REVIEW

Cardiorespiratory Fitness and the Incidence of Chronic Disease

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ABSTRACT

An inverse association between cardiorespiratory fitness and the incidence of chronic disease has been established by large, well-designed epidemiologic studies. Collectively, the findings support that these health benefits are realized at relatively moderate levels of exercise or physical activity and increase in a dose-response fashion. This supports the concept that physical activity should be promoted by health care professional for optimal health. This review is focused on the influence of physical activity and cardiorespiratory fitness on the incidence of cardiometabolic risk factors and diseases. *Journal of Clinical Exercise Physiology*. 2018;7(2):37–45.

INTRODUCTION

Over the last 2 decades, considerable evidence from large and well-designed epidemiologic studies with diverse populations supports the preventive role of cardiorespiratory fitness (CRF) on the incidence of hypertension (HTN), diabetes type 2 (DM2), atrial fibrillation (AF), chronic kidney disease (CKD) and major adverse cardiovascular events (MACE), including heart failure (HF), myocardial infarction, coronary artery bypass surgery, stroke, and death. The association is graded and independent of other comorbidities. Cohort studies from the Veterans Affairs Health Care System have been particularly helpful in this regard since these data sets not only include an array of metabolic risk factors, arrhythmias, MACE, and many other chronic conditions, but objective measures of CRF. A synopsis of the available evidence related to CRF and these health conditions is discussed herein, with a special focus on information derived from the Department of Veterans Affairs data.

CRF AND THE INCIDENCE OF HTN

In aggregate, numerous studies now support the notion that age-related increases in arterial stiffness, systolic blood pressure, and incident HTN are not inevitable and that structured exercise regimens, increased lifestyle related physical activity (PA), or both, that improve CRF can attenuate and even reverse this process (1-7). Several reviews (8-10) and a meta-analysis of 13 prospective cohort studies (11) have confirmed an inverse, dose-response association between leisure-time PA, CRF, and the risk of developing HTN.

In a cohort of 2,303 pre-hypertensive, middle-aged male veterans followed for over 9.2 years, we reported that higher CRF, as reflected by peak metabolic equivalents (METs; 1 MET = 3.5 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$) achieved during a progressive exercise test to volitional fatigue and/or adverse signs/symptoms, was inversely associated with the rate of progression to HTN. Compared to individuals with the highest exercise capacity (> 10 METs), the multivariate-adjusted risk for developing HTN was 36% higher for those with an exercise capacity between 8.6 and 10 METs; 66% higher for those between 6.6 and 8.5 METs, and 72% higher for individuals who achieved ≤6.5 METs (12). Similarly, a large cohort of normotensive Korean men (n = 3800) had their fitness assessed directly by cardiopulmonary exercise testing. After approximately 10 years of follow-up, the incidence of

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HTN in obese, unfit men was approximately 91% higher compared with the non-obese, fit men. For obese but fit men, the incidence of HTN did not increase significantly (13). In the same cohort and after the second examination (10-year follow-up) the largest decline in CRF between evaluations (−62.1% to −20.2%) was associated with a 4.33-fold adjusted risk of incident HTN compared to men with the smallest decrease or improvement in CRF (−8.8% to 82.0%; $P < .001$) Collectively, these findings suggest that increased CRF attenuates the risk for developing HTN in individuals at increased risk for HTN and that poor CRF should be considered a causal risk factor for developing HTN (14).

CRF AND THE INCIDENCE OF DM2

Considerable evidence from epidemiologic and interventional studies suggests that increased exercise capacity and/or greater habitual PA generally delay or prevent the development of DM2 (15). The incidence of DM2 was inversely related to leisure-time PA among 5990 male alumni of the University of Pennsylvania (16) and after 105 141 person-years of follow-up of 21 271 US males participating in the Physicians' Health Study (17). Likewise, in the Nurses' Health Study (18), the relative risk for developing DM2 in women (n = 70 102) was inversely related to the level of CRF as well as exercise volume and intensity in a dose-response fashion. Equivalent energy expenditures from different activities and intensities conferred similar protective benefits.

These epidemiological findings are also supported by 2 relevant interventional studies (19,20). In the Finnish Diabetes Prevention Study (19), 522 middle-aged, overweight men (n = 172) and women (n = 350) with impaired glucose tolerance were randomized to either a comprehensive lifestyle intervention or to a control group and followed for a mean duration of 3.2 years. The intervention group was given detailed advice regarding a healthy diet (decrease fat intake to < 30% of energy intake; reduce saturated fat intake to < 10% of energy intake; increase fiber intake to at least 15 g/1000 kcal), and reduce body weight by ≥ 5%. Participants were also instructed to engage in aerobic activities (walking, jogging, swimming, etc.) as a way to increase aerobic capacity and improve CRF and resistance-training exercise, aiming to improve functional capacity and strength of the large muscle groups. At the end of the follow-up period, insulin and glucose concentrations measured 2 hours after oral glucose challenge were significantly lower in the intervention group (-14 ± 37 mg·dL^{-1}), and no significant changes were observed in the control group (0 ± 44 mg·dL^{-1}). The risk for DM2 was 58% lower in the intervention group compared to the usual-care control group. The average weight loss was 3.5 ± 5.5 kg and 0.8 ± 4.4 kg in the intervention and control groups, respectively.

The substantially larger Diabetes Prevention Program Research Group Study (20) included 3234 non-diabetic, overweight/obese (mean body mass index 34.0 ± 6.7 kg·m^{-2}) subjects (68% women) with impaired fasting and post-load glucose concentrations. Subjects were randomly assigned to placebo, metformin (850 mg/twice daily), or lifestyle-modification program that included diet and exercise aiming to achieve at least 150 minutes of PA per week and 7% weight loss. After an average follow-up period of 2.8 years, both lifestyle modifications and metformin were effective in lowering the incidence of DM2 significantly. Compared with the control group, the incidence of DM2 was 58% lower in the lifestyle-intervention group and 31% lower in the metformin group. When comparing the lifestyle-intervention versus the metformin groups, the incidence of DM2 was 39% lower in the former. To prevent one case of DM2, the investigators calculated that 6.9 persons would need to participate in the lifestyle-intervention versus 13.9 for those receiving metformin. Lifestyle intervention also resulted in more participants maintaining normal blood glucose values over a follow-up period of 3 years as compared to those in the metformin or placebo groups. Finally, a review of 9 randomized, controlled trials among patients at high risk for diabetes reported that significant comprehensive lifestyle interventions effectively decreased the subsequent incidence of DM2 (15). Collectively, the findings of the aforementioned studies provide strong evidence that lifestyle interventions that include proper diet and exercise are efficacious in reducing the risk for developing DM2.

The relative contributions of CRF and body composition to predict incidence of DM2 was prospectively investigated in 3770 apparently healthy Korean men without baseline evidence of diabetes, cardiovascular disease, or HTN. Participants were divided into 3 groups by body mass index (BMI) as normal weight (BMI 18.5 to 24.9 kg·m^{-2}), overweight (BMI 25.0 to 29.9 kg·m^{-2}), and obese (BMI ≥ 30.0 kg·m^{-2}). CRF was directly measured by peak oxygen uptake (VO_2 peak) and categorized into unfit and fit cohorts based on the median value of age-specific peak oxygen uptake. During a median follow-up of 5 years, obese-unfit men had 1.81 times greater risk of incident DM2, but not obese-fit men compared with fit-normal weight men. These results suggest that CRF appears to attenuate the risk of developing diabetes in obese men (21).

Several meta-analyses of randomized controlled trials have reported a higher risk for developing DM2 in those treated with statins as compared to placebo or standard care (22-24). We have shown that both statin therapy and increased CRF were independently associated with lower mortality risk in veterans referred for exercise testing. Additionally, the combination of statin therapy and increased CRF was more effective in lowering mortality risk than either intervention alone (25,26).

We have also evaluated the relation between CRF and the incidence of DM2 in dyslipidemic middle-aged patients treated with and without statins (27). The incidence of DM2 was 24% higher in statin-treated (n = 4092) as compared with non-statin treated (n = 3,001) patients ($P < .001$). However, when fitness was considered in the fully adjusted model, DM2 risk progressively decreased as exercise capacity increased. Compared to the least-fit cohort, adjusted risk declined progressively with increasing fitness; incidence of

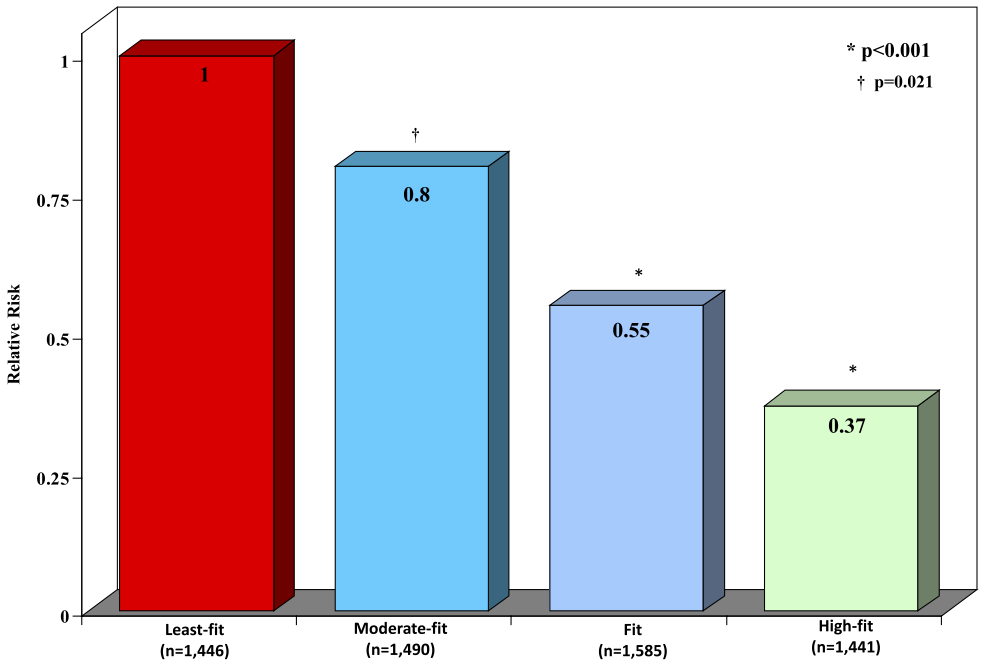

FIGURE 1. Risk for developing AF according to exercise capacity. (48)

DM2 was 24% and 34% lower for moderate-fit and high-fit patients, respectively. To further assess the impact of CRF on risk of developing diabetes, we used the non-statin treated cohort as the reference group and compared it to the CRF categories in the statin-treated cohort. Compared to the high-fit quartile, DM2 incidence was significantly elevated for individuals in the least-fit (50% higher) and low-fit (22% higher) groups. There was no significant increase in DM2 risk for the moderate-fit and high-fit individuals. These findings suggest that the risk of DM2 incidence in dyslipidemic patients treated with statins may be significantly attenuated by achieving moderate levels of CRF (27).

CRF AND THE INCIDENCE OF AF

AF is associated with increased morbidity and mortality (28,29). Although the relation between PA, CRF, and incident AF is complex, some observational studies suggest a higher prevalence of AF in middle-aged and older elite athletes and those participating in long-term strenuous PA regimens as compared with the general population (30-36). This association appears to be directly related to intensity and exercise volume (hours or number of days per week engaged in vigorous PA) (30,31,33,35). Suggested potential mechanisms for the higher risk of AF secondary to chronic vigorous PA include a disruption in autonomic balance, increased left atrial stretch, enlargement, fibrosis, myocardial injury, inflammation, or combinations thereof. There are also limited data suggesting that regular *moderate* intensity exercise, as recommended by national and international guidelines on PA and health, may increase the risk of AF (31,33,36). This has significant public health implications since moderate intensity exercise is recommended to improve health and reduce the risk of mortality regardless of age and other comorbidities (10,26,37-47).

Since reports of increased incidence of AF with moderate intensity exercise were largely based on PA questionnaires (31,33,36-47), we assessed the association between CRF, assessed objectively by graded exercise testing, and the incidence of AF (48). Our study population included 5962 veterans (mean±SD age 56.8±11.0 years) from the Veterans Affairs Medical Center in Washington, DC. None had evidence of AF or myocardial ischemia at the time of or prior to exercise testing. During a median follow-up period of 8.3 years, 722 (12.1%) developed AF. Exercise capacity was assessed in METs using the Bruce treadmill protocol and estimated from standard equations based on peak exercise time. Peak METs were inversely related to AF incidence. The risk for developing AF was 21% lower for every 1-MET increase in exercise capacity. The cohort was then stratified into quartiles based on their age-adjusted peak METs achieved, and risk was assessed using the least-fit group as the referent. The risk of developing AF progressively decreased with increased fitness, ranging from 20% lower for individuals in the moderate fitness category (n=1490; 6.7±1.0 METs) to 45% lower for fit individuals (n=1585; 7.9±1.0 METs) and 63% lower for those in the highest-fit group (n=1441; 9.3±1.2 METs) (Figure 1). The results were similar when we excluded patients treated with β-blockers and calcium channel blockers (medications known to influence AF), and when the cohort was stratified by age (<65 and ≥65 years of age). The above findings are also supported by the FIT Project results, where an inverse relationship was noted between CRF and incidence of AF, which was even more marked in obese people (49).

Thus, previous suggestions that even moderate increases in PA increase AF incidence are refuted by these findings based on objectively estimated CRF. Conversely, these findings indicate that moderate intensity PA levels as

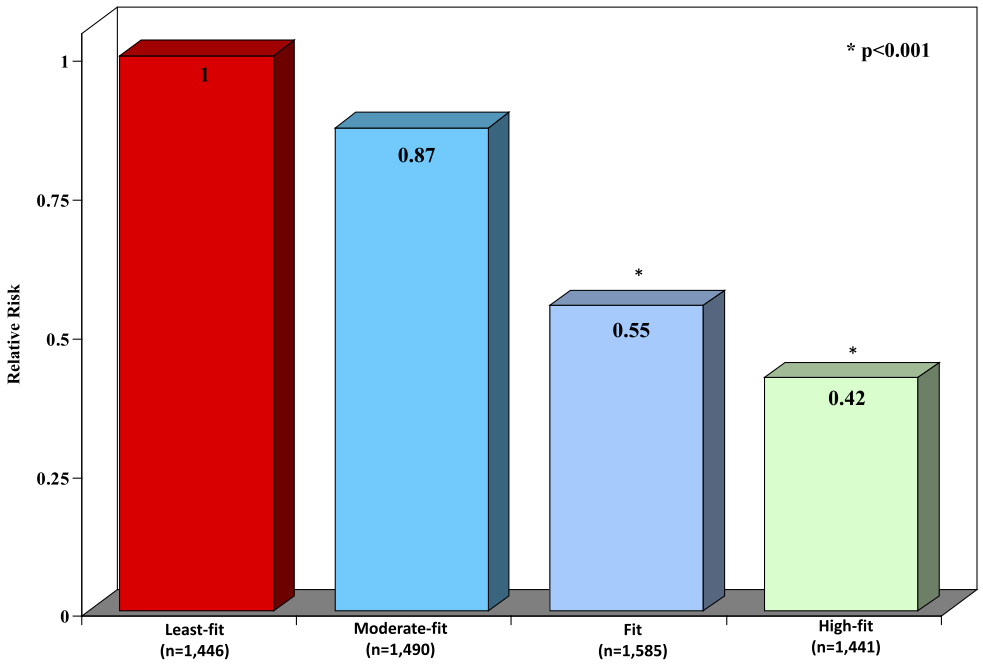

FIGURE 2. Risk for developing CKD according to exercise capacity. (38)

recommended by national and international guidelines to improve CRF, offer protection against AF.

CRF AND THE INCIDENCE OF CKD

CKD is defined as an estimated glomerular filtration rate (eGFR) of <60 mL·min^{-1} per 1.73 m^2 for ≥ 3 months (stages III to IV) and substantially increases mortality risk (50). Increased CRF also attenuates the incidence of HTN (12) and DM2 (19,20), which are strong contributors to CKD (51). To clarify the impact of CRF on the risk of developing CKD, we evaluated a cohort of 5812 male veterans (mean±SD age, 58.4±11.5 years) who had an estimated glomerular filtration rate of ≥ 60 mL·min^{-1} per 1.73 m^2 for ≥ 6 months before undergoing a symptom-limited exercise test. Four CRF categories were established on the basis of age-stratified quartiles of peak METs achieved. During a median follow-up period of 7.9 years, 1010 subjects developed CKD. Exercise capacity was inversely related to CKD incidence; for every 1-MET increase in exercise capacity, the adjusted risk for developing CKD was 22% lower ($P<.001$). Comparisons across CRF categories using the least-fit individuals as the reference group revealed an independent, inverse, and graded association between increased fitness and risk of CKD. The CKD risks for fit and high-fit individuals were 45% and 58% ($P<.001$ for both) lower compared to the least-fit group. These findings suggest that a higher exercise capacity is associated with a reduced risk for developing CKD (38) (Figure 2). Similarly, the Aerobic Center Longitudinal Study, evaluating 17 979 individuals over 116 973 person-years of observation, showed that higher fitness levels decreased the risk of CKD later in life (52). Finally, in another study, aerobic exercise for 12 weeks improved kidney function in DM2 patients with stage II-III CKD (53).

CRF AND THE INCIDENCE OF HF

Although HF remains one of the most common reasons for hospitalization among older individuals (≥ 65 years), the association between CRF and risk for developing HF is largely unexplored. Other than control of traditional risk factors (particularly blood pressure and obesity), treatment strategies to prevent HF are relatively limited (54). Given that CRF is inversely related to the incidence of many chronic illnesses that are associated with HF, such as obesity, HTN, and DM2, we (55) and others (55-58) have tested the hypothesis that moderate-to-high levels of CRF may be protective against the risk of developing HF.

In a large cohort of middle-aged individuals (mean age, 49 years) from the Cooper Aerobics Center Longitudinal Study, after adjusting for age and traditional risk factors, higher mid-life fitness was associated with 18% to 20% lower risks for HF hospitalization per each 1-MET increase in exercise capacity after the age of 65 years (56,58). Similar findings were reported in a large cohort of subjects (n=66 329; 53.8% men) free of HF who underwent treadmill exercise testing at Henry Ford Health System between 1991 and 2009 (54). After adjusting for potential confounders, each 1-MET increase in exercise capacity was associated with a 16% lower risk for developing HF. When the cohort was stratified according to peak METs achieved, the risk for developing HF was 81% lower among those in the highest CRF cohort (≥ 12 METs) compared to those in the lowest CRF group (< 6 METs).

This issue was recently addressed in a cohort of 21 080 veterans drawn from the Veterans Exercise Testing Study, an ongoing prospective evaluation of veterans designed to address exercise test responses, clinical, and lifestyle factors and their association with health outcomes. All participants (mean±SD age=58.2±11.0 years) completed a peak or

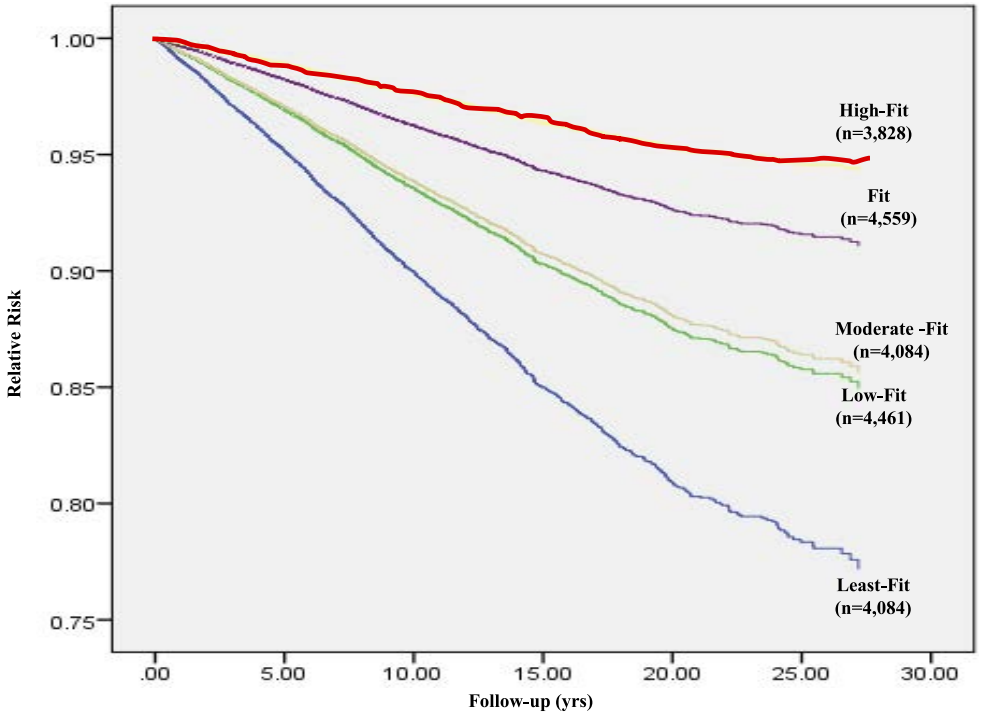

FIGURE 3. Risk for developing HF according to exercise capacity. (55)

symptom-limited treadmill exercise test and had no evidence of HF at the time of exercise testing. After a mean follow-up of 12.3 ± 7.4 years, 1902 individuals developed HF. When estimated fitness was considered as a binary variable (fit/unfit), the risk of HF was 91% higher for unfit individuals. CRF emerged as a stronger predictor of risk than traditional risk factors, including HTN, DM2, smoking, and sleep apnea. Each 1-MET increment in exercise capacity achieved was associated with a 19% reduction in risk for developing HF. When the cohort was stratified into CRF quintiles, HF risk derived from the fully adjusted model was 36% lower for the low-fit individuals compared to the least-fit (reference group) and declined progressively to 41% for the moderate-fit, 67% for the fit, and 76% for the high-fit, as depicted in the survival analysis curves (Figure 3). These findings suggest that CRF is inversely and independently associated with the incidence of HF in veterans referred for exercise testing. The 36% lower risk for HF observed in those with a low level of CRF (mean peak MET level: 6.0 ± 1.2) suggests that a relatively modest improvement in fitness would have a considerable impact on reducing the likelihood of HF later in life (55).

CRF AND THE INCIDENCE OF MACE

We have shown that increased CRF protects against the development of certain chronic illnesses such as HTN (12) and CKD (38). We (55) and others (56-58) have also reported an inverse association between CRF and the incidence of HF, myocardial infarction, and coronary revascularization (56,59-61), suggesting that increased CRF may protect against future cardiovascular events. To investigate this further, we assessed the association between CRF and the risk for MACE in a cohort of 20 590 veterans. MACE was defined as the initial occurrence of myocardial infarction (fatal and nonfatal), congestive HF, cerebrovascular accident (fatal and nonfatal), or coronary artery bypass graft surgery (62). All participants had no history of MACE or evidence of myocardial ischemia at the time of or before their exercise tolerance test. We formed CRF categories based on age-specific quintiles of exercise capacity achieved, defined the age-specific MET level associated with no risk for MACE (hazard ratio = 1.0), and formed 4 additional CRF categories based on METs achieved below (least-fit and low-fit) and above (moderately fit and highly fit) that level. Multivariate Cox models were applied to estimate hazard ratios and 95% CIs for mortality across fitness categories.

In the fully adjusted model, higher exercise capacity was inversely related to the risk for MACE. For every 1-MET increase in exercise capacity, the risk for MACE was 16% lower ($P < .001$). The adjusted risk of MACE across CRF categories declined progressively as exercise capacity increased. When compared with the least-fit individuals (reference group), the risk was 30% lower for the low-fit, 40% lower for the moderately fit, 57% lower for the fit, and 68% lower for the highly fit. The impact of CRF was similar for both black and white subjects and for those < 60 and ≥ 60 years. We also examined the risk for MACE below and above the age-specific MET threshold. The risk was progressively higher in the 2 CRF categories that included individuals with a peak MET level below the threshold. Specifically, the risk was 41% higher for individuals with an exercise capacity 1 to 2 METs below their respective age-specific MET threshold and 95% higher for those with an exercise capacity > 2 METs below the threshold. Conversely,

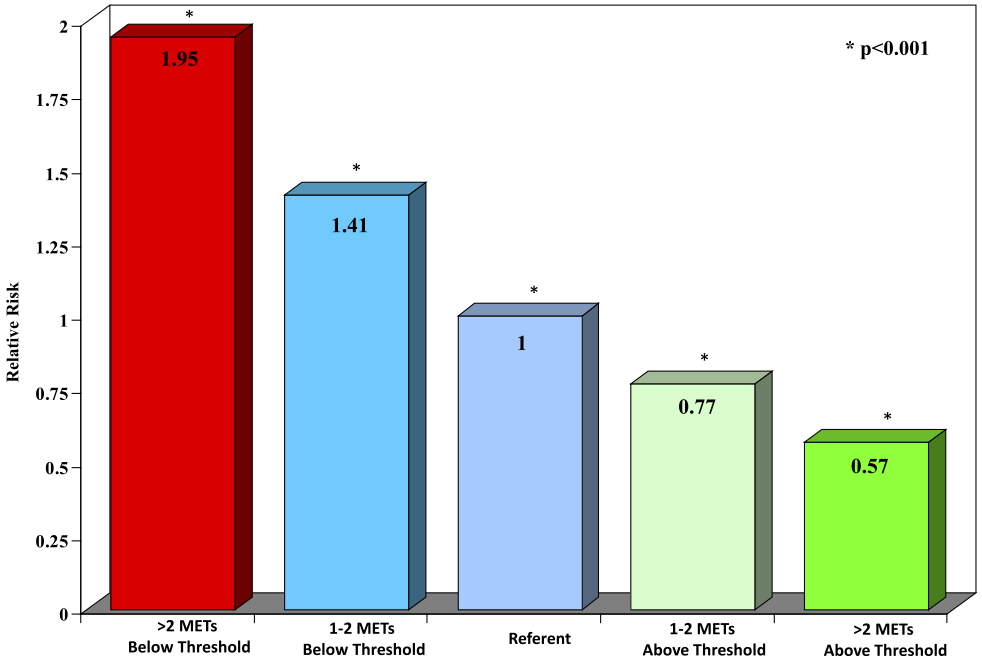

FIGURE 4. Risk for developing MACE according to exercise capacity below and above an age-specific MET threshold for risk. (62)

the risk was 23% lower for those with an exercise capacity 1 to 2 METs above the threshold and 43% lower for individuals with an exercise capacity >2 METs above the threshold (Figure 4).

Findings of prospective trials also support the protective role of CRF against MACE. In a post-hoc analysis of the Look AHEAD trial, an increase of ≥2 METs in fitness resulted in a 27% reduction in secondary end-points (adjusted HR 0.77, 95% CI: 0.61–0.96; $P=0.023$) (63). In the HF-ACTION study, exercise training in patients with congestive HF did not significantly reduce mortality, cardiovascular mortality, cardiovascular hospitalization, or HF hospitalization. However, on a pre-specified supplementary analysis adjusted for highly prognostic baseline characteristics, the exercise training group had a small but significant decrease in cardiovascular mortality or HF hospitalization (64). On a gender-based analysis of participants in HF-ACTION, women assigned to exercise training had a significant 26% reduction in the primary endpoint of all-cause mortality or hospitalization. This was not noted in men undergoing exercise training even though both men and women showed a significant increase in maximum oxygen uptake at 3 months (65). These findings suggest that overall, higher fitness independently protects against the occurrence of MACE.

CONCLUSIONS

Collectively, these data and related reports suggest that higher levels of CRF, generally estimated from peak or symptom-limited exercise test time/workload attained, are associated with a reduced risk of developing HTN, DM2, AF, CKD, HF, and MACE. This inverse association of lower incidence of DM2 with PA has also been noted against the diabetogenic effects of statins. Perhaps, William C. Roberts, MD, Editor of the *American Journal of Cardiology* summed it up best when he commented on the medicinal properties of exercise (66) as "*an agent with lipid-lowering, antihypertensive, positive inotropic, negative chronotropic, vasodilating, diuretic, anorexigenic, weight-reducing, cathartic, hypoglycemic, tranquilizing, hypnotic and anti-depressive qualities.*"

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