Training for Longevity: The Reverse J-Curve for Exercise

by Evan L. O'Keefe, MD, Noel Torres-Acosta, MD, James H. O'Keefe, MD & Carl J, Lavie, MD

If one's goal is to decrease the risk of CV events and improve life expectancy, a regular regimen of moderate activity is adequate.

Abstract

A wealth of scientific literature backs the unique therapeutic benefits of exercise for quality of life, cardiovascular (CV) health, and longevity. Consequently, many have assumed that more exercise is always better. However, chronic excessive endurance exercise might adversely impact CV health. Ultra-endurance races can inflict acute myocardial damage, as evidenced by elevations in troponin and brain natriuretic peptide. Moreover, sudden cardiac arrest occurs more often in marathons and triathlons than in shorter races. Veteran endurance athletes often show abnormal cardiac remodeling with increased risk for myocardial fibrosis and coronary calcification. Chronic excessive exercise has been consistently associated with increased risks of atrial fibrillation (AF), and along with some attenuation of longevity benefits. The optimal dose of exercise remains unknown and probably differs among individuals. Current studies suggest that 2.5 to 5 hours/week of moderate or vigorous physical activity will confer maximal benefits; >10 hours/week may reduce these health benefits.




From left: Evan L. O'Keefe, MD, is at Tulane Medical Center, New Orleans, Louisiana. Noel Torres-Acosta, MD, is at the University of Kansas Medical Center, Kansas City, Kansas. James H. O'Keefe, MD, MSMA member since 2003, is at Saint Luke's Mid America Heart Institute, Kansas City, Missouri and University of Missouri-Kansas City, Kansas City, Missouri. Carl J. Lavie, MD, is in the Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School, the University of Queensland School of Medicine, New Orleans, Louisiana.

Introduction

Physical inactivity and obesity are among the leading causes of death and disability, with myriad adverse effects, especially for the cardiovascular (CV) system. Today in the United States (U.S.) about half of all adults have some form of CV disease (CVD).[1] Thus, physical activity and exercise training have become among our most powerful tools for the prevention and treatment of noncommunicable disease—CVD in particular.[2] Physical activity and an improved cardiorespiratory fitness lessen the incidence and burden of coronary artery disease (CAD) and reduces risk of major adverse CVD events (MACE). Each metabolic equivalent (MET) gain in fitness confers a 30% reduction in all-cause mortality in unfit individuals (those with an initial < 5 MET exercise capacity).[3] The most physically active cohort in middle age has a predicted life expectancy eight years longer than a sedentary cohort; and for patients with established CVD, undertaking cardiac rehabilitation consistently improves prognosis and quality of life.[4]

Exercise positively affects virtually every aspect of the body and brain, and its unique ability to improve physical and mental wellbeing has convinced the general public that staying physically active is one of the best ways to stay healthy and enhance longevity. In fact, maintaining a high level of CV fitness (aerobic and muscular fitness) improves prognosis independently of other therapies, and plausible arguments can be made that exercise/fitness is the most potent medical

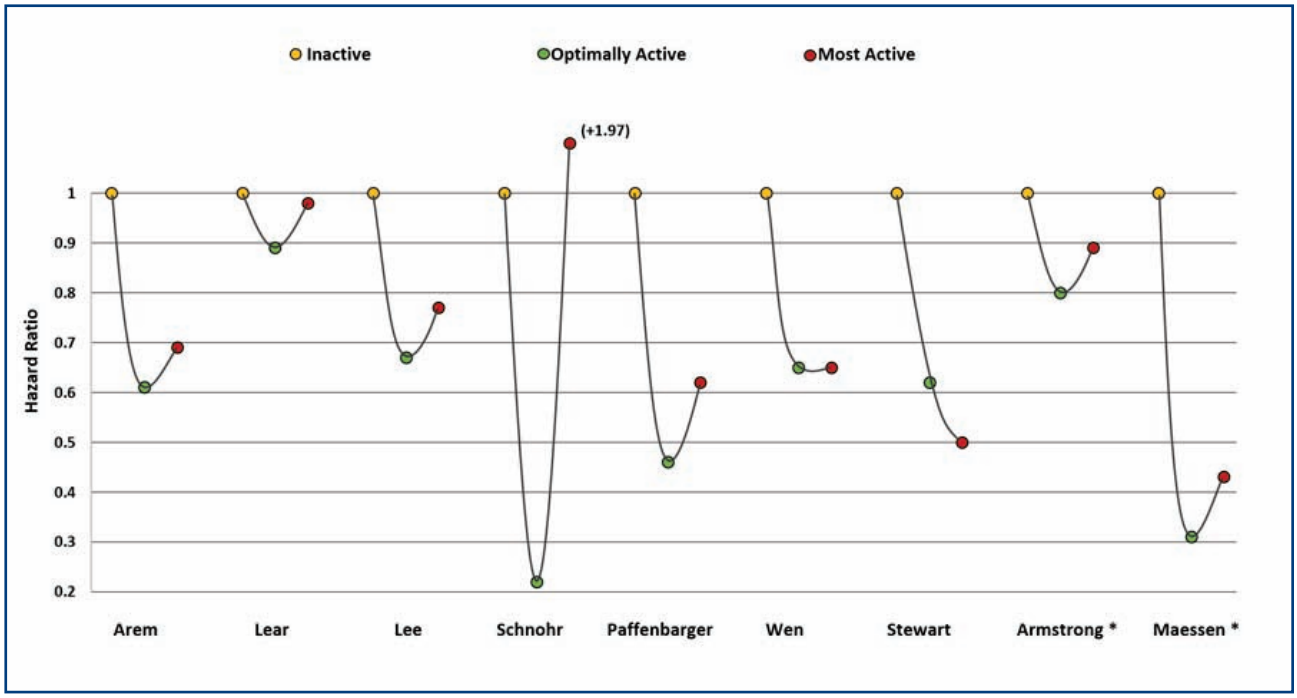

Figure 1. All-cause mortality and incident cardiovascular diseases from epidemiological studies. Overview of curvilinear dose-response association between physical activity volume and cardiovascular health outcomes. Adapted from Franklin et al., Paffenbarger et al., Stewart et al.[15,16,52]
*Indicates incident cardiovascular disease as outcome.

therapy we have in the battle against CVD.[5] Although the ideal dose of exercise remains unknown; it is clear that at least half of Americans are not meeting the physical activity guidelines recommendations of > 150 minutes/week of moderate exercise. Importantly, significant longevity benefits are conferred by even just 15 minutes/day of light or moderate physical activity, which is about half the recommended minimum dose of daily exercise, with the steepest risk reductions seen in the cohort going from completely sedentary to just mildly active.[6] At the other end of the spectrum, about 2.5% of U.S. adults may be overdoing exercise, thereby exposing themselves to potential deleterious health outcomes.[7]

The ideal dose of exercise for conferring robust health and optimal longevity is being hotly debated in the scientific literature. The aim of this article is to clarify this issue, focusing on the cumulative data.[8-14]

Reverse J-Curves of Exercise

The optimal dose of physical activity for maximizing health benefits is unknown,[15] and even 2,500 years ago, Hippocrates taught: "if we could give every individual the right amount of nourishment and exercise—not too little and not too much—we would have found the safest way to health."[7] This suggests that there might be a dose range of physical activity that is optimal for improving wellbeing and life expectancy, with attenuation of these benefits when the amount of exercise is above or below this ideal range. Indeed, Paffenbarger back in 1986 reported a reverse J-shaped association between exercise (walking, stair climbing, and sports play) and all-cause mortality. That prospective study followed 16,936 male Harvard alumni for 16 years and found that death rates declined inversely as energy expended on physical activity increased from < 500 to 3,500 kcal/week.[16] However, the 18% of men exercising > 3,500 kcal/week had attenuation of the age-adjusted reduction in risk of death, showing a 38% reduction compared to a 54% mortality reduction for those doing 3,000 to 3,500 kcal/week.[16]

Since then multiple large observational studies, together comprising over three million individuals, have reported similar results suggesting there is likely an upper threshold for the benefit of exercise whereby very high doses of strenuous physical activities appear to be associated with loss of some of the longevity

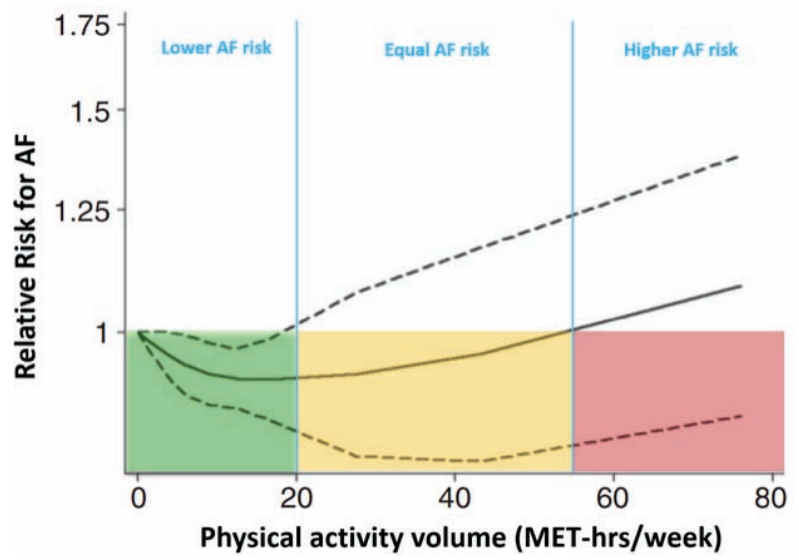

Figure 2. Dose–response association between physical activity volume and AF risk. Individuals performing physical activity for 5 to 20 MET-h/wk demonstrate a significant risk reduction for AF, whereas higher exercise volumes do not appear to attenuate AF risk. A trend toward increased AF risk is apparent among individuals reporting >55 MET-h/wk. AF = Atrial fibrillation; MET-hrs/week = metabolic equivalents of task hours per week. Adapted from Franklin et al.[15]

benefits conferred by less extreme doses of vigorous exercise. As depicted in Figure 1, nearly all of the large observational studies reproduce this reverse J-curve. In this relationship, the risks of CVD and premature mortality go down in dose dependent fashion, until a threshold of exercise is exceeded, at which point the benefits are attenuated compared to less extreme doses of physical activity. In many studies the drop-off in risk reduction noted with very high dose exercise did not reach statistical significance due to the small number of individuals in the upper extreme cohort. Yet, this reverse-J pattern is recurring theme, and in very large studies the attenuation of health benefits noted with extremely high doses of exercise does meet statistical significance.[8]

Arrhythmias

Physical exercise has been associated with a number of CV adaptations, both structural and electrical, including enlargement of all chambers of the heart, improved function, increased cardiac and arterial compliance, sinus bradycardia, and in some individuals increased PR interval and right bundle branch block.[17,18] The increased incidence of atrial fibrillation (AF) seen in endurance athletes is one of the best documented cardiac maladaptations and is thought to be one of the hallmark characteristics of cardiac overuse syndrome. In 1998 Karajalainen et al. examined 300 veteran endurance athletes and reported a five-fold greater incidence of AF as compared to a sedentary control cohort.[19] AF since then has been associated with higher intensity exercise regimens, faster competitive finishing times and absolute number of endurance races completed.[20] Long-term endurance exercise— ≥ 2,000 hours and/or ≥ 20 years of training—displays a strong correlation with AF even in individuals without CV risk factors.[21,22] While individual studies have reported that chronic endurance sports participation increases risk of AF anywhere between two- and ten-fold, a recent meta-analyses quantified an odds ratio for overall risk of AF at just above five-fold.[23]

Similar to many other health outcomes, moderate doses of physical activity are effective in preventing AF, whereas both low and high volumes of exercise are associated with increased risk of AF. As compared to more fit subjects, those with < 6 METs exercise capacity showed elevated incident rates of AF, and after adjustment each 1 MET gain in fitness was associated with a 7% lower risk of incident AF (hazard ratio 0.93, 95% confidence interval 0.92-0.94, P<0.001).[24] In regards to weekly dose of physical activity, even small doses of exercise, such beginning with 5 MET-hours/week appear to reduce risk of AF, with maximal benefits seen at 20 MET-hours/week (Figure 2).[25] Above 55 MET-hours/week, which is approximates to 10 hours of vigorous exercise/week, the risk of developing AF begins to exceed that of the sedentary cohort, displaying a J-curve relationship.[25]

Atrial flutter and/or AF were noted in a significant cohort of former Swiss professional cyclists.[26] Following the successful ablation of atrial flutter, previous endurance sport participation and an ongoing practice of high level exercise increased the risk of recurrent AF.[27] Furthermore, a group of former professional cyclists had a five-fold increased prevalence of

ventricular tachycardia as compared to 309 male senior leisure time golfers (15% vs. 3%, P=0.05).[26] Although complex ventricular tachyarrhythmias are sometimes seen in competitive athletes, and have been included as one manifestation of the "athlete's heart syndrome," it is unclear whether this constitutes a benign or high-risk cardiac condition.[28,29] Some authors argue that the adverse structural changes in the ventricles and atria induced by chronic strenuous endurance exercise produces the substrate for a development and progression of a proarrhythmogenic state.[30] Other potential contributors to arrhythmias in veteran endurance athletes include: excessive sympathetic activity/catecholamine overload, increased oxidative stress, myocardial fibrosis, electrolyte abnormalities.

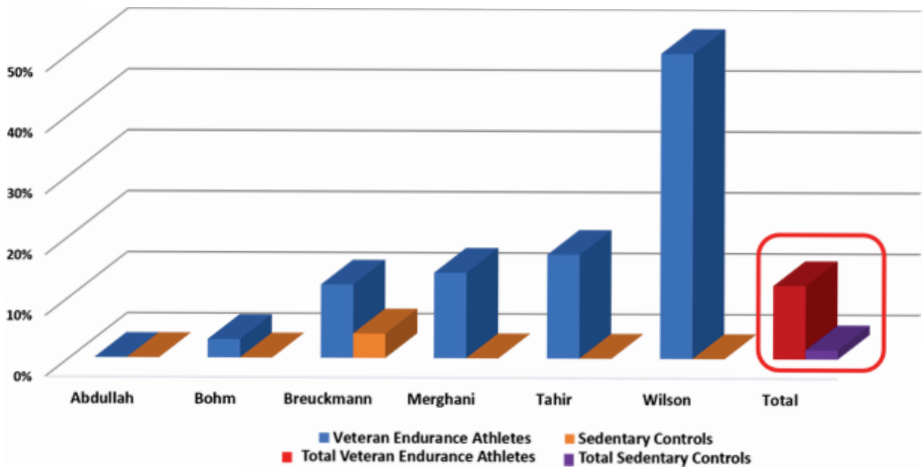

Figure 3. Overview of studies comparing prevalence of LGE between male athletes and control subjects. LGE = Late gadolinium enhancement Adapted from Franklin et al.[15]

Myocardial Fibrosis

Myocardial fibrosis is a nonspecific response to a variety of cardiac injuries such as: acute myocardial infarction (MI), myocarditis, uncontrolled hypertensionand valvular dysfunction. This pathological fibrosis in the heart predisposes to myocardial stiffness, arrhythmias and adverse cardiac outcomes.[31] Myocardial fibrosis is best visualized with cardiac magnetic resonance imaging (MRI), specifically demonstrated by late gadolinium enhancement (LGE).

Chronic endurance sport training/racing has been shown to increase risk of showing LGE, and this has been documented in otherwise healthy, asymptomatic lifelong endurance athletes.[31-33] Moreover, LGE is significantly and directly correlated with the number of years spent training, and the number of marathons and other ultra-endurance competitions completed.[32,34] During times of strenuous exercise cardiac output increases approximately five-fold above resting values, rising from 5 L/min to 25 L/min or more, leading to disproportionately distributed strain on the heart with increases in wall stress of 125% vs. 4% on the right and left ventricles, respectively.[35] These physical strains in conjunction with sustained elevations in catecholamines and reactive oxygen species likely cause cumulative injuries in the myocardium—ultimately leading to scarring as demonstrated by LGE.

The evidence regarding the clinical relevance of this resultant myocardial fibrosis is lacking. One small study of four veteran athletes with LGE reported wall motion abnormalities corresponding to the fibrosed myocardial segments.[36] Additionally, during two years of follow-up, MACE and coronary revascularization occurred more commonly among endurance athletes with myocardial LGE compared to veteran athletes without fibrosis, suggesting that this myocardial damage may play a prognostic role.[33] Interestingly, not only number of ultra-endurance races completed, but also the severity of coronary artery calcification (CAC) independently predicted presence of LGE.[34] The cumulative data on cardiac MRI shows a 12% prevalence of LGE in veteran endurance athletes, which is eight-fold higher than the 1.5% prevalence among the control group of individuals who were doing not more than the minimum dose of daily physical activity recommended by the World Health Organization (Figure 3).[15]

Coronary Artery Calcification

The evidence in regards to CAC in veteran endurance athletes is complicated. A large and consistent body of data shows that the amount of calcium in the coronary arteries is an accurate predictor of risk for MACE.[37] Paradoxically, although exercise

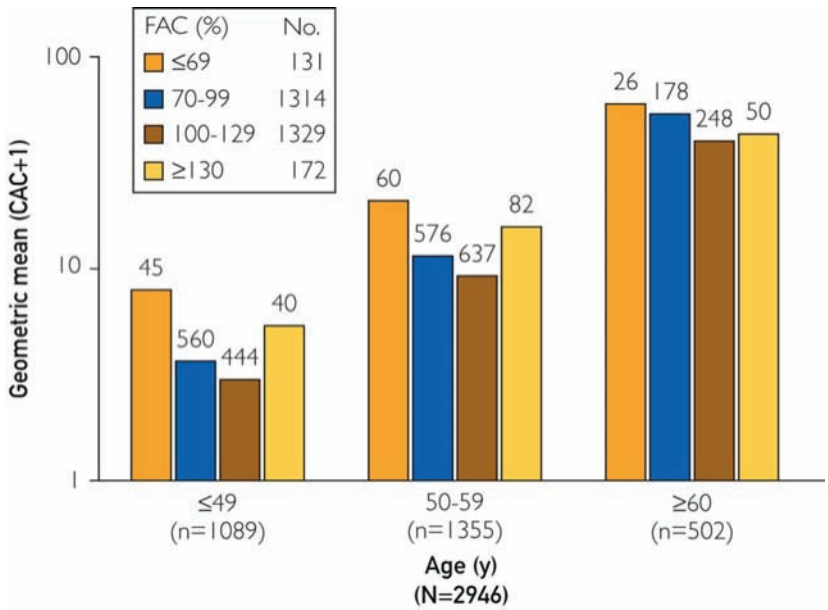

Figure 4. Association of fitness levels with CAC burden. CAC = coronary artery calcium; FAC = functional aerobic capacity. Adapted from Kermott et al. [38]

decreases CAD risk, high volume endurance training appears to substantially increase the CAC burden with Kermott and colleagues demonstrating the presence of the familiar reverse J-curve (Figure 4).[38] Merghani et al. reported that masters athletes 54±8 years of age were approximately twice as likely to have atherosclerotic plaque as compared to healthy controls, and these endurance athletes were more likely to show CAC scores ≥ 300 (11.3%) and luminal stenosis ≥ 50% (7.5%).[39]

Generally, studies have confirmed that veteran endurance athletes have increased coronary calcification compared to sedentary controls, but they tend to be less likely to have high-risk volatile plaques of mixed calcific and lipid laden morphology.[39-41] An observational study of 21,758 individuals found that those with at least 3,000 MET-min/wk had a higher CAC burden compared to less active cohort. Even so, those same highly active individuals showed a nonsignificant trend towards a decrease in mortality (HR 0.77, 95% CI 0.52-1.15) as compared to the less active cohort.[40] Another study reported that very-vigorous-intensity exercise was the most strongly predictive of CAC, but was also associated with reduced prevalence of mixed plaques.[41] Thus, the veteran athletes doing the highest volumes exercise will often have more coronary calcification, but they also tend to have a more stable and benign plaque composition.[41,42]

Taken together, these data suggest that very high doses of strenuous physical activity are associated with increased risk of coronary calcification but are not associated with dangerous plaque composition or increased risk of all-cause or CVD mortality, even among veteran athletes with high CAC scores. Much like the evidence for exercise-induced myocardial fibrosis, it is difficult to conclude that CAC and other cardiac maladaptations are completely benign. However, currently the functional relevance of such findings is of undetermined significance and this issue will require more study with larger patient populations of veteran endurance athletes.

Acute Risk Associated with Vigorous Exercise

Up to 90% of all exercise-related sudden cardiac deaths (SCD) occur in recreational athletes rather than competitive athletes, with an estimated incidence raging from 1:22,000 -1:69,000 in adult recreational athletes, versus 1:50,000 in young competitive athletes.[43,44] The riskiest period for SCD is during and shortly after exercise.[15] In the U.S. Physician study, the risk of SCD was transiently elevated 17-fold during and 30 minutes after vigorous physical activity. This risk was much higher in individuals who were the least active when compared to subjects who exercised more often (relative risk 74 vs 11).[15] Similarly, another study found that the most sedentary cohort had a 25-fold increase risk of SCD compared to those who were at least moderately active.[15] In athletes aged > 35 years, over 80% of the SCDs are cause by CAD; whereas among younger athletes (< 35 years) congenital abnormalities of the heart muscle, coronaries and conduction system are the most common cause of SCD.[45]

Longer and more physically demanding races

appear to pose a higher risk for SCD. Data from almost 11 million long distance race participants showed a higher incidence of SCD in marathons (1.01/100,000) compared to half marathons (0.27/100,000); only 29% of victims survived the cardiac arrest.[46] Of note, the death rate of males was more than double of the female race participants (0.98 vs 0.41/100,000).[47] This gender difference has been seen with respect to many aspects of the cardiac overuse syndrome, whereby women appear to be less susceptible than men to adverse cardiac effects of chronic high-dose endurance exercise.

The rate of SCD in triathlon athletes has been reported to be higher than marathon races. In a case series of 4.7 million triathlon participants the incidence of SCD was estimated to be 1.74/100,000 participants.[48] Similar to marathons, males had three times higher risk when compared to females (2.40 vs 0.74/100,000). Also, there was a three-fold higher risk in men > 40 years when compared to younger participants.[48]

Acute MI also occurs at an increased rate during or soon after vigorous exercise. Several studies have demonstrated a two- to ten-fold increased risk for MI within one hour of physical activity.[15] Endurance events including marathons and ultra-marathons have been associated with derangements in cardiac biomarkers. In marathon runners, significant post-race troponin elevations have been detected in direct correlation with exercise intensity.[49] A rise in brain natriuretic peptide levels was also seen in the marathon runners, but these elevations bore no relationship to exercise intensity.[49]

In addition to biochemical changes, functional changes are also present following intense exercise. One study of 40 athletes competing in endurance races (marathon, endurance triathlon, alpine cycling) found that the post-race right ventricle (RV) ejection fraction (EF) decreased by nine percentage points, with no change in left ventricular (LV) EF. The greatest reduction in RVEF was seen in the athletes who completed the longest event (ultra-triathlon).[50] Moreover, LGE on MRI was seen at the site of the RV attachment to the interventricular septum in 13% of the endurance athletes and commonly was seen in conjunction with pulmonary hypertension in these same individuals. Interestingly those athletes who had been competing for more years (20 years vs eight years) had significantly lower resting RVEF.[50] Repeated insults to the RV as seen during protracted strenuous exercise could cause myocardial necrosis ultimately leading to scarring and irreversible RV remodeling, creating the substrate for arrhythmias. The approximate amount of exercise required for this effect is speculated to be about > 20 hours/week for > 20 yrs.[43]

Conclusion

If one's goal is to decrease the risk of CV events, and improve life expectancy, a regular regimen of moderate activity is adequate. Very high doses of strenuous exercise may attenuate some of the benefits bestowed by less extreme efforts. The best forms of exercise for improving mental health and longevity appear to be social sports such as tennis, golf, badminton, soccer, basketball, volleyball, and group exercise, which not only improves fitness, but also promote interpersonal bonding and tend to reduce stress.[51] The current body of data is not strong enough to recommend that recreational athletes reduce their exercise dose, especially if this is something that improves their quality of life, or is needed to optimize performance in competitions, as the risks appear to be modest and somewhat uncertain yet. Even so, we should emphasize that the maximal benefit for CVD risk reduction occurs at much lower, safer and more moderate exercise doses.

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Disclosures

None reported.

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