REVIEW

The Impact of Cardiorespiratory Fitness on Cardiometabolic Risk Factors and Mortality

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ABSTRACT

The association between physical activity and health has been recognized since antiquity. Yet daily physical activity in modern societies, especially for the last 100 years, has declined greatly. Additionally, people tend to become less physically active as they age. This is unfortunate because of the known link between physical activity and health. Physical inactivity can lead to many physiologic maladaptations that can increase the risk of cardiometabolic abnormalities and death. This manuscript reviews the influence of physical activity on cardiometabolic health and mortality. *Journal of Clinical Exercise Physiology*. 2017;6(4):71–77.

Keywords: physical activity, exercise, reverse causality

INTRODUCTION

Chronic increases in physical activity or structured exercises of adequate intensity, duration, and volume lead to certain physiologic adaptations that encompass the musculoskeletal, cardiovascular, and metabolic systems. Collectively, these physiologic adaptations lead to a higher capacity to perform physical work, resilience to injury, and ultimately, improved human health and longevity. The link of physical activity to better health, well-being, and longevity has been noted since antiquity. Hippocrates was the first physician to not only state that regular exercise is essential for well-being and longevity, but he was also the first recorded physician to provide a written exercise prescription of walking for his patients. His statements "walking is the best medicine" and "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" clearly emphasized moderation as essential in promoting health and warned against excess in both exercise and nutrition. Scientific scrutiny of these concepts and a plethora of evidence accumulated from large and well-designed epidemiologic studies with diverse populations and diseases unequivocally support these concepts. In this review, we are presenting a comprehensive synopsis of the evidence accumulated over the last 6 decades.

PHYSICAL ACTIVITY, CARDIORESPIRATORY FITNESS, AND MORTALITY

The landmark work by Morris and coworkers (1) opened the way for a rigorous and systematic scrutiny of the impact of physical activity and physical fitness on human health. Since then, large and well-designed epidemiologic studies mostly from United States and Europe have been conducted focusing on the connection between physical activity, cardiorespiratory fitness (CRF), and health. In general the accumulated evidence has provided indisputable evidence that improved CRF, as determined by a maximal exercise test or a physically active lifestyle of adequate intensity, duration, and volume to increase CRF, is associated with a reduced risk for cardiovascular and all-cause mortality in apparently healthy individuals (2-8) and in patients with cardiovascular risk factors (9-20) and documented cardiovascular disease (21-23). Several features of these studies are noteworthy. First, the CRF-mortality risk association is robust, inverse, graded, and independent of age, gender, race, risk factors, or other co-morbidities. The reduction in mortality risk for each one metabolic equivalent (1-MET) increase in exercise capacity

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ranges between 10% to 25%, with no substantial gender differences (15,16,21). Second, exercise intensity, duration, and volume threshold are necessary beyond which health benefits accumulate exponentially, before reaching a plateau (S-shaped curve association). Third, the largest portion of the health benefits is realized at relatively lower levels of physical activity once the threshold is overcome. Finally, there is support that excessive amounts of physical activity (work volume) are counterproductive and even harmful. The exercise volume threshold and the level of work at which exercise becomes counterproductive are both undoubtedly influenced by age, health and fitness status, and genetics, and a precise definition may be difficult. Traditionally, peak exercise capacities of 4 to <9 METs have been used to establish least fit reference groups, with the remaining CRF categories defined by incremental increases of about 2 to 3 METs. (4,15,24-26) Generally, exercise thresholds below 6 METs have been associated with higher mortality as observed in the National Coronary Artery Surgery Study and other studies (27,28). In middle-aged US veterans, the optimal CRF threshold for reduction in mortality risk was 7.0 METs. Those below this threshold had a 2.6-fold increase in risk for mortality (P<0.001) compared with those above it (5). When age is considered the MET threshold for individuals <50 years of age is between 8 to 9 METs and declines by 1 MET per decade to a threshold between 5 to 6 METs for those ≥70 years (2). A progressively lower mortality risk is observed in those with CRF higher than these MET levels and higher in those with CRF below this level.

Regardless of the method used to define CRF categories, the inverse, independent, and graded association between CRF and health outcomes is consistent. However, the need to standardize fitness categories is still apparent.

CARDIORESPIRATORY FITNESS AND MORTALITY RISK IN THE ELDERLY

The exercise-related reduction in mortality risk has been reported in older populations and in those with various comorbidities. The association between exercise capacity and mortality risk for individuals >70 years of age has been found to be inverse, graded, and similar to younger individuals. In elderly men, mortality risk for those with an exercise capacity >5 METs (moderate to high-fit) was 45% to 60% lower when compared to those with an exercise capacity of ≤5 METs (4). Similar results were reported for hypertensive individuals ≥70 years of age (25). This association, including the degree of change in mortality risk, is similar to that observed in younger populations (20,21,25).

RACIAL DIFFERENCES

Relatively few studies have examined the role of racial difference on the CRF-health outcomes relationship. Evidence suggests that black men and women have a lower CRF and an elevated risk of cardiovascular disease compared with white men and women. Black individuals may also have an attenuated increase in CRF following exercise training (29). Race may account for up to 20% of the variance in CRF (30). Apparently CRF is higher in white men and women compared to black men and women (26,31). Although the inverse relationship between CRF and mortality does not appear to be influenced by race (similar trends observed for both races) (5,26), some evidence suggests that the impact of per unit increase in CRF may be different. For example, in our study of black and white men with type 2 diabetes, the CRF-related reduction in mortality risk was stronger and more graded for white than for black men. For each 1-MET increase in exercise capacity the mortality risk was 19% lower for white and 14% for black men (P <0.001). When the cohort was stratified by CRF categories, the risk was 43% lower for moderate-fit and 67% lower for high-fit whites. In black individuals, the comparable reductions were 34% and 46%, respectively (12). Similarly, in a study of 13,345 patients who completed 2 exercise tests, at least 12 months apart at Henry Ford Hospital, change in CRF from low or moderately fit to highly fit resulted in 59% and 35% lower all-cause mortality risk for white and black individuals, respectively (32).

REVERSE CAUSALITY

When examining the association between CRF and health outcomes, it should be considered that the relatively higher mortality rates observed in individuals with low CRF may be the outcome of subclinical illness. This phenomenon, known as reverse causality, if it exists, is likely to overestimate the beneficial effects of CRF for individuals with moderate and high exercise capacity. Epidemiologic studies cannot directly account for the possibility of reverse causality. However, statistical procedures and scientific scrutiny of the data can provide evidence in support of or against such probability. In this regard, if we assume that subclinical disease is the cause of both low CRF and high mortality rates (reverse causality), systematically removing individuals with certain physiologic characteristics suggestive of subclinical chronic diseases from the analyses and re-analysis of the data is likely to substantially change the CRF-mortality risk association. Conversely, if there is no reverse causality, the mortality trends will not change substantially.

To account for the possibility that the higher mortality rates observed in the low-fitness categories were the result of underlying diseases or musculoskeletal or peripheral vascular issues and not low fitness per se (reverse causality), we undertook 3 approaches: (1) we excluded those who died within the initial 2 years of follow-up; (2) we excluded those who were not treated with beta-blockers but did not achieve at least 85% of their age-predicted maximal heart rate (HR) (to account for factors that may have impaired exercise performance); and (3) we excluded those in the 2 lowest fitness categories (≤5 METs) with BMI <20 $kg \cdot m^{-2}$. We then repeated the survival analyses separately (for each exclusion), as well as with all exclusions combined. In all 4 scenarios, the association between exercise capacity and mortality risk remained robust, and the risk reduction did not deviate substantially from that observed in the entire cohort. Finally, we examined the association between change in

fitness and mortality in 867 individuals who had a second exercise tolerance test (ETT) at least 6 months after the initial test. Compared with unfit individuals in both tests, mortality risk was 61% lower in those who were physically fit by both ETTs and 34% lower for individuals defined as unfit by the initial ETT who became fit by the second test. In addition, fit individuals who drifted into the unfit category by the second test maintained 41% lower risk compared with those who were unfit on both tests (4). In a similar design and a much larger cohort with 2 fitness assessments (mean interval between assessment 4.9 years), Blair et al. (7) reported that the highest age-adjusted all-cause death rate was observed in men who were unfit at both assessments and the lowest death rate in men who were physically fit at both assessments. Those who improved from unfit to fit between the first and subsequent assessment had a 44% reduction in mortality risk relative to men who remained unfit at both examinations. Similarly, in the FIT Project, 13,345 patients who completed 2 exercise tests at least 12 months apart (mean time between the tests was 3.4 years) change in CRF from low or moderately fit to highly fit resulted in 35% and 59% lower all-cause mortality risk for blacks and whites, respectively (32).

Thus, the findings that changes in fitness status are associated with respective changes in mortality risk collectively strengthen the argument that the lower mortality rate in fit individuals is the result of increased fitness, not spurious or artificially inflated by the higher mortality among low fit individuals due to subclinical diseases. Another clinically important finding is that the fitness related health benefits are not ephemeral but are likely to endure for some years. This notion is supported by the observation that fit individuals who drifted into the unfit category by the second test maintained 41% lower risk compared with those who were unfit on both tests (4).

PHYSICAL ACTIVITY, CARDIORESPIRATORY FITNESS, AND HYPERTENSION

Increased physical activity and CRF have been shown to lower blood pressure (BP) and mortality risk in hypertensive patients regardless of age (21,25,33-35). The consensus of several reviews and meta-analyses over the years is that structured aerobic exercise training programs or increased physical activity of moderate intensity and adequate volume result in an independent reduction of approximately 4 to 10 mm Hg in systolic and 3 to 8 mm Hg in diastolic BP for individuals with stage 1 hypertension (HTN) regardless of age or gender (21,33,34,36,37). We have also noted significant reduction in BP in male veterans with stage 2 HTN and left ventricular hypertrophy (LVH) after 16 weeks of moderate-intensity aerobic exercise training. At 32 weeks, BP reduction was more pronounced even after a 33% reduction in antihypertensive medication in the exercise group, while BP in the no-exercise group increased substantially (38). We also noted a significant reduction in cardiac wall thickness and left ventricular mass, resulting in a 12.3% regression in LVH, similar to that observed with most antihypertensive medications (39). LVH is considered an independent risk factor for mortality and therefore regression of LVH with exercise is clinically significant (40).

Thus, appropriate lifestyle interventions including increased physical activity designed to enhance CRF are recommended by national and international committees, experts, and organizations as initial therapy to prevent, treat, and control HTN (41,42).

CARDIORESPIRATORY FITNESS AND MORTALITY RISK IN HYPERTENSIVE INDIVIDUALS

The CRF-mortality risk association in hypertensive patients has been assessed by large and well-controlled epidemiologic studies. The consensus of these studies supports that the inverse CRF-mortality risk association is independent and graded (11,22,43). For example, in a cohort of 4,631 hypertensive veterans with multiple cardiovascular risk factors who successfully completed a graded ETT, mortality risk was 13% lower for every 1-MET increase in exercise capacity (11). When compared to the least-fit individuals (exercise capacity ≤5 METs), mortality risk was 34% lower for those in the next fitness category (5.1 to 7.0 METs) and progressively declined by more than 70% for individuals with the highest exercise capacity (>10 METs). When the presence or absence of additional risk factors within fitness categories (least fit to most fit) was considered, the least-fit individuals (≤5 METs) with additional risk factors had a 47% higher mortality risk than those without risk factors. This 47% increased risk was eliminated in the next fitness category (5.1 to 7.0 METs) and declined to approximately ≥50% in those with an exercise capacity >7.0 METs, regardless of cardiovascular risk factor status.

We also evaluated the interaction between exercise capacity, body mass index (BMI), and mortality risk in hypertensive veterans. Progressively lower mortality rates with increased exercise capacity were observed within each BMI category. The mortality risk reduction ranged from approximately 40% in those with an exercise capacity of 5.1 to 7.5 METs to 70% in those with >7.5 METs (43). To explore the fitness-fatness and mortality risk relationship further, we compared normal-weight, low-fit individuals to overweight or obese, but fit individuals. The mortality risk was 47% and 60% lower for the overweight-moderate-fit and overweight-high-fit individuals, respectively. Similarly, the risk was 55% lower for the obese-moderate-fit and 78% lower for the obese-high-fit individuals. These findings suggest that it is more beneficial to be fit and overweight or obese rather than normal weight and unfit. Furthermore, it appears that obese hypertensive individuals may benefit at least as much (if not more) from fitness as their overweight or normal weight counterparts (43).

In summary, strong evidence supports that regularly performed exercise, or a chronic increase in physical activity that leads to increased CRF, lowers BP and the risk of mortality, independent of other risk factors. The dose-response association between increased CRF, BP, and mortality risk reduction supports the existence of a causal mechanism(s).

However, the mechanism or mechanisms are not well understood. It is likely that the favorable effects CRF, exercise, and physical activity have on several biological systems and traditional risk factors (21) are likely to share the credit.

CARDIORESPIRATORY FITNESS AND MORTALITY RISK IN INDIVIDUALS WITH TYPE 2 DIABETES

Individuals with type 2 diabetes mellitus (DM2) have a 50% to 60% higher risk of all-cause and cardiovascular mortality than those without DM2, and cardiovascular disease (CVD) remains the primary cause of death in the U.S. among diabetic patients (44). Findings from exercise training studies support the concept that both aerobic and anaerobic exercise training regimens improve glucose uptake and insulin sensitivity (45-47). The exercise-related increased glucose uptake by the working muscle cells involves activation of the GLUT-4 transporter, independent of insulin (48). Evidence from large cohort studies supports the concept that physical activity reduces the risk of mortality in diabetics. All-cause mortality risk is 2 times higher in unfit or sedentary diabetics compared to physically fit diabetics regardless of body weight (24,49-52).

In the Veterans Exercise Testing Study (12) we assessed the exercise capacity and all-cause mortality relationship in black and white men with DM2. We found that exercise capacity is a strong predictor of mortality in both black and white diabetics. The age-adjusted reduction in mortality was graded and more pronounced in whites than in blacks. Each 1-MET increase in exercise capacity yielded a 14% and a 19% lower risk for whites, respectively. In black individuals the risks were 34% and 46% lower for moderate-fit and high-fit versus the low-fit category, respectively. For whites, the comparable reductions were 43% and 67%, respectively. These findings suggest that racial differences may exist in the impact of exercise on mortality in diabetic patients. This is clinically significant since black individuals have a 2- to 6-fold higher risk for developing DM2 and approximately double the DM2 death rate compared with whites (53). In a meta-analysis of 17 studies in diabetics, the investigators reported an inverse association between physical activity (PA) and all-cause mortality, and any amount of habitual PA was better than inactivity. The pooled relative risk reduction was 40% lower for physically active versus sedentary individuals, and more PA was associated with a larger reduction in all-cause mortality (54).

Findings from interventional studies have provided mixed results on the efficacy of increased CRF in decreasing mortality risk in patients with DM2 (55). Look AHEAD, was the largest trial (n=5,145) designed to assess the efficacy of favorable lifestyle changes (dietary modifications and exercise) in reducing mortality risk in patients with DM2. The study was terminated early after a futility analysis. Despite no difference in event rates, the lifestyle intervention group exhibited improvements in several cardiometabolic risk parameters and risk factors, with lower side effects, improved quality of life, and reduced overall healthcare costs (56). Failure to yield favorable findings has been attributed to several factors, including relatively lower than expected mortality rate (56,57). The implementation of the intervention and specifically the exercise program also seems problematic. For example, the CRF status of the intervention group at baseline was relatively low (approximately 5.5 METs), suggesting a relatively sedentary cohort. Furthermore, exercise capacity increased by approximately 1-MET only by the end of the initial year of follow-up and then declined thereafter to baseline levels by the fourth year. The relatively anemic increase suggests that adherence to the exercise program was less than adequate even during the first year and certainly declined over the remaining years. Interestingly, change in body weight, waist circumference, and hemoglobin A1c (HA1c) were concomitant to changes in CRF, lending additional support that adequate implementation of the lifestyle intervention program was not sustained after the initial year. In contrast, a relatively small study (n=160) reported long-term clinical benefit of lifestyle interventions (58). All-cause mortality rates, cardiovascular death, and cardiovascular events were 56%, 57%, and 59% lower in the lifestyle group compared to standard care group. It is of interest that in this study, the overall mortality rate in the control group was 50% compared to the <8% rate in the Look AHEAD trial. This further supports the concept that the very low event rate seen in the Look AHEAD trial may have contributed to the lack of favorable outcomes in that trial (55,57).

CARDIORESPIRATORY FITNESS, OBESITY, AND MORTALITY RISK

Excess accumulation of body fat that leads to overweight and obesity result in cardiovascular, neurohormonal, and metabolic maladaptations, ultimately leading to a number of chronic health conditions, including DM2, HTN, coronary heart disease (CHD), and premature mortality (59). In addition, obesity accentuates CHD risk and mortality indirectly through its adverse effects on several established risk factors, including insulin resistance and HTN. Although the causes of obesity are complex, physical inactivity is considered to play an important role, despite relatively modest weight reductions associated with structured programs of physical activity. The relative risk of obesity among individuals physically active in leisure time (≥5 bouts of physical activity per week) was ≥50% lower than among those who were physically inactive (60).

Significantly lower risk of CVD and all-cause mortality have been reported among physically active versus sedentary individuals regardless of weight loss. In two follow-up publications from the Aerobics Center Longitudinal Studies (n=25,714), higher fitness levels were associated with lower risk of mortality in normal-weight, overweight, and obese men (61,62). Compared with other risk factors (total cholesterol, HTN, and smoking), having a low fitness level carried similarly heightened risks in each weight category for both cardiovascular and all-cause mortality. Fitness also predicted mortality independent of measures of body dimensions. Higher waist circumference was associated with higher

mortality, but this association was not significant after adjustment for fitness (61). These findings suggest that it is as important for health providers to evaluate fitness status of overweight or obese patients as it is to evaluate the established risk factors.

Similarly, in the Nurses' Health Studies, after adjustment for age, smoking status, parental history of CHD, menopause, hormone use, and alcohol consumption, higher levels of physical activity (>1 hour/week) were associated with reduced mortality risk across all categories of body weight (63). Interestingly, being physically active attenuated but did not eliminate the adverse effects of obesity on coronary risk, and being lean did not counteract the increased risk associated with being physically inactive (64). This finding suggests that physical inactivity may be more deleterious to human health than obesity. This concept is supported by the findings of other prospective studies that have assessed the independent and joint associations between fitness, physical activity patterns, and health outcomes. In each of these studies, higher levels of physical activity attenuated the mortality risk in all categories of adiposity, and both physical inactivity and excess weight were independently associated with the risk of CVD (65,66).

Recent findings of large epidemiologic studies reported an inverse association between BMI and mortality, often termed the obesity paradox (67-72). This phenomenon may be the result of undefined chronic illness, resulting in weight loss and poor exercise capacity (67). This is suggested by our recent studies from the Veterans Affairs database. When we considered the fitness status of the participants in the cohort, the inverse association was attenuated (68). This was further supported by a larger study (n=18,033). During the follow-up period (median, 10.8 years), the adjusted mortality risk was 21% higher for individuals with a BMI of 20.1 to 23.9 kg/m^2 and 56 % higher for those with the lowest BMI (18.5 to 20.0 kg/m^2) than for those with a BMI of 24.0 to 27.9 kg/m^2. When the cohort was stratified by fitness, the trend was similar for low-fit and moderate-fit individuals. However, mortality risk was not increased for high-fit individuals across BMI categories. Thus, fitness greatly affects the paradoxical BMI-mortality risk association. Furthermore, these findings indicate that lower BMI levels do not increase the risk for premature death as long as they are associated with high fitness. Thus, the paradoxically higher mortality risk observed with lower body weight as represented by lower BMI is likely the result of unhealthy reduction in body weight and, perhaps most importantly, considerable loss of lean body mass (73).

CONCLUSION

Improvement in CRF, whether as a result of structured exercise training or adequate physical activity, has an independent and graded protective effect against mortality in a large spectrum of disease states. The intensity and volume of physical activity necessary to realize health benefits are relatively moderate and within the capacity of most middle-aged and older individuals. Accordingly, the public health significance of increased CRF is enormous.

REFERENCES

1. Morris JN, Heady JA, Raffle PA, Roberts CG, Parks JW. Coronary heart-disease and physical activity of work. Lancet. 1953;265(6796):1111-20.
2. Kokkinos P, Faselis C, Myers J, Sui X, Zhang J, Blair SN. Age-specific exercise capacity threshold for mortality risk assessment in male veterans. Circulation. 2014;130(8):653-8.
3. Kokkinos P, Myers J, Doumas M, Faselis C, Manolis A, Pittaras A, Kokkinos JP, Singh S, Fletcher RD. Exercise capacity and all-cause mortality in prehypertensive men. Am J Hypertens. 2009;22(7):735-41.
4. Kokkinos P, Myers J, Faselis C, Panagiotakos DB, Doumas M, Pittaras A, Manolis A, Kokkinos JP, Karasik P, Greenberg M, Papademetriou V, Fletcher R. Exercise capacity and mortality in older men: a 20-year follow-up study. Circulation. 2010;122(8):790-7.
5. Kokkinos P, Myers J, Kokkinos JP, Pittaras A, Narayan P, Manolis A, Karasik P, Greenberg M, Papademetriou V, Singh S. Exercise capacity and mortality in black and white men. Circulation. 2008;117(5):614-22.
6. Kokkinos P, Doumas M, Myers J, Faselis C, Manolis A, Pittaras A, Kokkinos JP, Papademetriou V, Singh S, Fletcher RD. A graded association of exercise capacity and all-cause mortality in males with high-normal blood pressure. Blood Press. 2009;18(5):261-7.
7. Blair SN, Kohl HW III, Barlow CE, Paffenbarger RS Jr, Gibbons LW, Macera CA. Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. JAMA. 1995;273(14):1093-8.
8. Blair SN, Kohl HW III, Paffenbarger RS Jr, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality. A prospective study of healthy men and women. JAMA. 1989;262(17):2395-401.
9. Kokkinos P, Faselis C, Myers J, Kokkinos JP, Doumas M, Pittaras A, Kheirbek R, Manolis A, Panagiotakos D, Papademetriou V, Fletcher R. Statin therapy, fitness, and mortality risk in middle-aged hypertensive male veterans. Am J Hypertens. 2014;27(3):422-30.
10. Kokkinos P, Faselis C, Myers J, Sui X, Zhang J, Tsimploulis A, Chawla L, Palant C. Exercise capacity and risk of chronic kidney disease in US veterans: a cohort study. Mayo Clin Proc. 2015;90(4):461-8.
11. Kokkinos P, Manolis A, Pittaras A, Doumas M, Giannelou A, Panagiotakos DB, Faselis C, Narayan P, Singh S, Myers J. Exercise capacity and mortality in hypertensive men with and without additional risk factors. Hypertension. 2009;53(3):494-9.
12. Kokkinos P, Myers J, Nylen E, Panagiotakos DB, Manolis A, Pittaras A, Blackman MR, Jacob-Issac R, Faselis C, Abella J, Singh S. Exercise capacity and all-cause mortality in African American and Caucasian men with type 2 diabetes. Diabetes Care. 2009;32(4):623-8.
13. Kokkinos PF, Faselis C, Myers J, Narayan P, Sui X, Zhang J, Lavie CJ, Moore H, Karasik P, Fletcher R. Cardiorespiratory fitness and incidence of major adverse cardiovascular events in US veterans: a cohort study. Mayo Clin Proc. 2017;92(1):39-48.

14. Kokkinos PF, Faselis C, Myers J, Panagiotakos D, Doumas M. Interactive effects of fitness and statin treatment on mortality risk in veterans with dyslipidaemia: a cohort study. Lancet. 2013;381(9864):394-9.
15. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, Sugawara A, Totsuka K, Shimano H, Ohashi Y, Yamada N, Sone H. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. JAMA. 2009;301(19):2024-35.
16. Gulati M, Pandey DK, Arnsdorf MF, Lauderdale DS, Thisted RA, Wicklund RH, Al-Hani AJ, Black HR. Exercise capacity and the risk of death in women: the St James Women Take Heart Project. Circulation. 2003;108(13):1554-9.
17. Manson JE, Greenland P, LaCroix AZ, Stefanick ML, Mouton CP, Oberman A, Perri MG, Sheps DS, Pettinger MB, Siscovick DS. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. N Engl J Med. 2002;347(10):716-25.
18. Manson JE, Hu FB, Rich-Edwards JW, Colditz GA, Stampfer MJ, Willett WC, Speizer FE, Hennekens CH. A prospective study of walking as compared with vigorous exercise in the prevention of coronary heart disease in women. N Engl J Med. 1999;341(9):650-8.
19. Balady GJ, Larson MG, Vasan RS, Leip EP, O'Donnell CJ, Levy D. Usefulness of exercise testing in the prediction of coronary disease risk among asymptomatic persons as a function of the Framingham risk score. Circulation. 2004;110 (14):1920-5.
20. Goraya TY, Jacobsen SJ, Pellikka PA, Miller TD, Khan A, Weston SA, Gersh BJ, Roger VL. Prognostic value of treadmill exercise testing in elderly persons. Ann Intern Med. 2000;132(11):862-70.
21. Kokkinos P, Myers J. Exercise and physical activity: clinical outcomes and applications. Circulation. 2010;122(16): 1637-48.
22. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med. 2002;346(11):793-801.
23. Blair SN, Kampert JB, Kohl HW III, Barlow CE, Macera CA, Paffenbarger RS Jr, Gibbons LW. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. JAMA. 1996;276(3):205-10.
24. Church TS, Cheng YJ, Earnest CP, Barlow CE, Gibbons LW, Priest EL, Blair SN. Exercise capacity and body composition as predictors of mortality among men with diabetes. Diabetes Care. 2004;27(1):83-8.
25. Faselis C, Doumas M, Pittaras A, Narayan P, Myers J, Tsimploulis A, Kokkinos P. Exercise capacity and all-cause mortality in male veterans with hypertension aged ≥70 years. Hypertension. 2014;64(1):30-5.
26. Al-Mallah MH, Qureshi WT, Keteyian SJ, Brawner CA, Alam M, Dardari Z, Nasir K, Blaha MJ. Racial differences in the prognostic value of cardiorespiratory fitness (results from the Henry Ford Exercise Testing Project). Am J Cardiol. 2016;117(9):1449-54.
27. Morris CK, Ueshima K, Kawaguchi T, Hideg A, Froelicher VF. The prognostic value of exercise capacity: a review of the literature. Am Heart J. 1991;122(5):1423-31.
28. Myers J, Kaykha A, George S, Abella J, Zaheer N, Lear S, Yamazaki T, Froelicher V. Fitness versus physical activity patterns in predicting mortality in men. Am J Med. 2004;117(12):912-8.
29. Swift DL, Johannsen NM, Lavie CJ, Earnest CP, Johnson WD, Blair SN, Church TS, Newton RL. Racial differences in the response of cardiorespiratory fitness to aerobic exercise training in Caucasian and African American postmenopausal women. J Appl Physiol (1985). 2013;114(10):1375-82.
30. Ceaser TG, Fitzhugh EC, Thompson DL, Bassett DR Jr. Association of physical activity, fitness, and race: NHANES 1999-2004. Med Sci Sports Exerc. 2013;45(2):286-93.
31. Lavie CJ, Kuruvanka T, Milani RV, Prasad A, Ventura HO. Exercise capacity in adult African-Americans referred for exercise stress testing: is fitness affected by race? Chest. 2004;126(6):1962-8.
32. Ehrman JK, Brawner CA, Al-Mallah MH, Qureshi WT, Blaha MJ, Keteyian SJ. Cardiorespiratory fitness change and mortality risk among black and white patients: Henry Ford Exercise Testing (FIT) Project. Am J Med. 2017;130: 1177-83.
33. Kokkinos P. Cardiorespiratory fitness, exercise, and blood pressure. Hypertension. 2014;64(6):1160-4.
34. Pescatello LS, Franklin BA, Fagard R, Farquhar WB, Kelley GA, Ray CA. American College of Sports Medicine position stand. Exercise and hypertension. Med Sci Sports Exerc. 2004;36(3):533-53.
35. Riebe D, Ehrman JK, Liguori G, Magal M. ACSM Guidelines for Exercise Testing and Prescription. 10th ed. Wolters Kluwer. Philadelphia PA; 2018.
36. Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. J Am Heart Assoc. 2013;2(1):e004473.
37. Brook RD, Appel LJ, Rubenfire M, Ogedegbe G, Bisognano JD, Elliott WJ, Fuchs FD, Hughes JW, Lackland DT, Staffileno BA, Townsend RR, Rajagopalan S; American Heart Association Professional Education Committee of the Council for High Blood Pressure Research, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, and Council on Nutrition, Physical Activity. Beyond medications and diet: alternative approaches to lowering blood pressure: a scientific statement from the American Heart Association. Hypertension. 2013;61(6):1360-83.
38. Kokkinos PF, Narayan P, Colleran JA, Pittaras A, Notargiacomo A, Reda D, Papademetriou V. Effects of regular exercise on blood pressure and left ventricular hypertrophy in African-American men with severe hypertension. N Engl J Med. 1995;333(22):1462-7.
39. Dahlof B, Pennert K, Hansson L. Reversal of left ventricular hypertrophy in hypertensive patients. A meta-analysis of 109 treatment studies. Am J Hypertens. 1992;5(2):95-110.
40. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med. 1990;322(22):1561-6.
41. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC Jr, Svetkey LP, Taler SJ, Townsend RR, Wright JT Jr, Narva AS, Ortiz E. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507-20.
42. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM,

Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F; Task Force Members. 2013 ESH/ESC practice guidelines for the management of arterial hypertension. Blood Press. 2014;23(1):3-16.
43. Faselis C, Doumas M, Panagiotakos D, Kheirbek R, Korshak L, Manolis A, Pittaras A, Tsioufis C, Papademetriou V, Fletcher R, Kokkinos P. Body mass index, exercise capacity, and mortality risk in male veterans with hypertension. Am J Hypertens. 2012;25(4):444-50.
44. Gregg EW, Cheng YJ, Saydah S, Cowie C, Garfield S, Geiss L, Barker L. Trends in death rates among U.S. adults with and without diabetes between 1997 and 2006: findings from the National Health Interview Survey. Diabetes Care. 2012;35(6):1252-7.
45. Miller JP, Pratley RE, Goldberg AP, Gordon P, Rubin M, Treuth MS, Ryan AS, Hurley BF. Strength training increases insulin action in healthy 50- to 65-yr-old men. J Appl Physiol (1985). 1994;77(3):1122-7.
46. Smutok MA, Reece C, Kokkinos PF, Farmer C, Dawson P, Shulman R, DeVane-Bell J, Patterson J, Charabogos C, Goldberg AP. Aerobic versus strength training for risk factor intervention in middle-aged men at high risk for coronary heart disease. Metabolism. 1993;42(2):177-84.
47. Smutok MA, Reece C, Kokkinos PF, Farmer CM, Dawson PK, DeVane J, Patterson J, Goldberg AP, Hurley BF. Effects of exercise training modality on glucose tolerance in men with abnormal glucose regulation. Int J Sports Med. 1994;15(6):283-9.
48. Shepherd PR, Kahn BB. Glucose transporters and insulin action–implications for insulin resistance and diabetes mellitus. N Engl J Med. 1999;341(4):248-57.
49. Hu FB, Leitzmann MF, Stampfer MJ, Colditz GA, Willett WC, Rimm EB. Physical activity and television watching in relation to risk for type 2 diabetes mellitus in men. Arch Intern Med. 2001;161(12):1542-8.
50. Wei M, Gibbons LW, Kampert JB, Nichaman MZ, Blair SN. Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. Ann Intern Med. 2000;132(8):605-11.
51. Church TS, LaMonte MJ, Barlow CE, Blair SN. Cardiorespiratory fitness and body mass index as predictors of cardiovascular disease mortality among men with diabetes. Arch Intern Med. 2005;165(18):2114-20.
52. LaMonte MJ, Blair SN, Church TS. Physical activity and diabetes prevention. J Appl Physiol (1985). 2005;99(3):1205-13.
53. Ness J, Nassimiha D, Feria MI, Aronow WS. Diabetes mellitus in older African-Americans, Hispanics, and whites in an academic hospital-based geriatrics practice. Coron Artery Dis. 1999;10(5):343-6.
54. Kodama S, Tanaka S, Heianza Y, Fujihara K, Horikawa C, Shimano H, Saito K, Yamada N, Ohashi Y, Sone H. Association between physical activity and risk of all-cause mortality and cardiovascular disease in patients with diabetes: a meta-analysis. Diabetes Care. 2013;36(2):471-9.
55. Schellenberg ES, Dryden DM, Vandermeer B, Ha C, Korownyk C. Lifestyle interventions for patients with and at risk for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2013;159(8):543-51.
56. Pi-Sunyer X. The look AHEAD trial: a review and discussion of its outcomes. Curr Nutr Rep. 2014;3(4):387-91.
57. Arterburn DE, O'Connor PJ. A look ahead at the future of diabetes prevention and treatment. JAMA. 2012;308(23):2517-8.
58. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med. 2008;358(6):580-91.
59. Oktay AA, Lavie CJ, Kokkinos PF, Parto P, Pandey A, Ventura HO. The interaction of cardiorespiratory fitness with obesity and the obesity paradox in cardiovascular disease. Prog Cardiovasc Dis. 2017;60(1):30-44.
60. King GA, Fitzhugh EC, Bassett DR Jr, McLaughlin JE, Strath SJ, Swartz AM, Thompson DL. Relationship of leisure-time physical activity and occupational activity to the prevalence of obesity. Int J Obes Relat Metab Disord. 2001;25(5):606-12.
61. Sui X, LaMonte MJ, Laditka JN, Hardin JW, Chase N, Hooker SP, Blair SN. Cardiorespiratory fitness and adiposity as mortality predictors in older adults. JAMA. 2007;298(21):2507-16.
62. Wei M, Kampert JB, Barlow CE, Nichaman MZ, Gibbons LW, Paffenbarger RS Jr, Blair SN. Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight, and obese men. JAMA. 1999;282(16):1547-53.
63. Hu FB, Willett WC, Li T, Stampfer MJ, Colditz GA, Manson JE. Adiposity as compared with physical activity in predicting mortality among women. N Engl J Med. 2004;351(26):2694-703.
64. Li TY, Rana JS, Manson JE, Willett WC, Stampfer MJ, Colditz GA, Rexrode KM, Hu FB. Obesity as compared with physical activity in predicting risk of coronary heart disease in women. Circulation. 2006;113(4):499-506.
65. Katzmarzyk PT, Church TS, Janssen I, Ross R, Blair SN. Metabolic syndrome, obesity, and mortality: impact of cardiorespiratory fitness. Diabetes Care. 2005;28(2):391-7.
66. LaMonte MJ, Blair SN. Physical activity, cardiorespiratory fitness, and adiposity: contributions to disease risk. Curr Opin Clin Nutr Metab Care. 2006;9(5):540-6.
67. Ades PA, Savage PD. The obesity paradox: perception vs knowledge. Mayo Clin Proc. 2010;85(2):112-4.
68. McAuley PA, Kokkinos PF, Oliveira RB, Emerson BT, Myers JN. Obesity paradox and cardiorespiratory fitness in 12,417 male veterans aged 40 to 70 years. Mayo Clin Proc. 2010;85(2):115-21.
69. Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. Am Heart J. 2008;156(1):13-22.
70. Lavie CJ, De Schutter A, Parto P, Jahangir E, Kokkinos P, Ortega FB, Arena R, Milani RV. Obesity and prevalence of cardiovascular diseases and prognosis-the obesity paradox updated. Prog Cardiovasc Dis. 2016;58(5):537-47.
71. Lavie CJ, Mehra MR, Milani RV. Obesity and heart failure prognosis: paradox or reverse epidemiology? Eur Heart J. 2005;26(1):5-7.
72. Lavie CJ, Oktay AA, Milani RV. The obesity paradox and obesity severity in elderly STEMI patients. Eur Heart J Qual Care Clin Outcomes. 2017;3(3):166-7.
73. Kokkinos P, Faselis C, Myers J, Pittaras A, Sui X, Zhang J, McAuley P, Kokkinos JP. Cardiorespiratory fitness and the paradoxical BMI-mortality risk association in male veterans. Mayo Clin Proc. 2014;89(6):754-62.