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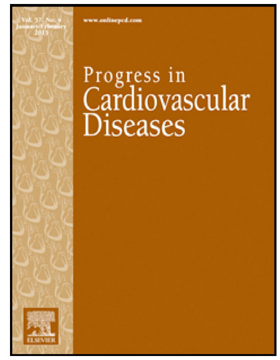

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Running Away from Cardiovascular Disease at The Right Speed: The Impact of Aerobic Physical Activity and Cardiorespiratory Fitness on Cardiovascular Disease Risk and Associated Subclinical Phenotypes

Short Title: Exercise, Cardiorespiratory Fitness, and Cardiovascular Disease Risk

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ABBREVIATIONS:

ACC: American College of Cardiology
AF: Atrial fibrillation
AHA: American Heart Association
ASCVD: Atherosclerotic cardiovascular disease
CAC: Coronary artery calcium
CARDIA: Coronary Artery Risk Development in Young Adults
CCTA: Coronary computed tomography angiography
CRF: Cardiorespiratory fitness
CV: Cardiovascular
CVD: Cardiovascular disease
EF: Ejection fraction
FRS: Framingham risk score
HF: Heart Failure
HFpEF: Heart Failure with preserved ejection fraction
HFrEF: Heart Failure with reduced ejection fraction
LA: Left atrial
LV: Left ventricular
MET: Metabolic equivalent
PA: Physical activity
RCTs: Randomized control trials
VO_{2max}: Maximal oxygen consumption
VO_{2peak}: Peak oxygen consumption
WOMAN: Women on the Move through Activity and Nutrition
WWF: Walking Women Follow-up

ABSTRACT

Higher levels of physical activity (PA) and cardiorespiratory fitness (CRF) are associated with lower risk of incident cardiovascular disease (CVD). However, the relationship of aerobic PA and CRF with risk of atherosclerotic CVD outcomes and heart failure (HF) seem to be distinct. Furthermore, recent studies have raised concerns of potential toxicity associated with extreme levels of aerobic exercise, with higher levels of coronary artery calcium and incident atrial fibrillation noted among individuals with very high PA levels. In contrast, the relationship between PA levels and measures of left ventricular structure and function and risk of HF is more linear. Thus, personalizing exercise levels to optimal doses may be key to achieving beneficial outcomes and preventing adverse CVD events among high risk individuals. In this report, we provide a comprehensive review of the literature on the associations of aerobic PA and CRF levels with risk of adverse CVD outcomes and the preceding subclinical cardiac phenotypes to better characterize the optimal exercise dose needed to favorably modify CVD risk.

Keywords: physical activity; fitness; prevention; coronary artery disease; heart failure; atrial fibrillation

INTRODUCTION

Physical activity (PA) and cardiorespiratory fitness (CRF) are important modifiable cardiovascular (CV) risk factors. Individuals who are sedentary have a higher risk of all-cause and CV disease (CVD)-related mortality as compared with their physically active counterparts.[1,2] Several studies have additionally demonstrated an inverse dose-response relationship between aerobic PA and incident CVD events, including atherosclerotic coronary artery disease (CAD) and heart failure (HF).[3-5] The favorable association between higher PA levels and CVD risk is thought to be mediated by traditional CVD risk factor modification, vascular conditioning, cardiac remodeling, and cardiomyocyte molecular adaptations.[6] Regular endurance exercise also protects against CVD through biochemical preconditioning against ischemic damage [7,8]. PA intensity is typically expressed as metabolic equivalents (METs) with 1 MET defined as the amount of energy expended while sitting at rest.[9] A number of modalities are utilized to gauge patient aerobic PA levels and information obtained from questionnaires,[10] accelerometers,[11] or pedometers[12] and is commonly stratified into light, moderate, vigorous, and very-vigorous PA, which correspond to absolute intensities of <3, ≥ 3 to <6, ≥ 6 to <9, and ≥ 9 METs, respectively.[13] However, a more accepted standard is relative intensity which represents a percentage of the individual's exercise or functional capacity, since a given MET load may correspond to highly varied relative intensities in younger versus older adults. Consequently, lower MET requirements may still place considerable stress on the CV system of unfit, older individuals and those with established CVD. Accordingly, vigorous PA is usually defined as ≥60% functional capacity, whereas moderate intensity PA approximates 40% to 59% functional capacity. [14]

Possibly more important than aerobic PA, CRF is a separate measure of physical wellness that captures the capacity of CV and respiratory systems to supply oxygen to skeletal muscles during progressive PA or incremental exercise to volitional fatigue.[15] Similar to PA levels, low levels of CRF are associated with higher overall mortality[16] and CVD, including both atherosclerotic CAD and HF.[17-19] These consistent findings prompted the American Heart Association (AHA) to release a scientific statement that builds the case for considering CRF, in addition to PA, as a clinical vital sign.[15,20] It is also important to note that low CRF is a distinct risk factor from low PA level as the relationship of CRF with CVD risk is different from the relationship of PA with CVD risk as demonstrated in the seminal meta-analysis by Williams.[21] The gold standard for CRF assessment is direct measurement of the highest attained oxygen consumption (VO_2) during cardiopulmonary exercise testing, and CRF is usually expressed as maximal oxygen consumption (VO_{2max}) in apparently healthy populations or peak oxygen consumption (VO_{2peak}) in patient populations.[22] Absolute VO_2 is generally expressed as liters of oxygen consumed per minute (l/min) or, in relative terms, as milliliters of oxygen consumed per kilogram of body weight per minute (ml/kg/min).[15,23] However, direct measurement of VO_{2max} or VO_{2peak} can be technically challenging, and predicted CRF derived from the highest attained work rate during graded, maximal or submaximal exercise protocols, is commonly used in large scale studies.[15]

A careful assessment of several epidemiologic studies reporting the consistent inverse association of PA and CRF with CVD risk reveals that the relationships with atherosclerotic CAD and HF risk are distinct. While the association with CAD risk is curvilinear, a more linear inverse relationship is observed with HF risk.[3,[illegible]] This observation is further substantiated by recent studies highlighting the association of extreme PA levels with accelerated subclinical coronary atherosclerosis and incident atrial fibrillation (AF) among endurance athletes. Therefore, personalizing exercise prescriptions with the goal of optimally augmenting PA and CRF levels in asymptomatic individuals is important. In this review, we discuss the associations of PA and CRF levels with CAD and HF risk along with the preceding subclinical cardiac phenotypes to better characterize the optimal exercise dose needed to optimize an individual's health trajectory.

Aerobic PA, CRF and CAD Risk

Substantial evidence accumulated primarily through comprehensive epidemiologic studies supports the inverse relationship of PA and CRF with CAD risk. In 1953, Morris and colleagues reported that CAD rates were ~50% lower among physically active British bus conductors (collecting tickets) as compared with British bus drivers who were habitually sedentary [24]. Subsequent observational studies over the past six decades have consistently shown that higher PA levels are independently associated with lower risk of CAD, across sex, race, geography, and socioeconomic strata. [21,25-32] This relationship is dose-dependent in a curvilinear fashion, with the greatest risk reduction achieved early in the dose-response curve. In a seminal meta-analysis by Sattelmair and colleagues, 150 and 300 minutes per week (min/week) of moderate intensity PA were associated with a 14% and 20% lower risk of CAD, respectively, as compared to a sedentary lifestyle (**Figure 1**).[3] People who were physically active at levels lower than the minimum recommended amount, that is, less than 150 min/week, also had a significantly lower risk of CAD. The association was stronger among women than men ($p = 0.03$). Importantly, subsequent benefits from PA doses beyond 300 min/week were only modest. These data suggest that transitioning from a completely sedentary lifestyle to even a modestly active one provides a significant reduction in CAD risk even at lower PA doses than commonly recommended, beyond which additional returns in CAD risk reduction are small. In fact, evidence indicates that regular physical movement confers health benefits. Recently, Arena et al. proposed a framework for PA discussion, with the focus on incrementally sitting less, taking more steps, and increasing time spent exercising, all of which are beneficial, both independently and synergistically **(Figure 2)** [33]. The illustration highlights the importance of knowing one's CRF, which will be discussed in subsequent sections.

Similar to PA, prospective observational studies with objective CRF assessment have demonstrated its inverse association with CAD risk [19,34-38]. In a cohort of middle aged men, higher CRF, as directly measured during treadmill exercise testing, was associated with lower risk of CAD, even after adjusting for traditional CVD risk factors [39]. In a large prospective cohort of >20,000 individuals from the Cooper Clinic, we previously reported that low CRF at midlife, estimated from treadmill time, was independently associated with a higher risk of CAD decades later, with a 10% higher risk for acute myocardial infarction for every 1-MET lower level of CRF achieved in men [19]. Recently, Tikkanen and colleagues analyzed a large cohort of >500,000 individuals and demonstrated that PA and CRF were inversely associated with atherosclerotic CVD (ASCVD), including individuals at high genetic risk for ASCVD [36]. Thus, 'at risk' individuals leading an active lifestyle and having high CRF are at a lower risk for ASCVD events compared to their sedentary and low-fit counterparts, respectively.

Aerobic PA, CRF, and Coronary Artery Calcification

Coronary artery calcium (CAC), a marker of subclinical coronary atherosclerosis, is a phenotype proximal to the development of atherosclerotic CAD.[40] Multiple studies have evaluated the predictive value of CAC score for incident CAD and have consistently reported a significant improvement in risk-discrimination and risk-reclassification indices beyond established risk assessment tools.[41-45] As per the American College of Cardiology (ACC)/AHA primary prevention guidelines, CAC scoring can be considered in asymptomatic individuals to aid CVD risk assessment.[46] Another commonly used diagnostic test to identify coronary atherosclerosis is coronary computed tomography angiography (CCTA), which in addition to evaluating the CAC score, also provides a detailed assessment of coronary artery anatomy.[47]

CAC in the General Population

Several cross-sectional studies over the past two decades have evaluated the association of PA with prevalent CAC in the general population (**Table 1A**). These studies have reported heterogenous observations with some reporting an inverse association with PA and CAC,[48,49] while others demonstrating no association between the two after adjustment for prevalent cardiovascular risk factors.[50-53]

Studies evaluating the association of CRF with CAC in the general population are summarized in **Table 1B**. An analysis of 2,373 participants of the CARDIA study demonstrated that high sex-specific CRF in young adulthood, measured as total time during maximal exercise testing using the Balke protocol had an independent inverse association with CAC presence after 15 years of follow up.[54] In a study of 5,341 healthy middle-aged women undergoing clinical examinations at the Cooper Clinic, CRF was estimated from maximal treadmill exercise testing using the Balke protocol and its association with CAC presence (score >0) and severity (score >100) was assessed.[55] Although women with high fitness (CRF quintiles 4 and 5) had a lower prevalence of CAC, this association was attenuated and no longer significant after adjustment for CVD risk factors.[55] In a subsequent study from the same cohort, Radford et al. reported that high CRF has an unadjusted inverse relationship with CAC score among healthy middle-aged men as well.[56] More recently, Kermott and colleagues reported the cross-sectional association of CRF, estimated using the standard Bruce protocol, with CAC in nearly 3,000 asymptomatic male participants of the Mayo Clinic Executive Health program.[57] The investigators found a U-shaped relationship between CRF and CAC such that individuals with high CRF (defined as functional capacity ≥130% of predicted) had a higher CAC burden despite having a more favorable CVD risk factor profile.[57] Collectively, these data suggest that PA and CRF likely have a J-shaped association with CAC burden.

The prognostic implications of these relationships were recently studied by Radford et al. and DeFina et al.[56,58] Radford et al. reported that among 8,245 asymptomatic men, CRF and CAC score were associated with CVD risk, but a 1-MET increase in CRF was associated with a decreased risk of CVD events (hazard ratio 0.89, 95% confidence interval 0.84-0.94) irrespective of CAC score at baseline.[56] DeFina and colleagues studied PA level and CAC among 21,758 asymptomatic men, and observed that men with ≥3000 MET-min/week of PA had a higher prevalence of CAC score ≥100 as compared with those accumulating less PA. CAC score retained its predictive value for all-cause and CVD-related death across all PA levels and importantly, the risk of death among those with PA ≥3000 MET-min/week and CAC score ≥100 (mean score 800) was similar to those with PA <1500 MET-min/week (hazard ratio 0.77, 95% confidence interval 0.52-1.15).[58] These findings suggest that highly active individuals with high CAC burden or 'hearts of stone' can generally continue to run safely, provided they remain asymptomatic, perhaps due to lower risk of calcified plaque rupture compared to sedentary individuals.[59]

CAC in Endurance Athletes

Atherosclerotic CAD is the most common cause of death during exercise among athletes older than 35 years.[60,61] There is a paucity of studies evaluating the association of PA and CRF with CAC among strength athletes. Two small studies have reported that the prevalence of CAC among retired American football players is similar to the general population,[62] and players in linemen positions tend to have higher CAC than non-linemen.[63]

The relationship of high-volume vigorous PA and high CRF with CAC among endurance athletes has been an area of considerable research interest and controversy in recent years. Studies evaluating evidence of subclinical coronary atherosclerosis among endurance athletes have reported CAC prevalence ranging from 20% to 70%.[64-66] Merghani and colleagues have recently shown that middle-aged masters endurance athletes with a low atherosclerotic CAD risk profile have similar CAC prevalence (score >0 or >70th percentile) as compared with sedentary controls.[67] Although female athletes had a similar plaque prevalence (>50% luminal stenosis) on CCTA as their sedentary counterparts, male athletes demonstrated a higher plaque prevalence (≥1 plaque) as compared with their sedentary counterparts. Moreover, athletes and controls had predominantly calcified and mixed atherosclerotic plaque, respectively.[67]

In contrast with Merghani et al., two recent studies have focused on the determinants of subclinical atherosclerosis among athletes alone.[66,68] Aengevaeren et al. studied participants of the Measuring Athlete's Risk of Cardiovascular Events cohort and examined the relationship between lifelong exercise volume, characterized as estimated MET-minutes per week, and coronary atherosclerosis, measured using CAC score and CCTA, among middle-aged athletes engaged in competitive or recreational leisure sports.[66] Investigators noted that 53% of study participants had prevalent CAC on imaging and that athletes with high lifelong exercise volume (>2000 MET-minutes per week) had a higher CAC score, CAC area, and nearly a 3-fold higher CAC and plaque prevalence when compared with participants with low lifelong exercise volume (<1000 MET-minutes per week).[66] High lifelong exercise volume and very-vigorous-intensity exercise (≥9 METs) were independently associated with CAC and coronary plaque presence.[66] Interestingly, among participants with prevalent atherosclerotic plaque on CCTA, those with high lifelong exercise volume had a lower prevalence of mixed plaque and more frequently had only calcified plaque when compared with those in the low lifelong exercise volume (<1000 MET-minutes per week) group.[66] These findings are qualitatively similar to the observations made by Merghani et al. More recently, Jafar and colleagues reported that 30 marathon runners (70% ultra-marathon runners) had a higher prevalence of CAC scores >0, >100, and above 50th percentile for age and sex (73%, 33%, and 70%, respectively) as compared with 26 short-distance runners (21%, 12%, and 19%, respectively).[68]

The exact mechanisms underlying the relationship of PA volume and CRF with coronary plaque formation and calcification among athletes remain elusive. It is plausible that high volume, vigorous-intensity exercise training over the long-term can lead to coronary endothelial damage that propagates the atherosclerotic plaque formation cascade in these vessels. This plaque in turn calcifies in response to repeated injurious stimuli and stabilizes over time due to heavy calcification.[69] This hypothesis is supported by others and despite the higher coronary plaque volume and prevalence in endurance athletes, the benign nature of these high-density plaques may portend a more favorable CV prognosis as compared with sedentary individuals of the general population.[66,70] However, these observations must be considered in light of the inherent limitations of cross-sectional studies given the inability to evaluate temporal relationships. Additionally, the low incidence rate of CVD outcomes in this study population makes it challenging to ascertain the prognostic significance of subclinical atherosclerosis among athletes. Analyses delineating risk of plaque progression versus risk of plaque rupture could help better elucidate the phenomenon of greater plaque burden but lower risk of adverse CV events among endurance athletes. Future studies focusing on subclinical atherosclerosis among strength athletes, such as American football players and weightlifters, are also needed.

Aerobic PA, CRF, and HF Risk

The association of PA and CRF with HF risk appears to be distinct and perhaps stronger as compared to the relation with atherosclerotic CAD. Similar to CAD, PA has an inverse, graded relationship with HF risk, that is consistent across age, race, sex, and geographical subgroups. However, in contrast to the curvilinear association with CAD, the relationship between PA and HF is more linear, and substantial reduction in HF risk can be observed with PA levels beyond the guideline recommended doses for atherosclerotic CAD prevention (**Figure 3**). [4,19,71]

Furthermore, HF risk associated with low PA predominantly manifests as HF with preserved ejection fraction (EF; HFpEF). In a pooled cohort analysis from the Women's Health Initiative, the Cardiovascular Health Study, and the MESA cohorts, we showed that lower leisure-time PA was associated with higher risk of HFpEF in a dose dependent fashion, but not HF with reduced ejection fraction (HFrEF) (**Figure 4**).[72] The differences in the association of PA with HFrEF versus HFpEF reflect the differences in mechanisms through which PA lowers HF risk. The association of PA with HFrEF is similar to that with CAD risk. It is possible that PA lowers HFrEF risk by reducing CAD risk factor burden and CAD progression. On the contrary, the association of PA with HFpEF risk is likely related to improvements in the key pathobiological determinants of HFpEF, including diastolic function, left ventricular compliance, systemic inflammation, visceral adiposity, and skeletal muscle oxygen utilization.[72] The importance of this observation lies in the fact that HFpEF will soon become the dominant phenotype of HF, partly due to an older, more obese population,[73-75] and there is a paucity of therapeutic options available for this HF subtype.[76] In the last decade, several observational studies characterized the relationship between objective measures of CRF and incident HF. CRF is inversely associated with risk of HF, independent of HF risk factors (**Table 2**). Notably low CRF at midlife is more strongly associated with risk of HF than risk of ASCVD, regardless of BMI.[5,19,77-80]

Aerobic PA, CRF, and Left Ventricular Structure and Function

Parameters of left ventricular (LV) structure and function provide meaningful prognostic information in asymptomatic individuals. Impaired LV systolic and diastolic dysfunction, LV mass, and LV concentricity are epidemiologically associated with higher risk of mortality and incident HF.[81-86] Importantly, these phenotypes represent intermediate stages in the progression to clinical HF and changes in these parameters provide insight into the mechanisms by which regular PA and improved CRF may reduce subsequent HF risk.

Cardiac Remodeling in the General Population

Several cross-sectional studies have linked PA and CRF to abnormalities in cardiac structure and function in the general population (**Table 3**). In an analysis from the Cooper Clinic, we showed that low CRF was strongly associated with higher LV filling pressure and impairment in diastolic filling.[87] On the other hand, CRF was not associated with reduced systolic function quantified by EF. However, in a cross-sectional analysis using the Dallas Heart Study, we observed an inverse, independent association between CRF at middle age and peak systolic circumferential strain.[88] Notably, impairment in diastolic filling and peak systolic circumferential strain are abnormalities associated with HFpEF.[89,90] Longitudinal analysis using data from the CARDIA cohort reinforced the notion that low CRF in young adulthood was independently associated with a heightened risk of impaired diastolic filling ~20 years later.[87,88,91] It is important to note that higher level of PA has been shown to be independently associated with greater right ventricular (RV) mass and volume among participants of the MESA study.[92] The prognostic implications of this association in the general population need to be further evaluated.

Furthermore, lifetime PA may favorably modify cardiac remodeling over time. Small observational cohort studies have shown that at least 30 minutes of committed or competitive exercise, 4-5 days a week over a lifetime, is associated with increased LV compliance, greater LV distensibility, and improved ventricular-arterial coupling,[93,94] intermediate phenotypes of HFpEF associated with aging.[89,95] Moreover, a temporal decline in CRF is associated with impaired (or deteriorating) subclinical systolic function and elevated diastolic pressures [91].

However, more studies are needed to determine which types of PA and muscle training may induce positive myocardial remodeling.

Cardiac Remodeling in Endurance Athletes

Athletes undergo regular exposure to extreme exercise training and competition compared to individuals in the general population, and therefore have distinct remodeling patterns that warrant exploration. Among Italian cohorts of elite athletes, Pellicia et al. reported that in contrast to healthy individuals, athletes may have greater LV wall thickness (≥13 mm), larger LV end diastolic diameters, and marked LV hypertrophy, findings that would be considered pathological in the general population.[96,97] Although most studies report preserved LV systolic function among athletes,[98] a longitudinal study reported that 11% had resting subclinical systolic dysfunction (EF <52%).[99] Increased LV chamber size with a sufficient cardiac output may be sufficient to meet the body's metabolic demands during exercise despite a slightly reduced EF. Furthermore, Scharhag et al. have shown that endurance exercise training was associated with increases in RV mass and volume, which was similar to what was observed with the LV mass and volume.[100] More recently, Abdullah et al. have demonstrated that a lifelong history of consistent PA, with dose ranging from sedentary to competitive marathon running, was not associated with focal myocardial fibrosis on cardiac MRI.[101] Nevertheless, additional investigation is needed to clarify the long-term effects of athletic exercise on systolic function with LV and RV remodeling. Other studies report an association between athletic training and enhanced early diastolic filling as measured by tissue doppler and E-wave velocity, an important positive LV adaption that allows for augmentation of stroke volume during exercise at high heart rates.[102-104]

Given that most of the relevant reports are based on cross-sectional analyses, the clinical implications of these remodeling patterns are less established. Historically, changes in LV structure and function associated with athletic training were thought to be pathological. However, a recent longitudinal study of Italian Olympic athletes showed that these remodeling patterns were not associated with subsequent systolic dysfunction or CVD.[105] Little is known on how these remodeling patterns evolve temporally, whether the associated serial changes occur in a dose-dependent fashion in response to vigorous exercise, or whether certain types of exercise induce distinct remodeling patterns in the athletic heart, all of which represent areas for further investigation. Collectively, the limited longitudinal evidence available suggests that the remodeling patterns associated with regular high-volume, high-intensity PA reflect beneficial physiologic adaptations rather than intermediate phenotypes at risk for CVD, with AF as a possible exception.

Role of Aerobic PA and CRF in Modifying CAD and HF Risk

The association of PA and CRF with future CAD and HF risk among asymptomatic individuals sparked the hypothesis that increases in these variables may decrease the risk of subsequent adverse CV events. Indeed, a prospective observational study of older men in Britain showed that increases in PA were associated with lower risk of non-fatal CAD events.[106] In a sub-analysis of the Cooper Clinic cohort, we showed that temporal increases in CRF were associated with lower risk of HF in older age. Similarly, in both the Framingham and Atherosclerosis Risk in Communities studies, interim increases in PA were associated with a lower subsequent risk of HF.[107,108]

In the landmark Look AHEAD trial, > 5,000 individuals with diabetes were randomized to intensive lifestyle changes, including unsupervised exercise training, versus usual care to evaluate the impact of lifestyle changes on CVD risk.[109] Unfortunately, the trial failed to demonstrate a significant difference between treatment arms for the risk of primary atherosclerotic cardiovascular as well as HF events. However, there were fewer HF events in the intensive lifestyle treatment arm. Several possible explanations for these findings merit consideration. Although individuals in the treatment arm were randomized to a more physically active lifestyle, major progress in weight loss and improvements in CRF observed at the beginning of the intervention largely regressed to the mean at the end of the study. Furthermore, it is logistically challenging to confirm adherence to unsupervised exercise recommendations in a large cohort of individuals over a prolonged period of time, an important limitation in ensuring the treatment arm received the designated intervention. Sustained increases in CRF may be necessary to modify downstream risk of CVD and especially HF given the robust dose response relationship between PA and HF risk. More large-scale randomized controlled trials (RCTs) are needed to assess the effect of moderate-to-vigorous exercise intensities, in varying doses (MET-min/week), on the risk of CVD and HF.

There are several potential mechanisms by which higher CRF and longitudinal improvement in CRF levels may modify the risk of atherosclerotic CVD and HF. First, higher CRF levels are associated with improvements in the CVD risk factor profile, which may decrease the subsequent risk of CVD. Furthermore, as discussed above, higher CRF levels are also associated with a direct salutary effect on cardiac structure and function, which may also favorably modify the downstream risk of HF. In aggregate, the pleotropic indirect and direct favorable effects of CRF are key to modifying future risk of CVD (**Figure 5**).

Aerobic PA, CRF and Atrial Fibrillation Risk

Atrial fibrillation (AF) comprises a substantial portion of CVD worldwide [110] and unlike CAD and HF, the associations between PA, exercise patterns, and risk of AF are complex and vary by nature of the study population, intensity of PA, and overall levels of PA.

Association between PA and Risk of AF in the General Population and Athletes

Several cohort investigations have evaluated the association between self-reported PA and risk of AF in community-dwelling, non-athlete populations with inconsistent patterns of association reported across studies, with some showing no association and others demonstrating a reverse J or U-shaped relation.[111-121] In a recent dose-response meta-analysis that pooled 19 cohort studies with over 30,000 incident AF events, Ricci et al reported a non-linear, J-shaped association between dose of PA and risk of AF with a modest but statistically significant reduction in AF risk up to PA levels of 1200 MET-min/week and no association between the two at doses of PA above this threshold.[122] Similar patterns of association have also been reported in other cohort studies and pooled analysis.[123] In contrast, at extremely high levels of PA, a non-significant trend towards higher risk of AF is noted in some cohort studies among community-dwelling individuals, highlighting the potential role of extreme levels of PA in development of AF.[120]

The potential adverse effects of extremely high levels of PA in the development of AF is further characterized in cohorts of elite athletes with studies demonstrating a 2- to 4-fold higher risk of AF in such individuals as compared with the general population.[124] The higher risk of AF among endurance athletes, in particular, is associated with long-term exposure to high-volume, high-intensity physical activity regimens. For example, in a cohort of skiers, Myrstad et al. showed that the risk of AF was heightened among skiers who completed a greater number of races and/or those who had faster finishing times. Furthermore, cumulative years of endurance exercise also have prognostic significance, with a 4-fold increased risk of incident AF observed above the threshold of 2000 hours of lifetime endurance training.[114,125-129]

There are multiple mechanisms by which PA may modify risk of AF. Mild to moderate intensity PA has a positive influence on CVD risk factors such as hypertension, diabetes, obesity, and dyslipidemia, and likely reduces AF risk via optimization of risk factor burden.[6,75] In contrast, long term vigorous-to-high intensity endurance exercise results in physiological changes to the CV system which manifest as chamber dilatation, lower resting heart rate, and increased vagal tone. Higher lifetime exposure to endurance training is associated with left atrial (LA) enlargement, with greater exposure leading to higher LA dimensions.[130,131] Studies have reported an association between LA dimensions and risk of AF among cross-country skiers and marathon runners, such that athletes with larger LA dimensions were more likely to develop AF.[132,133] Similar mechanical changes in LA volume and function have also been reported with short duration intensive exercise training, suggesting that LA remodeling in response to prolonged vigorous exercise may contribute to AF risk.[134,135] Moreover, heightened vagal tone has been implicated in the development AF. In a cohort of endurance runners, higher lifetime training hours were associated with greater vagal tone and higher burden of atrial ectopy, which has a robust association with incident AF.[136,137] Mechanistically, pronounced vagal tone shortens the atrial refractory period, which can render the atria susceptible to micro-reentrant circuits.[138] Future studies are needed to further characterize the definitive causal pathways linking prolonged vigorous exercise and incident AF.

Despite the increased risk of AF among athletes with higher lifetime exposure to endurance exercise, the downstream risk of CVD complications such as stroke and HF is lower among those with higher levels of exercise prior to AF development.[129,139] Accordingly, higher levels of pre-morbid exercise may have a legacy effect on AF related adverse CVD outcomes and thus, athletes and individuals with higher levels of lifetime PA may continue to reap CV benefits of exercise even after development of AF.

Association Between CRF and Risk of AF

Similar to self-reported PA, studies evaluating the association between CRF and AF have yielded varied results. In a cohort of Finnish middle-aged men, Khan et al. reported a nonlinear association between CRF as determined by cycle ergometer testing and AF. In the adjusted analysis, fitness levels between 6 to 9 METs afforded the greatest benefit in AF risk reduction; however, at 10 to 12 METs, there was an increased risk of AF.[140] A similar pattern was observed in a cohort of 1.1 million Swedish men, with a U-shaped relationship between CRF and risk of AF.[141] In contrast, studies from the US demonstrated a more linear association between higher CRF and lower risk of AF among referred individuals who underwent clinically indicated exercise stress testing.[140,142-144] These discordant findings may be related to differences in study populations, with lower baseline CRF levels, older age, higher co-morbidity burden, clinically referred participants, and inclusion of both men and women in the US versus European studies. Future studies are needed to further clarify how higher levels of CRF may modify left atrial structure, function, and AF risk in both the general population and in athletes.

Aerobic PA, CRF and Cardiovascular Disease Phenotypes

The association of PA and CRF with multiple CVD outcomes (CAD, HF, and AF) within the same cohort has been evaluated in a few studies. We have shown that CRF had a stronger association with HF risk than CAD risk among healthy, middle-aged adults of the Cooper Clinic cohort.[19] Similar observations were reported by Khan and colleagues who studied Finnish participants of the Kuopio Ischemic Heart Disease study.[145] In the same cohort, Khan et al. have demonstrated a J-shaped association between CRF and AF risk.[140] These findings have now been corroborated in larger study populations by reports from the young Swedish men cohort[141] and the Henry Ford exercise testing project.[77,146]

Current Guidelines for Aerobic PA and their Implications in Prevention of CVD

The PA guidelines for Americans were updated by the US Department of Health and Human Services in 2018.[147] These guidelines recommend that all healthy adults should engage in at least 150 to 300 minutes of moderate-intensity aerobic exercise (40% to 59% functional capacity or 3 to 5.9 METs) each week, or 75 to 150 minutes of vigorous-intensity aerobic PA (≥60% functional capacity or ≥6 METs), or an equivalent combination thereof.[147] The minimal weekly PA dose of 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic activity has also been recommended by the ACC and AHA in the 2019 primary prevention guidelines.[148] These guidelines suggest that the inverse, dose-response relationship between the amount of moderate-to-vigorous PA and incident atherosclerotic CAD risk is curvilinear (**Figure 6**).[148] The maximum benefit for CAD prevention is afforded at the transition between little or no PA to moderate amounts and beyond 300 minutes of moderate-intensity or 150 minutes of vigorous-intensity PA per week the ASCVD risk reduction benefit is diminished.[148] Furthermore, the greatest benefit for reductions in risk of AF are also achieved at guideline recommended doses of PA (**Figure 6**). Additionally, in our prior running studies, maximal benefits were obtained at relatively low doses of vigorous-to-high-intensity PA, with plateauing and potential loss of benefit at very high doses.[149,150] Similarly, Wen et al. reported that the all-cause mortality reduction associated with vigorous PA leveled-off beyond 35-40 minutes of daily exercise.[2] Importantly, the ACC/AHA primary prevention guidelines acknowledge that the specific PA dose recommendations for HF prevention are likely to be different because the relation between increasing PA level and incident HF risk is linear.[148] Thus, exercise doses beyond 300 minutes of moderate-intensity or 150 minutes of vigorous-intensity PA per week might offer selective HF prevention benefits with only modest incremental effects on CAD risk (**Figure 6**).

Conclusion

In summary, regular endurance exercise and maintaining higher CRF and aerobic PA levels represent an important potential strategy to reduce risk of CVD, but maximal effectiveness will require far more proactive, comprehensive lifestyle-based preventive interventions for CVD. During the past 50 years, our understanding of how aerobic PA and CRF modify risk of CVD has grown substantially. The benefits of endurance exercise as a preventative strategy have robust epidemiological support; however, more large scale RCTs are needed to inform our practice, the goal being to prescribe exercise as we prescribe medicine, targeting those patient subsets that will derive the greatest benefit, detailing the dose, type of exercise, and frequency. The benefits of greater doses of aerobic PA and CRF appear to be more pronounced for HF and plateau for CAD at the current guideline recommended levels. On the other hand, the harmful effects of vigorous-to-high intensity endurance training on accelerating AF risk must be considered. At a population level, more vigorous promotion of regular PA is needed to combat the current physical inactivity pandemic in the US and worldwide.[151]

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Declaration of conflicting interests

The authors declare that there is no conflict of interest.

Author contributions

Anurag Mehta: conceptualization, writing – original draft, Nitin Kondamudi: writing – original draft, Jari A. Laukkanen: writing – review and editing; Ulrik Wisloff: review and editing, Barry A. Franklin: review and editing, Ross Arena: review and editing, Ambarish Pandey: conceptualization, writing – original draft, and Carl J. Lavie: conceptualization, writing – original draft.

Table 1 Association of Physical Activity or Cardiorespiratory Fitness with Subclinical Coronary Atherosclerosis Among the General Population

Study, year	Location	Population characteristics	Traditional risk factors measured	Physical Activity/ Cardiorespiratory Fitness measurement	CAC imaging modality	CAC categories	Association
A. Physical Activity and CAC among the General Population							
Taylor, 2002 [50]	USA, Single-center	N=630 42 years (mean) 18% Female	BMI HDL cholesterol LDL cholesterol Insulin level	Baecke physical activity Index	EBCT	Absent CAC or CAC score >0	Baecke physical activity Index was not associated with CAC in

							both men and women
Desai, 2004 [48]	USA, Single-center	N=779 55 years (mean) 33% Female	Age Dyslipidemia Family history of premature CVD Hypertension Obesity Tobacco status	Self-reported leisure-time PA stratified into three categories: Sedentary (no PA, referent) Moderate-duration PA (<30 minutes 1 to 2 times/week) Long-duration PA (>30 minutes, ≥3 times/week)	EBCT	Advanced CAC (≥ or < 75th age- and sex-specific percentile) Absent CAC or CAC score >0	Long-duration PA: Men OR 0.54, 95% CI 0.32-0.93 Women OR 0.39, 95% CI 0.19-0.78 Men OR 0.68, 95% CI 0.40-1.16 Women OR 0.65, 95% CI 0.38-1.19
Storti, 2010 [51]	USA, Single-center	WOMAN N=173 57 years (mean) WWF N=121 74 years (mean) 100% Female	Age BMI Current hormone therapy use Systolic BP Total Cholesterol	Number of Steps measured using a pedometer for 7 days: Low PA level (quartile 1) High PA level (quartile 4 – referent group)	EBCT	Absent CAC or CAC score >0	WOMAN Low PA level not associated with CAC WWF Low PA level OR 1.31, 95% CI 0.99-1.73
Kulinski, 2016 [52]	USA, Single-center	N=2,031	Age Sex Ethnicity	Moderate-to-vigorous physical	MDCT	CAC score >10 or	OR 0.99, 95% CI 0.94-1.04

			BMI Hypertension Diabetes Total cholesterol HDL-cholesterol Statin use Smoking Income Education Marital Status Employment	activity (>1,500 accelerometer counts per minute) Sedentary Time (<100 accelerometer counts per minute)		score <10	OR 1.12, 95% CI 1.02-1.23
Delaney, 2013 [49]	USA, Multi-center	N=5,656 61 years (mean) 53% Female 41% White 36% Black 22% Hispanic 12% Asian	Age Alcohol use BMI Diabetes Dyslipidemia Education Ethnicity Family history of MI Gender Hypertension Income Tobacco use	Self-reported PA assessed using the Typical Week Physical Activity Survey MET-minutes per week of PA was calculated from reported PA levels in the survey	EBCT or MDCT	Incident CAC (CAC score >0 on follow-up among those with 0 score at baseline) Log-transformed CAC progression (increase in score by 25 Agatston units)	Vigorous PA and incident CAC: RR 0.97, 95% CI 0.94-1.00 Sedentary behavior and CAC progression RR 0.027, 95% CI 0.002-0.052
Laddu, 2017 [53]	USA, Multi-center	N=3,175 25 years (mean) 57% Female	Age BMI Gender Diabetes Dyslipidemia	Self-reported leisure-time PA assessed using CARDIA Physical	MDCT	Absent CAC or CAC score >0	Meeting PA guidelines: OR 1.00, 95% CI

		53% White 47% Black	Ethnicity Education Hypertension Tobacco	Activity History questionnaire: Total PA score (Exercise Units) calculated Participants stratified into 3 categories based on guideline-recommended PA: Below guideline Meeting guideline 3-times guideline			0.80-1.15 3-times PA guidelines: OR 1.27, 95% CI 0.95-1.70
B. Cardiorespiratory Fitness and CAC among the General Population							
Lee, 2009 [54]	USA, Multi-center	N=2,373 24 years (mean) 52% Female 58% White	Age Alcohol use Anti-hypertensive medications Diabetes Fasting Insulin Gender Education Ethnicity Systolic Blood Pressure Tobacco Use Waist girth	Maximal treadmill exercise test using Balke protocol and total endurance time used as index of aerobic power. Stratification using sex-specific quartiles: Low fit (quartile 1 - referent) Moderate fit (quartiles 2 and 3) High fit (quartile 4)	EBCT and MDCT	Absent CAC or CAC score >0	Moderate fit OR 0.80, 95% CI 0.56-1.16 High fit OR 0.59, 95% CI 0.36-0.97

Sung, 2012 [152]	South Korea, Single-center	N=8,565 51 years (mean) 100% Men	Age Hypertension Diabetes Smoking Hemoglobin A1c Lipid profile C-reactive protein BMI Exercise habits	Treadmill exercise testing using modified Bruce protocol: Stratification by maximum oxygen consumption quartiles (quartile 1 referent)	MDCT	Advanced CAC (≥ 75th age-specific percentile)	Quartile 2 OR 0.83, 95% CI 0.68-0.99 Quartile 3 OR 0.74, 95% CI 0.62-0.90 Quartile 4 OR 0.60, 95% CI 0.48-0.73
DeFina, 2014 [55]	USA, Single-center	N=5,341 52 years (mean) 100% Females	Age BMI Diabetes Hyperlipidemia Hypertension Family History of CAD Smoking History	Maximal treadmill exercise test using Balke protocol: Stratification using maximal treadmill time quintiles: Unfit (quintile 1 - referent) Moderate fit (quintiles 2 and 3) High fit (quintile 4 and 5)	EBCT	Absent CAC or CAC score >0 CAC score ≥ 100 or score <100	Not significant for moderate or high fit Not significant for moderate or high fit
Ekblom-Bak, 2017 [153]	Sweden, Single-center	N=678 50-65 years age 52% Female	Age Family history of CVD Education Metabolic Syndrome Psychological stress	Maximal oxygen uptake using submaximal cycle ergometer testing: stratification using sex-	MDCT	CAC score ≥ 100 or score <100	High fitness (tertile 3) OR 0.47, 95% CI 0.23-0.96 OR 0.50, 95% CI

			Tobacco use	specific tertiles Moderate-to-vigorous PA and sedentary time using hip-worn accelerometers: proportion of daily wear time			0.24-1.04 (adjustment for sedentary and moderate-to-vigorous PA time)
Kermott, 2019 [57]	USA, Single-center	N=2946 52 years (mean) 100% Male	Age Race Diabetes Hypertension Blood pressure Smoking Total cholesterol HDL-cholesterol Family history of CVD BMI	Functional aerobic capacity (achieved METs divided by predicted METs based on age and sex) measured using the standard Bruce protocol Functional aerobic capacity stratified as ≤69%, 70-99%, 100-129%, and ≥130%	EBCT or MDCT	Median CAC [25th – 75th percentile] score	Functional aerobic capacity categories ≤69%: 21 [1-125] 70-99%: 4 [0-60] 100-129%: 2 [0-59] ≥130%: 18 [0-129]

Abbreviations: PA: physical activity, MI: myocardial infarction, BMI: body mass index, BP: blood pressure, LDL: low density lipoprotein, HDL: high density lipoprotein, CVD: cardiovascular disease, EBCT: electron beam computed tomography, MDCT: multi-detector computed tomography, RR: risk ratio, OR: odds ratio, CI: confidence interval

Table 2 - Cardiorespiratory Fitness and Heart Failure Risk Across Different Cohorts

Study Cohort	Number of Participants	Male (%)	Number of HF events	CRF Categories	Hazard Ratio for Adjusted Model [95% Confidence Interval]
UK Biobank 2019 [154]	374,493	47	66	Highest CRF category quartile 4 (mean METs 12.6) Lowest CRF category quartile 1 (mean METs 4.9)	3.52 [1.86-6.67] and 6.05 [2.92-12.5] for lowest CRF vs. highest CRF category among those with high grip strength and low grip strength respectively
US Veterans 2019 [5]	20,254	100	8987	Highest CRF category (mean METs 11.2) Lowest CRF category (mean METs 4.5)	0.37 [0.30-0.47], 0.37 [0.28-0.40], 0.27 [0.22-0.34] for highest CRF vs. lowest CRF category among those normal weight, overweight, and obese respectively
FIT Project 2017 [77]	66,329	54	4,652	Highest CRF category greater than 12 METs Lowest CRF category less than 6 METs	0.19 [0.14-0.29], for highest CRF vs. lowest CRF category
Young Swedish Men 2017 [35]	1,226,623	100	7656	Highest CRF category (stanine score 7-9) Lowest CRF category (stanine score 1-3)	1.60 [1.44-1.77], for lowest CRF vs. highest CRF category

Finnish Men 2017 [78]	2,089	100	221	Highest CRF category quartile 4 of CRF measured by VO2 Lowest CRF category quartile 1 of CRF measured by VO2	0.49 [0.30-0.80] for highest CRF vs. lowest CRF category
US Veterans 2017 [79]	21,080	100	1902	Highest CRF category greater than 80% predicted CRF Lowest CRF category less than or equal to 20% predicted CRF	1.91 [1.74-2.09] for low fitness vs. fit category
Finnish Men 2013 [80]	1873	100	152	Highest CRF category quartile 4 of CRF (VO2 35.4-65.4 mL/kg/min) Lowest CRF category quartile 1 of CRF (VO2 25.7-30.4 mL/kg/min)	0.47 [0.25-0.90] for highest CRF vs. lowest CRF category
Cooper Center Longitudinal Study 2013 [19]	20,642	79	1051	Highest CRF category quintile 1 Lowest CRF category quintile 4 and 5	Men: 0.31 [0.24-0.41] Women:0.38 [0.20-0.71] for highest CRF vs. lowest CRF category
Abbreviations: HF: Heart failure; CRF: Cardiorespiratory fitness levels; MET: Metabolic Equivalent Task: VO2; Maximal oxygen uptake					

Table 3 – Association between Cardiorespiratory Fitness & Abnormalities in Cardiac Structure and Function

Study Cohort	Study Design	Number of Participants	Male (%)	CRF Categories	LV Structure and Function Outcome

FAT associated CardiOvasculaR dysfunction (FATCOR) 2019 [155]	Cross-Sectional	469	40	Highest CRF category designated as fit by VO2 Lowest CRF category designated as unfit by VO2	High fitness independently associated with higher (more negative) GLS in obese patients
Coronary Artery Risk Development in Young Adults (CARDIA) 2017 [91]	Longitudinal	3,433	43	Highest CRF category tertile 3 Lowest CRF category tertile 1	Low fitness independently associated with greater downstream risk of impaired contractility (more negative GLS) and high diastolic pressures (elevated E/e')
Dallas Heart Study (DHS) 2017 [88]	Cross-Sectional	1,617	42	Highest CRF category quartile 4 Lowest CRF category quartile 1	Low fitness independently associated with worse (more negative) Ecc
Cooper Center Longitudinal Study (CCLS) 2014 [87]	Cross-Sectional	2,934	57	Highest CRF category quartile 4 Lowest CRF category quartile 1	Higher fitness independently associated with larger LA volume, larger LVEDV, and smaller LV wall thickness

Abbreviations: HF: Heart failure; CRF: Cardiorespiratory fitness levels; LV: Left ventricular; VO2: Maximal oxygen uptake; GLS: Global longitudinal strain; Ecc: Peak midwall systolic circumferential strain; LA: Left atrial; LVEDV: Left ventricular end diastolic volume, E/e' measured by transthoracic echocardiography

Figure 1 - Relative Risk of Coronary Heart Disease by Doses of Leisure-time Physical Activity (Reproduced from Sattelmair, et al. Circulation 2012 with permission from the publishers, **Reference 3**) Generalized least squares (GLST) regression spline (smoothed fit) models with 95% confidence intervals (CIs). CHD indicates coronary heart disease; LTPA, leisure-time physical activity

Figure 2 - New Framework for Assessing and Promoting Increased Physical Movement. **(**Reproduced from Arena, et al. 2018 with permission from the publishers, **Reference 32)**

Figure 3 - Dose-response Association Between Physical Activity and Heart Failure Risk. The graph shows spline (smoothed fit) and 95% confidence interval of pooled relative risk of heart failure by metabolic equivalent (MET) – min/week (Reproduced from Pandey, et al. Circulation 2016 with permission from the publishers, **Reference 4**)

Figure 4 - Association Between Increasing Levels of Leisure-Time Physical Activity and Risk of Different Heart Failure Phenotypes. HFpEF – heart failure with preserved ejection fraction; HFrEF – heart failure with reduced ejection fraction; MET – metabolic equivalent task; PA – physical activity (Reproduced from Pandey, et al. JACC 2018 with permission from the publishers, **Reference 74**)

Figure 5 - Association of cardiorespiratory fitness with risk of acute myocardial infarction and heart failure. MI - myocardial infarction; HFrEF – heart failure with reduced ejection fraction; HFpEF – heart failure with preserved ejection fraction

Figure 6 – Association of physical activity with risk of coronary artery disease, heart failure, and atrial fibrillation. METS – metabolic equivalents

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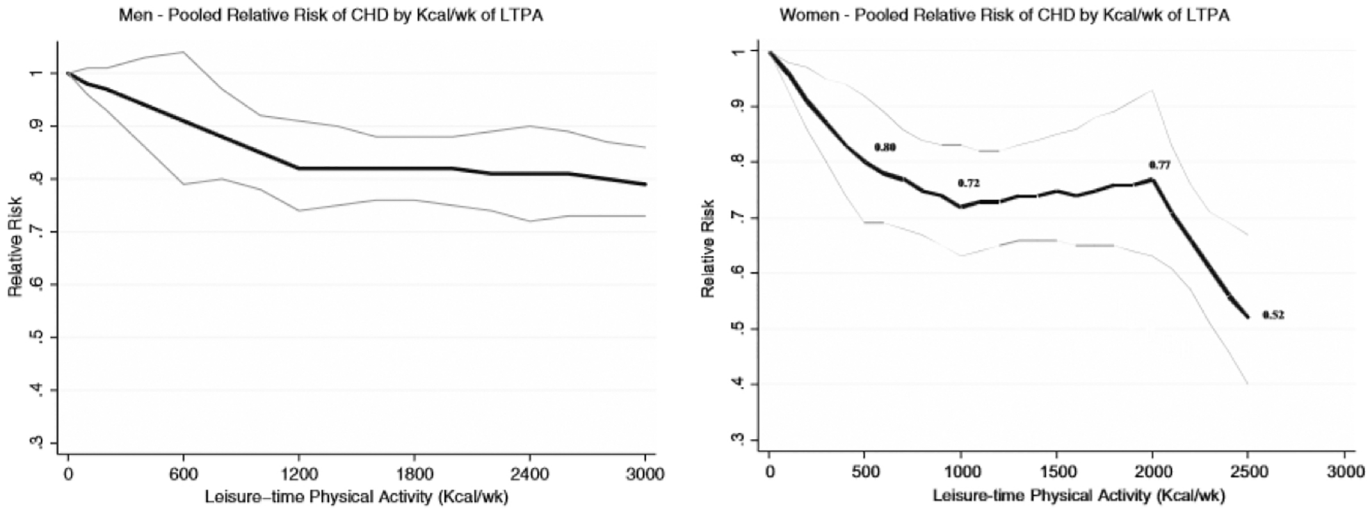
KEY POINTS

- Regular moderate intensity aerobic exercise reduces the risk of atherosclerotic coronary artery disease
- Higher levels of exercise, above the current guideline recommended levels of 500-1000 MET-min/week, may be needed to significantly lower the risk of heart failure
- Low fitness and physical inactivity associated risk of heart failure is driven by greater risk of heart failure with preserved ejection fraction
- Prolonged high intensity aerobic exercise over a lifetime may accelerate subclinical coronary atherosclerosis and increase the risk of atrial fibrillation



Men - Pooled Relative Risk of CHD by Kcal/wk of LTPA
Relative Risk
.3
.4
.5
.6
.7
.8
.9
1
0
600
1200
1800
2400
3000
Leisure–time Physical Activity (Kcal/wk)
Women - Pooled Relative Risk of CHD by Kcal/wk of LTPA
Relative Risk
.3
.4
.5
.6
.7
.8
.9
1
0.80
0.72
0.77
0.52
0
500
1000
1500
2000
2500
3000
Leisure-time Physical Activity (Kcal/wk)

Figure 1

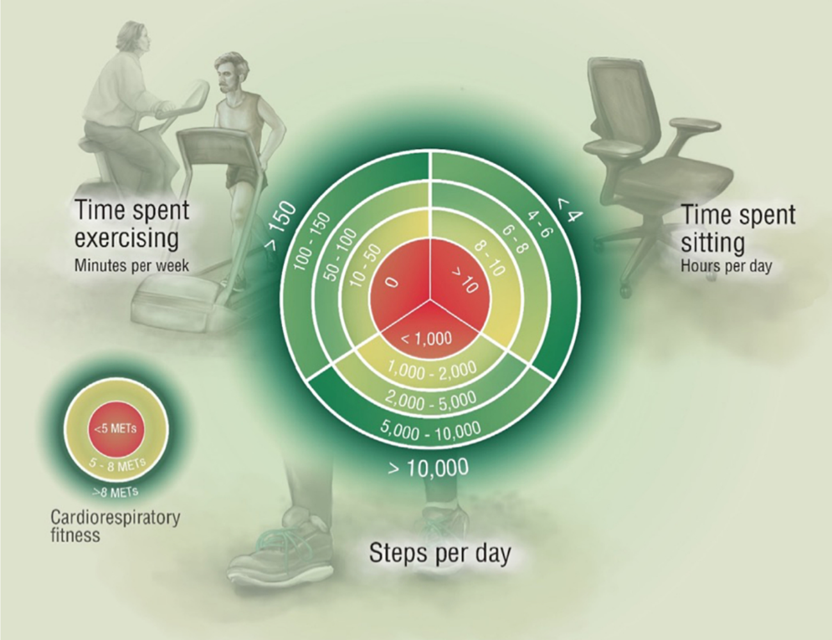

Time spent
exercising
Minutes per week
Time spent
sitting
Hours per day
> 150
100 - 150
50 - 100
10 - 50
0
< 4
4 - 6
6 - 8
8 - 10
> 10
< 1,000
1,000 - 2,000
2,000 - 5,000
5,000 - 10,000
> 10,000
<5 METs
5 - 8 METs
>8 METs
Cardiorespiratory
fitness
Steps per day

Figure 2

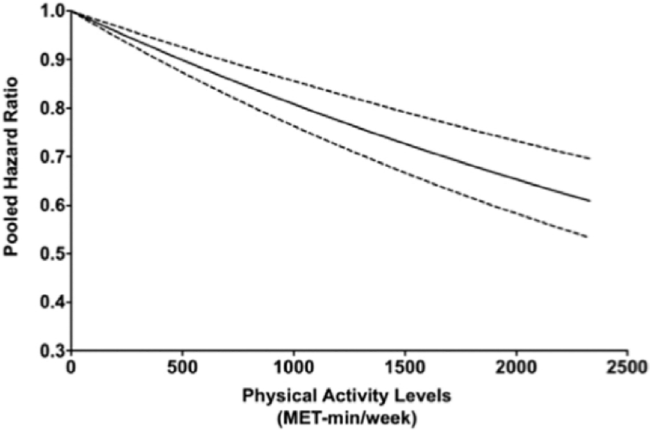

1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
Pooled Hazard Ratio
0
500
1000
1500
2000
2500
Physical Activity Levels
(MET-min/week)

Figure 3

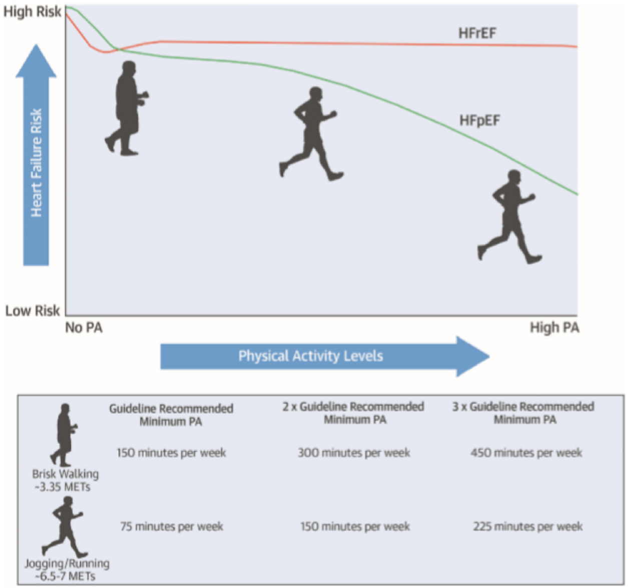

High Risk
Heart Failure Risk
Low Risk
HFrEF
HFpEF
No PA
High PA
Physical Activity Levels
Guideline Recommended Minimum PA
2 x Guideline Recommended Minimum PA
3 x Guideline Recommended Minimum PA
Brisk Walking ~3.35 METs
150 minutes per week
300 minutes per week
450 minutes per week
Jogging/Running ~6.5-7 METs
75 minutes per week
150 minutes per week
225 minutes per week

Figure 4

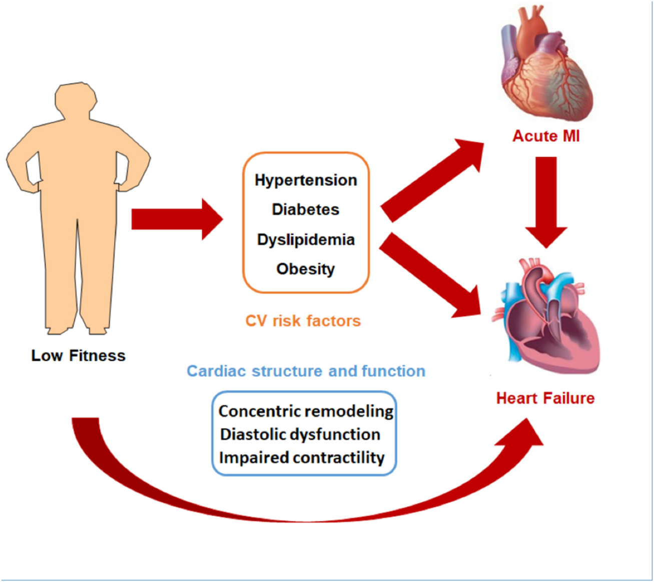

Acute MI
Hypertension
Diabetes
Dyslipidemia
Obesity
CV risk factors
Low Fitness
Cardiac structure and function
Concentric remodeling
Diastolic dysfunction
Impaired contractility
Heart Failure

Figure 5

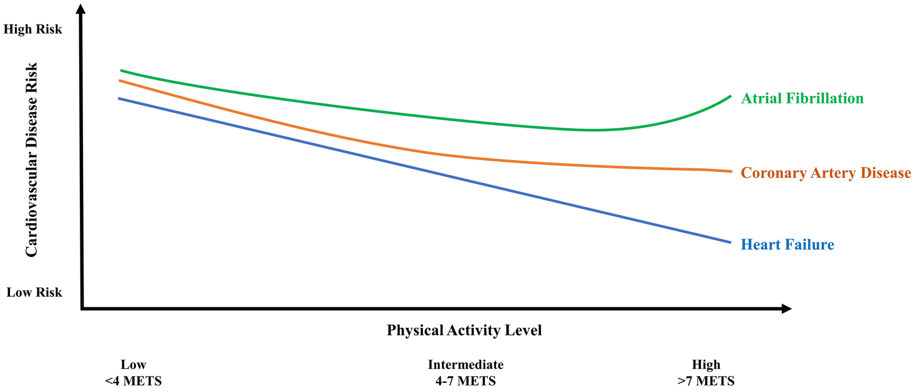

High Risk
Cardiovascular Disease Risk
Low Risk
Atrial Fibrillation
Coronary Artery Disease
Heart Failure
Physical Activity Level
Low
<4 METS
Intermediate
4-7 METS
High
>7 METS

Figure 6