risk of CABG across CRF quintiles. The relative risk for CABG was determined for each fitness quintile using the least-fit group as the reference. The models were adjusted for age, body mass index (BMI), race, CVD, PCI before ETT, CV medications, and other medical comorbidities. p-values < 0.05 using two-sided tests were considered statistically significant. Standard deviations are presented with all means. All statistical procedures were performed with Statistics Package for Social Science (SPSS) (version 28.0, Armonk, New York 10504-1722, United States). This study was approved by the Washington DC VA Institutional Review Board.

Results

The mean follow-up period of the 740,075 participants was 10.3 ± 5.2 years. During that time, 2% (14,860) underwent CABG. The mean age and BMI were 61.2 ± 9.8

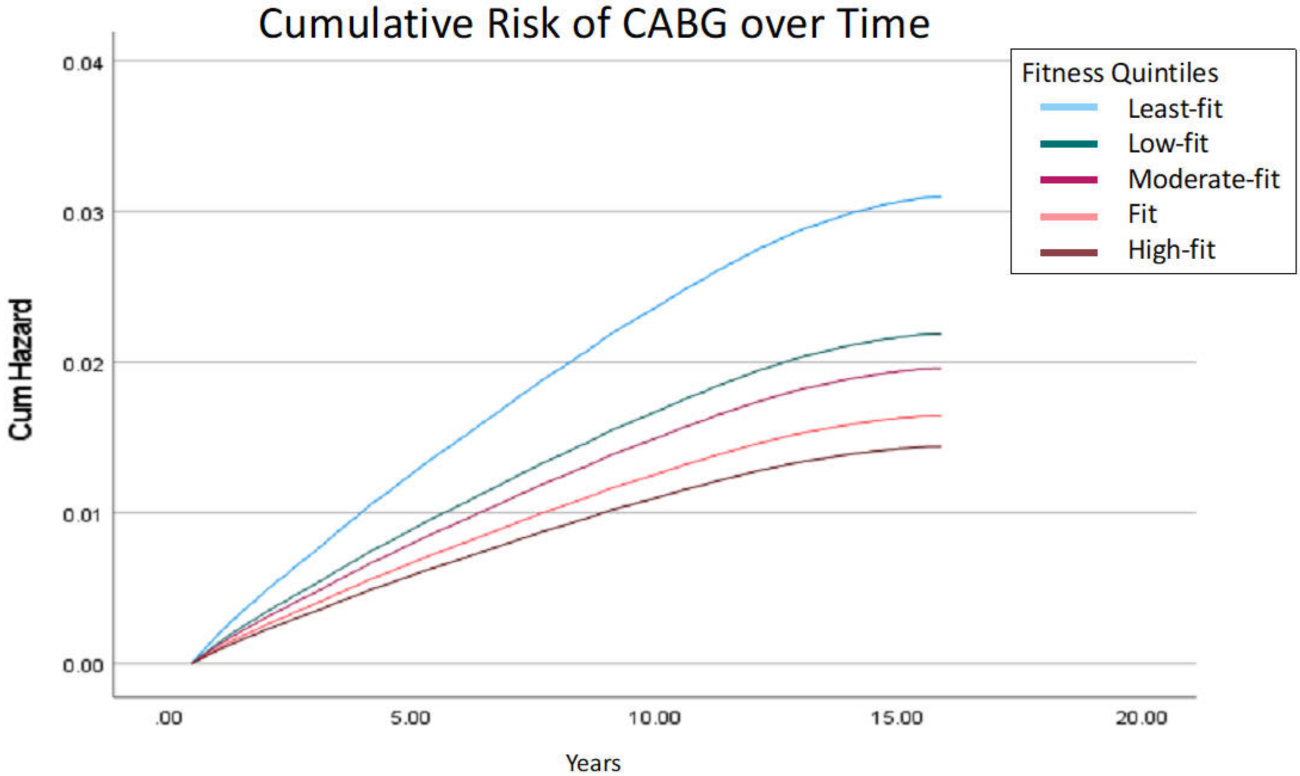

Fig. 1. Survival curve for freedom from undergoing CABG over time by fitness quintile.

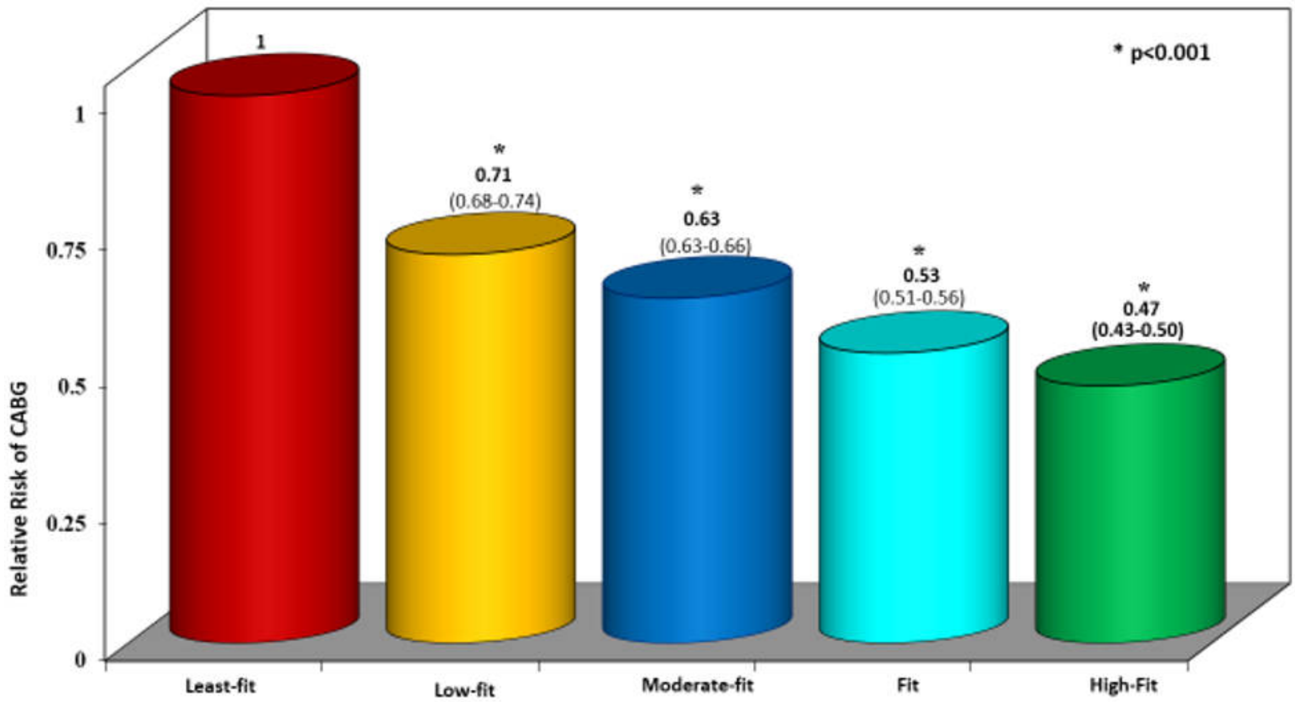

Fig. 2. Relative risk of undergoing CABG according to CRF categories.

years and 29.6 ± 4.7 kg/m^2, respectively. The demographic and clinical data for each CRF quintile are presented in Table 1. The exercise capacities for the CRF quintiles were 4.7 ± 1.5 METs for the Least-fit (n = 141,893), 7.2 ± 0.9 METs for Low-fit (n = 181,550), 8.5 ± 1.3 METs for the Moderate-fit (n = 142,895), 10.5 ± 1.0 METs for the Fit (n = 192,061) and 13.5 ± 1.8 METs for the High-fit (n = 81,676). BMI was progressively lower in the higher fitness groups.

The higher fitness quintiles also had lower rates of medical comorbidities including atrial fibrillation (Afib), prior major adverse cardiovascular events (MACVE), Diabetes mellitus (DM), hypertension (HTN), chronic kidney disease (CKD), and smoking. Statins, hypoglycemic, and cardiac medications were less prevalent in the higher fit groups.

After adjusting for confounding variables, the predictors for undergoing CABG are reported in Table 2. MACVE and CKD had the highest hazard ratios (HR) for undergoing future bypass. When the rate of CABG was assessed across fitness categories (Fig. 1), we observed an inverse association between fitness level and the cumulative risk of undergoing CABG.

The survival curve for the freedom from undergoing CABG over time was shown for the five CRF groups in Fig. 1. The relative risk of undergoing CABG by CRF quintile is represented in Fig. 2. Compared to the Least-fit group, the hazard ratio for the Low-fit group was 0.71 (95% CI 0.68–0.74), 0.63 (95% CI 0.60–0.66) for Moderate-fit, 0.53 (95% CI 0.51–0.56) for Fit, and 0.47 (95% CI 0.43–0.50) for High fit. In Veterans referred for exercise testing, the association between CRF and the risk of undergoing CABG was inverse and graded. When compared to the individuals in the least-fit category, the risk was approximately 25% lower for those in the next CRF category and declined progressively to 50% for those in the highest fitness category.

Discussion

Our findings support an inverse, independent, and graded association between objectively measured CRF and the risk of undergoing future CABG in our large veteran population. Specifically, for every 1-MET increase in exercise capacity, the risk of undergoing CABG decreased by 10%. When risk was assessed across CRF categories, using the Least-fit group as the referent, the risk for CABG in the Low-fit group was 29% lower, 37% lower in the Moderate-fit, 47% lower in the fit quintile, and 53% lower in the High-fit group. The 29% to 47% lower risk of CABG associated with those achieving relatively moderate levels of CRF (approximately 7–9 METs) has significant public health implications. This level of CRF is achievable by most middle-aged and older individuals who meet the current recommendations of $\geq$150 minutes per week of moderate-intensity physical activity [17].

Our study is the largest to date to evaluate the association between CRF assessed objectively by a standardized treadmill test and the incidence of CABG. Although others have also reported an inverse association between physical activity status and the likelihood of CABG or risk of mortality after CABG, physical activity status was based on self-reported questionnaires, which are inherently limited by recall bias [14,18]. The recently published HUNT2 study reported an inverse association between estimated CRF and the risk of undergoing isolated CABG [19]; however, the analyses were done using subjective CRF estimates from patient estimates of weekly hours of exercise and exercise intensity. In a study comparing the results of the International Physical Activity Questionnaire and accelerometer data for 1751 adults, Dyrstad *et al*. [20] found that there was a significant discrepancy between physical activity reporting and physical activity data, with participants underreporting sedentary time and overestimating vigorous-intensity physical activity. This discrepancy was noted to be worse in male and older participants which is particularly relevant to our Veteran population with a mean age of 61.2 years [20].

The study's retrospective nature does not demonstrate causation, regardless of the strong CRF-CABG association. Accordingly, we cannot discern whether the increased rate of CABG risk was the outcome of poor CRF or subclinical disease, which underlies low CRF (reverse causality). To minimize the probability of reverse causality, we excluded individuals who suffered a major coronary event or underwent CABG within six months post-ETT. In addition, our findings are based on the results of a single ETT. We did not assess changes in CRF over time or the impact of such changes on the likelihood of having CABG. However, while this is important, it has been a well-recognized limitation for large studies regarding the impact of fitness on health outcomes. The significant impact of increasing or decreasing CRF on CVD events has been reported by several studies [21–23]. Imboden *et al*. [21] demonstrated that each 1 mL/kg/min increase in CRF was associated with a 15% reduction in CVD mortality. This effect was replicated in the Ball State Adult Fitness Longitudinal Lifestyle Study, with a 20% and 38% reduction in long-term mortality per 1 MET increase in CRF in men and women, respectively, who completed four months of exercise training [21]. Some studies have also attempted to find a dose response for exercise. This is of particular concern for individuals who did not show a predicted increase in CRF following exercise training regimens [24,25]. However, assessing change in fitness was beyond the scope of this particular study as we only reviewed single CRF assessments per Veteran. To advocate for programs to increase CRF, prospective studies are needed to assess the impact that changes in CRF may have on the risk for CABG. When viewing CRF as a modifiable risk factor, it is important to acknowledge that most individuals' fitness will decline with age upon repeat assessment. While there is some variation associated with lifestyle habits, a predictable age-related decline in CRF per year of life is well accepted [23,26–28]. Thus, our study does not indicate the CRF status of each patient at the time of surgery. Therefore, interventions aimed at increasing the Least-fit group's CRF may result in a stronger association than what was noted in this study.

As an observational study, our results were also limited to showing an association between a single-time fitness assessment and the risk of undergoing CABG, rather than causation. While similar results were noted in the HUNT I study regarding PCI, we were unable to evaluate the association between fitness level and the risk for severe CAD that was managed with an alternative therapy such as PCI [29]. While CABG served as a surrogate for severe CAD, our study was not able to capture Veterans who may have died before the recognition of severe CAD that would have benefited from CABG. Finally, the literature has acknowledged that the Veteran population has a unique medical comorbidity profile and environmental exposures that may limit the generalizability of our results to the civilian population [30,31].

In recent years, there has been an increased call for recognition of CRF as a modifiable risk factor for CAD that should be incorporated into national Cardiology and Cardiothoracic Surgery disease prevention guidelines [10]. Several studies have already shown that CRF is inversely associated with worse cardiac biomarkers, increased risk for the development of heart failure, MACVEs, CVD-associated mortality, and all-cause mortality [32–37]. In a 2009 meta-analysis evaluating 33 studies with over 100,000 participants, Kodama *et al.* [33] reported that compared to the most-fit participants, the least-fit quintile of patients was associated with a 56% higher risk of CVD related mortality. Additionally, Gupta *et al.* [38] reported a significant discrimination improvement in a short- and long-term CVD mortality risk calculator with the addition of a one-time fitness measurement. While this was beyond the scope of our results, future studies are needed to determine if the addition of CRF to surgery prediction tools may aid in forecasting patients at high risk for failing medical therapy alone.

Although the mechanisms involved in CRF protection against CABG are not entirely evident and beyond the scope of this study, some speculation is warranted. CRF has been shown to have a favorable effect on all the traditional cardiac risk factors and on the development and progression of coronary artery disease [10,12,26,33,34]. Accordingly, we can assume that CRF moderates the progression to severe CAD requiring CABG.

Conclusions

In U.S. Veterans referred for exercise testing, CRF was inversely and independently associated with the risk of requiring future CABG. Evidence has shown that even modest levels of fitness can dramatically impact the clinical course of CAD, suggesting that engaging in age-appropriate regular physical activity may lower the likelihood of CABG. Furthermore, adding CRF to a traditional CVD mortality risk calculator may significantly reclassify an individual's risk of requiring future CABG. The findings of our study highlight the importance of CRF in predicting a patient's future need for CABG. However, future research is warranted to determine the optimal approach to modifying this significant risk factor and reducing a Veteran's risk of undergoing future CABG. In summary, the findings of our study illuminate the importance of CRF in predicting the patient's future need for CABG. Based on our results, we suggest that CAD patients with physician clearance for exercise engage regularly in moderate-intensity exercise to improve cardiovascular health and attenuate the progression to CABG.

Availability of Data and Materials

Data and materials are available through direct request to the corresponding author.

Author Contributions

Conceptualization, SMA, JL, CF, PK, and GDT; Data curation, IS, JA and CF; Formal analysis, SMA, IS, and PK; Investigation, IS and CF; Methodology, JL, JA, and PK; Project administration, JA, CF and GDT; Resources, IS, CF and PK; Software, PK; Supervision, JA, PK and GDT; Validation, PK; Writing – original draft, SMA; Writing – review & editing, JL, JA, CF, PK and GDT. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

The study was carried out in accordance with the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the DC VAMC Research & Development Committee (R&DC) with the following project number: 1714947-1. Patient consent was waived due to the retrospective nature of the review and the impracticality to track a large patient population that enrolled in a fitness study potentially more than twenty years earlier. Patients did grant consent to have their data be included in future research at the time of initial exercise testing completion.

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Conflict of Interest

The authors declare no conflict of interest. GDT serves as editorial board member of this journal. GDT declares that he was not involved in the processing of this article and has no access to information regarding its processing.

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