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Exercise and Physical Activity Clinical Outcomes and Applications

Peter Kokkinos, PhD; Jonathan Myers, PhD

The association between physical activity and health was recognized as early as the fifth century BC by the Greek physician Hippocrates, who wrote the following: "All parts of the body, if used in moderation and exercised in labors to which each is accustomed, become thereby healthy and well developed and age slowly; but if they are unused and left idle, they become liable to disease, defective in growth and age quickly."

With the decline of the Hellenic civilization, this concept faded. For centuries, physical activity and fitness were considered largely for military purposes and associated with youth sports and athletics even through the post-World War II era.

The landmark work by Morris and coworkers¹ changed modern views of the relationship between physical activity, fitness, and health and inspired a new era in which the association between physical activity and human health, disease, and mortality was scrutinized scientifically. For more than half a century, a plethora of evidence has accumulated from large, long-term epidemiological studies that support a strong, inverse, and independent association between physical activity, health, and cardiovascular and overall mortality in apparently healthy individuals²⁻²³ and in patients with documented cardiovascular disease.⁸ The exercise-related health benefits are related in part to favorable modulations in both the traditional and novel cardiovascular risk factors that have been observed with increased physical activity patterns or structured exercise programs.¹⁰ In this review, we present a synopsis of some of the most influential studies examining the association between physical activity, fitness, and health. The studies cited represent only a small number of the many studies available, and more in-depth reviews are available on each of the topics discussed in the present review. In addition, the favorable effects of physical activity on the traditional and novel cardiovascular risk factors are discussed. Finally, we consider the clinical applications of this evidence and future directions.

Occupational and Leisure Time Physical Activity Studies

Early epidemiological evidence strongly supported an inverse association between occupational and leisure time physical activity and all-cause and cardiovascular mortality in men.²⁴ The contribution of physical activity to health outcomes is

independent even when the traditional cardiovascular risk markers and genetic factors are considered.^{2,8,11-14} Moreover, the degree of risk associated with physical inactivity is similar to and in some cases even stronger than the more traditional cardiovascular risk factors.^{2,8,11-14}

Similarly, more recent large cohort studies in women, including the Women's Health Study, the Lipid Research Clinics Research Prevalence Study, and the Women Take Heart Project, reported an inverse and graded association between increased physical activity and mortality.^{6,7,13-17} Some data even suggest that physical activity provides a greater degree of protection in women than men.^{13,14} In addition, a noteworthy finding was that sedentary women who became physically active between a baseline and a follow-up visit (≈ 6 years apart) had 32% and 38% lower all-cause and cardiovascular mortality rates, respectively, compared with women who were sedentary at both visits.¹⁷

Fitness Assessment Studies

Over the last 2 decades, a large number of follow-up studies using objective assessments of physical fitness by maximal exercise testing have enriched our understanding of the association between physical fitness and cardiovascular risk. In the Aerobics Center Longitudinal Study (ACLS), a strong and inverse association between fitness levels and mortality in a large sample of mostly white, middle-aged, and relatively healthy individuals was reported.³ Importantly, the largest reduction in mortality was observed between the least-fit and the next least-fit category (those achieving 6 to 8 metabolic equivalents [METs] versus those achieving < 6 METs). Mortality risk continued to decrease with increased fitness and reached an asymptote at ≈ 9 and 10 METs for men and women, respectively.³ Similar trends were noted in > 15 000 older veterans (Figure 1), suggesting an age-related threshold for mortality risk reduction at ≈ 4 to 6 METs and an asymptote occurring at ≈ 10 METs.

In subsequent studies from the ACLS, the risk for all-cause and cardiovascular mortality associated with fitness was similar to that for cigarette smoking and elevated cholesterol levels.⁴ When mortality risk was assessed in terms of change in exercise capacity between 2 visits (an average of 5 years

From the Cardiology Division, Veterans Affairs Medical Center, Georgetown University School of Medicine, and George Washington University School of Medicine and Health Sciences, Washington, DC (P.K.); and Cardiology Division, Veterans Affairs Palo Alto Health Care System, Palo Alto, Calif, and Stanford University, Stanford, Calif (J.M.).

Correspondence to Peter F. Kokkinos, PhD, Cardiology Division, Veterans Affairs Medical Center, 50 Irving St NW, Washington, DC 20422. E-mail peter.kokkinos@med.va.gov

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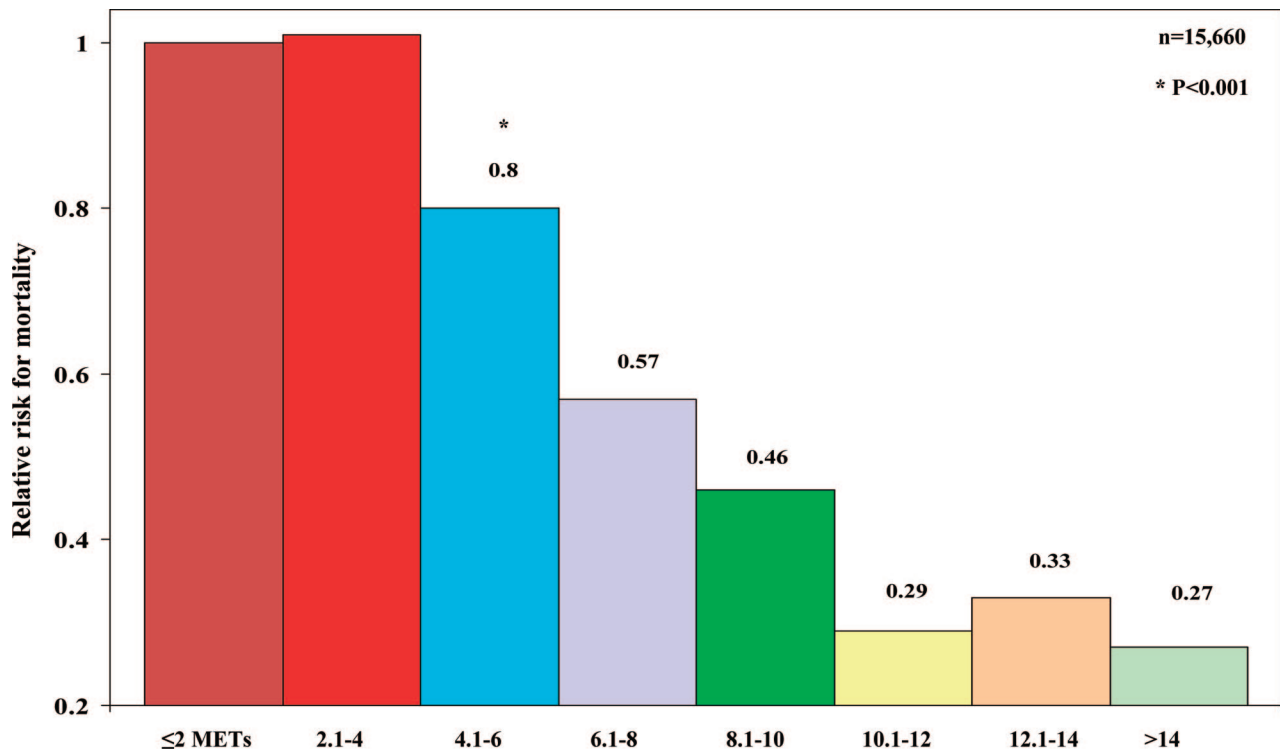


Figure 1. Mortality risk according to exercise capacity. Note that significant reductions in mortality are evident at >4 METs and reach an asymptote at >10 METs. Data from Kokkinos et al.²

apart), a 7.9% reduction in mortality was observed for every minute increase in peak treadmill exercise time between examinations. In addition, unfit men who improved their fitness status during subsequent visits had a 44% reduction in mortality risk.⁵ This and similar reports in women¹⁷ strengthen the assertion that the association between fitness and mortality is independent of other risk markers.

Several subsequent studies expressed this relationship in the context of survival benefit per MET increase in exercise capacity (Table). The reduction in mortality risk per MET in these studies has ranged between 10% and 25%.^{2,5,8,12-14,18-20} This is evident in both young and elderly subjects, men and women, and individuals with and without cardiovascular disease.^{8,18-20} In the Veterans Exercise Testing Study, similar findings have been observed recently among the elderly with multiple existing risk factors and among blacks.² In the latter group, a 15% lower mortality risk was reported for every 1-MET increase in exercise capacity, similar to that observed in whites.⁸

Association of Mortality Risk With Exercise Type, Duration, Intensity, and Volume

Although the physical activity–mortality risk relationship is well established, there remains a need to better define the independent contribution of the activity components (intensity, duration, frequency) and mode of exercise to mortality risk.²⁵ Guidelines on physical activity and health from major health organizations have generally recommended exercise intensities in the range of 3 to 6 METs and an overall energy expenditure of at least 1000 kcal/wk (the equivalent of walking for roughly 30 minutes per day). This is based on a 20% to 40% reduction in mortality associated with increased

physical activity patterns among middle-aged subjects followed for periods ranging between 5 and 15 years.^{9,21} Similar to fitness levels, health outcome benefits from physical activity appear to be most dramatic at the lowest end of the activity spectrum and reach a plateau among the most highly active individuals (>3500 kcal/wk).²²

The independent effects of exercise type, volume, and intensity on the risk for coronary heart disease (CHD) have been assessed in a large cohort of men (n=44 452) enrolled in the Health Professionals' Follow-up Study.²³ Walking pace (intensity) and exercise duration were both inversely related to the risk of CHD independent of walking volume. However, the much stronger association between exercise intensity and risk suggests that exercise intensity has a more significant effect on the incidence of CHD than duration. This was also the first study to provide evidence for the efficacy of resistance training on CHD risk. The reduction in CHD risk achieved by participation in resistance training was similar to that provided by brisk walking and rowing but was approximately half of that provided by running.

Similarly, in the Women's Health Study, exercise intensity (walking pace) and duration of walking were both inversely and independently related to the risk of coronary events.^{6,8} Women who walked 1 to 3 hours per week had between 30% and 50% reductions in CHD events compared with women who did no walking. However, for the same exercise volume achieved by either higher exercise intensity or longer duration, the risk reduction was substantially greater for exercise duration. In contrast to the findings reported in the Health Professionals' Follow-up Study of men,²³ this suggests that exercise duration is more effective in lowering the risk for coronary events than

Table. Survival Benefit per 1-MET Increase in Studies Using Maximal Exercise Testing as a Measure of Fitness

Cohort	Reference	Mortality Risk Reduction/MET Increase, %	Comments
Clinically referred middle-aged men with and without CHD (n=15 660)	2	13 (entire cohort)	Largest study to include blacks; moderately fit had 20–70% lower mortality in those with exercise capacity ≥5 METs vs those who achieved <5 METs
Black (n=6749)		15	
White (n=8911)		12	
Men completing 2 health evaluations 5±4 years apart (n=9777)	5	≈16	Improved survival in subjects who improved exercise capacity with serial testing
Clinically referred middle-aged men with and without CHD (n=6213)	8	12	Exercise capacity most powerful predictor of mortality
Clinically referred subjects for exercise testing (n=6213)	12	20	1-MET increment in exercise capacity roughly equivalent to 1000 kcal/wk adult activity
Asymptomatic women from the Lipid Research Clinics Prevalence Study (n=2994)	13	20	Fitness-related variables more strongly associated with survival than other exercise test variables
Healthy asymptomatic women in the St James Women Take Heart Project (n=5721)	14	17	Exercise capacity an independent predictor of mortality in women, higher than previously established in men
Asymptomatic men and women from the Framingham Offspring Study	18	13	Reduction in risk of events per MET among high-risk men in Framingham Offspring Study
Men (n=1431)			
Women (n=1612)			
315 post-myocardial infarction men randomized to a 6-month exercise program (n=315)	19	8–14	Increase in exercise capacity during cardiac rehabilitation had sustained benefits up to 19 years
Referred for exercise testing	20		Survival benefit per MET for younger and elderly subjects
Younger (n=2593)		14	
Elderly (n=514)		18	

exercise intensity. However, the inextricable complexity of the interactions between gender, exercise intensity, duration, and frequency cannot be resolved by epidemiological studies. Most importantly, and despite possible differences attributable to gender and exercise stimulus, the salient finding of these and other reports^{12,26} is that moderate activity such as walking has a considerable impact on CHD events, and walking or similar activities a few hours per week should be recommended to all adults, as suggested in various guidelines.^{27,28}

Hypertension

Chronic essential hypertension is a major risk factor for cardiovascular disease and is the most common risk factor present among subjects who develop cardiovascular events.²⁹ The mortality risk doubles for every 20-mm Hg increase in systolic blood pressure (BP) above the threshold of 115 mm Hg and for every 10-mm Hg increase above the diastolic BP threshold of 75 mm Hg.³⁰

The high prevalence of hypertension (estimated to be one third of the adult population in the United States¹) is due in part to lifestyle factors. Positive lifestyle modifications, including weight loss and increased physical activity, contribute significantly to BP control.^{31,32} Significant reductions in BP after aerobic exercise programs of mild to moderate intensity have been a consistent finding of many well-controlled studies. The general conclusion from these studies is that aerobic exercise training lowers BP in individuals with stage 1 hypertension by ≈3.4 to 10.5 mm Hg for systolic BP and 2.4 to 7.6 mm Hg^{33–36} for diastolic BP. The magnitude of the reduction may be related

to the initial level of BP,³⁷ whereas the influences of age or gender are not clear.³⁸ However, similar BP reductions in middle-aged and older individuals with stage 2 hypertension have been reported after 16 and 32 weeks of exercise despite a 33% reduction in antihypertensive medication achieved by the end of the study (week 32).³⁹

Exercise-induced changes in BP over a 24-hour period (ambulatory BP) have been reported by a limited number of studies and are estimated to be less dramatic than for BP assessed from a single measurement (mean 3.0- and 3.2-mm Hg reductions for systolic and diastolic BP, respectively).^{34,35} However, daytime ambulatory BP differences between fit and unfit prehypertensive men and women (n=650) are similar to the BP changes reported after exercise training.⁴⁰ Consequently, increased physical activity is now strongly recommended as part of the lifestyle modifications as an adjunct to pharmacological therapy proposed by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and recent European Society of Hypertension/European Society of Cardiology guidelines.^{29,41}

BP reductions are evident at low-to-moderate exercise intensities (35% to 79% of age-predicted maximum heart rate), with some studies suggesting that low exercise intensity may be more effective in lowering BP than high exercise intensity.^{37,42,43} Others have noted that the favorable effects of training on BP are not influenced or are only minimally influenced by exercise intensity, frequency, type, or duration.⁴⁴ Overall, the evidence that the BP response to regular exercise differs according to training intensity is not convincing.³³

BP Response to Acute Exercise

Evidence suggests that the systolic BP response at the exercise level of 5 METs is associated with increased risk for left ventricular (LV) hypertrophy.⁴⁵ Middle-aged, prehypertensive individuals (n=790) with similar resting BPs who achieved a systolic BP ≥ 150 mm Hg at 5 METs had a significantly higher LV mass index compared with those with systolic BPs below this level. The risk of LV hypertrophy increased 4-fold for every 10-mm Hg rise in systolic BP beyond the threshold of 150 mm Hg at 5 METs.⁴⁵

The rationale for the exercise systolic BP and LV mass relationship is that the BP response at exercise workloads of ≈ 5 METs reflects daytime BP during most daily activities. Support for this contention is provided by the similarity between the exercise BP at ≈ 5 METs and daytime ambulatory BP obtained in 650 prehypertensive individuals.^{40,45} Thus, it is reasonable to assume that the daily exposure to relatively high BP provides the impetus for an increase in LV mass even at the prehypertensive stage.

Evidence suggests that the BP response to exercise is modulated by fitness. Exercise capacity has been shown to be inversely related to exercise BP and to LV mass.⁴⁵ When fitness was considered, the systolic BP at 5 METs was ≈ 10 mm Hg lower for moderately and highly fit individuals compared with the BP of the individuals in the low-fitness category. LV mass index was also significantly lower in the moderately and highly fit individuals. For every 1-MET increase in the workload achieved, a 42% reduction in the risk for LV hypertrophy was observed.⁴⁵ Finally, 16 weeks of aerobic training resulted in significantly lower BPs at ≈ 3 and 5 METs,⁴⁶ and regular exercise was associated with LV mass regression in older individuals with stage 2 hypertension.³⁹

Resistance Exercise and Hypertension

Strength training as a way to lower BP was traditionally discouraged by physicians and other health professionals largely because excessive elevations in BP have been noted during high-resistance weight-lifting exercises (80% to 100% of 1-repetition maximum).⁴⁷ However, resistance training has been widely recommended in recent years for the elderly, in cardiac rehabilitation programs, and for the public because it is associated with numerous health benefits, including reducing the risk of falls by reversing or attenuating the age-related decline in bone mineral density, muscle mass, and power.⁴⁸ Information available on the effects of strength training on resting BP is limited and conflicting. The conclusion of a recent meta-analysis was that the average systolic BP reduction as a result of resistance training was ≈ 3 mm Hg. This is substantially less than that reported for endurance exercise.⁴⁹ Consequently, the recommendation of the American College of Sports Medicine is for resistance training to serve as an adjunct to an aerobic-based exercise program for BP reduction.³⁵ Despite the limited favorable changes in BP, strength training is associated with numerous other health benefits, and in accordance with recommendations from the American Heart Association and the American College of Sports Medicine, resistance exercise should be implemented as part of a complete exercise program.^{50,51}

Hypertension, Fitness, and Mortality

Increased exercise capacity is associated with lower mortality in hypertensive individuals.^{8,52,53} In 4631 hypertensive veterans with multiple cardiovascular risk factors, an inverse and graded association between exercise capacity and mortality risk was reported. After adjustment for age and other risk factors, mortality was 13% lower for every 1-MET increase in exercise capacity. The subjects were then categorized into 4 groups on the basis of their fitness level (least fit to most fit) and on the presence or absence of additional risk factors. Among the least-fit individuals, those with additional risk factors had a 47% higher mortality rate than those without risk factors. The increased risk imposed by a low fitness level and additional cardiovascular risk factors was eliminated by relatively small increases in exercise capacity, and the risk declined progressively with higher exercise capacity (Figure 2).⁵³

Similar associations between exercise capacity and mortality risk have been observed in prehypertensive individuals.⁵⁴ Compared with the least-fit individuals, reductions in mortality risk ranged from 40% for those in the next to the least-fit category to 58% and 73% for the individuals in the moderately and highly fit categories, respectively. A noteworthy observation was that for every 1-MET increase in exercise capacity, the risk was reduced by 18% in the younger group (≤ 60 years) and 12% in the older individuals, suggesting that the impact of exercise capacity on mortality may be strongly related to age.

Diabetes Mellitus

Exercise is an insulin-independent stimulus for increased glucose uptake by the working muscle cells via the GLUT-4 transporter.⁵⁵ Findings from exercise training studies support the concept that both aerobic and anaerobic exercise training regimens improve glucose uptake and insulin sensitivity.^{56,57}

Evidence from large cohort studies demonstrates that physical activity in general provides a highly effective way to delay or avert the development of diabetes mellitus. In addition, physical activity has been shown to reduce the risk of mortality in diabetics. The incidence of type 2 diabetes mellitus was inversely related to leisure time physical activity among men in the Harvard Alumni Study⁵⁸ and in US male physicians.⁵⁹ Likewise, in the Nurses' Health Study⁶⁰ (n=70 102), the relative risk for developing diabetes mellitus in women was inversely related to the level of fitness as well as exercise volume and intensity in a dose-response fashion. Equivalent energy expenditures from different activities and intensities conferred similar health benefits.

These epidemiological findings are supported by 2 interventional studies.^{61,62} In the Finnish Diabetes Prevention Study,⁶¹ 522 middle-aged, overweight men and women were randomized to either an intervention group or a control group. The intervention group was counseled to follow a healthy diet, reduce weight, and increase physical activity. At the end of 3.2 years of follow-up, the cumulative incidence of diabetes mellitus was 11% for the intervention group and 23% for the control group. The overall risk for diabetes mellitus was reduced by 58% in the intervention group. The Diabetes Prevention Program Research Group Study⁶² provided strong evidence that lifestyle modifications, including

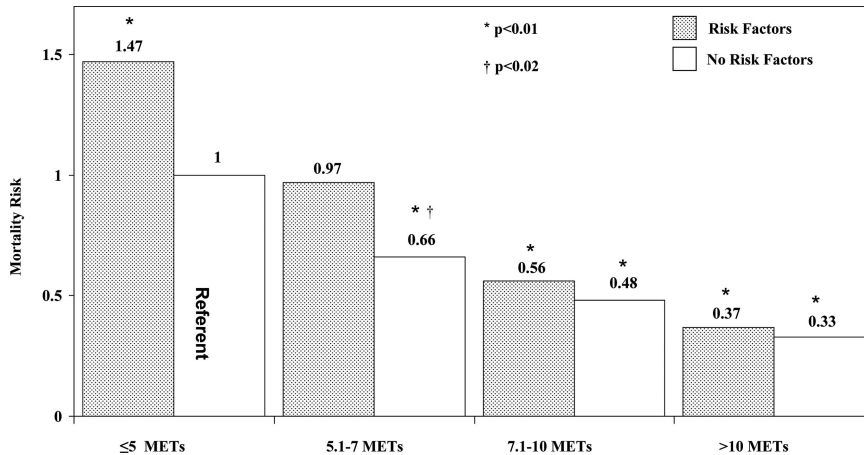


Figure 2. Mortality risk within each fitness category for hypertensive individuals with and without additional risk factors. *Different from the very-low fitness with no risk factors group (referent). †Different from the low-fitness with risk factors group. Adapted from Kokkinos et al.⁵³

diet and exercise, were more effective in reducing the incidence of diabetes than treatment with metformin. Compared with the control group, the incidence of diabetes mellitus was 58% lower in the lifestyle-intervention group encouraged to exercise 150 min/wk and 31% in the metformin group. The incidence of diabetes mellitus was 39% lower in the lifestyle-intervention group than in the metformin group. To prevent 1 case of diabetes mellitus, the investigators calculated that 6.9 persons would have to participate in the lifestyle-intervention group and 13.9 would have to receive metformin. Finally, lifestyle intervention resulted in more participants maintaining normal blood glucose values over a period of 3 years compared with the metformin or placebo group.

Evidence also suggests that the all-cause mortality risk in physically unfit or sedentary diabetics is >2 times higher compared with physically fit men and women diabetics regardless of body weight.⁶³⁻⁶⁵ Because blacks have a 2- to 6-fold higher risk for developing diabetes mellitus⁶⁶ and approximately double the diabetes mellitus death rate⁶⁷ compared with whites, the relationship between exercise capacity and all-cause mortality in black and white diabetic individuals was assessed in the Veterans Exercise Testing Study.⁶⁸ The findings support the concept that exercise capacity is a strong predictor of mortality in black and white men with type 2 diabetes mellitus. The age-adjusted reduction was graded and more pronounced in whites than in blacks; each 1-MET increase in exercise capacity yielded 14% and a 19% lower risk for blacks and whites, respectively. Similarly, the risks were 34% and 46% lower for moderately and highly fit blacks versus blacks in the low-fitness category, respectively. For whites, the comparable reductions were 43% and 67%, respectively (Figure 3).

Lipids

Most evidence from epidemiological and randomized controlled trials supports the concept that aerobic exercise of adequate intensity, duration, and volume results in favorable and independent alterations of blood lipids and lipoproteins in both normolipidemic and dyslipidemic individuals.⁶⁹⁻⁷¹ The most consistent findings have been demonstrated for increases in high-density lipoprotein (HDL) cholesterol, with less consistency for reductions in total cholesterol, triglycerides, and low-density lipoprotein cholesterol concentrations.⁷¹ The combination of exercise

and dietary changes may result in low-density lipoprotein cholesterol reductions beyond those achieved by diet or exercise alone in both men and women who are dyslipidemic.⁷² Exercise training can also attenuate the reductions in HDL cholesterol^{72,73} usually observed with low-fat diets.^{74,75}

Greater HDL cholesterol changes in men versus women, particularly when exercise is combined with a prudent diet, have been reported by some^{72,75} but disputed by others.^{76,77} Overall, no consistent evidence is available to indicate that HDL cholesterol changes related to exercise are associated with age, ethnicity, or gender.⁷¹ Some studies suggested that exercise training does not appear to improve HDL cholesterol concentrations beyond the improvements seen with hormone replacement therapy,⁷⁸ whereas others have shown synergistic effects between hormone replacement therapy and exercise training.⁷⁹

Accumulated epidemiological evidence also suggests that the magnitude of the changes in HDL cholesterol is related more to the volume of exercise than the intensity.^{69,70} This was supported by the findings of a recent interventional study designed to assess the independent contributions of exercise volume and intensity on the lipoprotein-lipid profile. Improvements in lipids and lipoproteins were related to the amount of activity and not to the intensity of exercise or improvement in fitness.⁸⁰

The exercise volume for achieving significant HDL cholesterol changes is estimated at ≈1000 to 1500 kcal/wk.⁸¹ This parallels an earlier study in which a mean estimated weekly energy expenditure of 1245 kcal for individuals running ≈7 to 10 miles per week (average, 9 miles) and 1688 kcal for those running 11 to 14 miles per week (average, 12 miles) resulted in 7% and 11% increases in HDL cholesterol concentrations, respectively.⁸² Others have reported similar changes in HDL cholesterol among individuals running similar weekly distances for ≈9 to 12 months.^{83,84} It is likely that other modes of physical activity will invoke similar increases in HDL cholesterol concentrations as long as they meet or exceed the caloric expenditure of 1200 to 1600 kcal.

A dose-response relationship between the volume of exercise and HDL cholesterol changes has also been suggested in various cohorts of runners. In 2906 middle-aged men classified by exercise volume (from sedentary to running as much as 60 miles per week), a 0.31-mg/dL increase in HDL cholesterol concentration for each mile increase in weekly

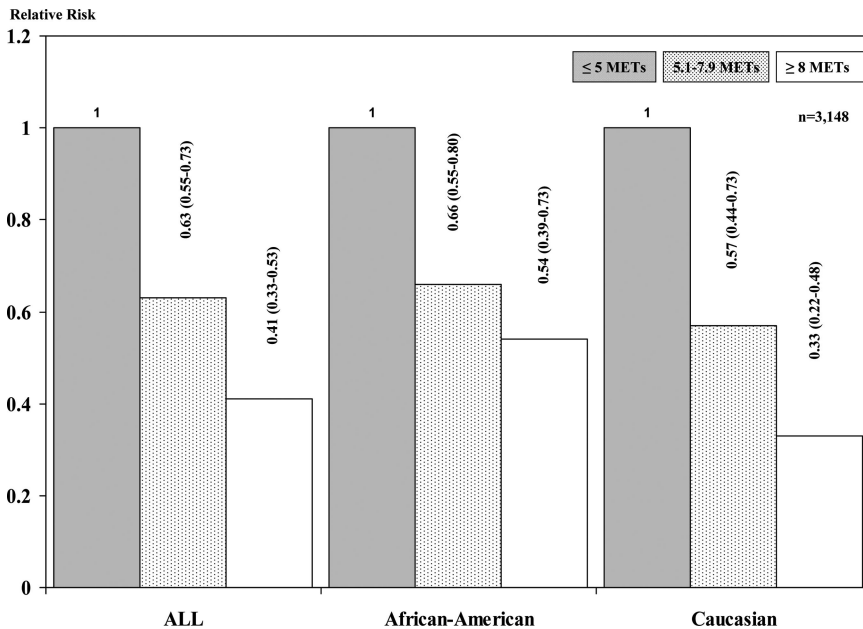


Figure 3. Exercise capacity and relative risk of all-cause mortality in individuals with type 2 diabetes mellitus according to MET levels achieved. Data from Kokinos et al.⁶⁸

distance was observed. Compared with the sedentary group, HDL cholesterol concentrations were 7%, 11%, 12%, and 19% higher for individuals in the groups running average distances of 9, 12, 17, and 31 miles per week, respectively.⁸² Similarly, in the National Runners' Health Study of 8283 men, HDL cholesterol concentrations were progressively and significantly higher for every 10-mile incremental increase in weekly mileage up to ≈ 50 miles per week.⁸⁵ In women, menopausal status does not appear to influence this dose-response relationship.⁸⁶

The potential for the complementary effects of exercise training among individuals treated with lipid-lowering medications merits scientific scrutiny. However, no studies have been designed to specifically address this issue.

Obesity

Obesity and overweight are considered to be leading risk factors for a number of chronic health conditions, including diabetes mellitus, hypertension, CHD, and premature mortality. Obesity not only increases CHD risk directly but also enhances it indirectly through its adverse effects on several established risk factors, including insulin resistance and hypertension. Although the causes of obesity are complex, physical inactivity is considered to be an important causal factor. For example, in a representative sample of American adults, the relative risk of obesity among individuals physically active in leisure time (≥ 5 bouts of physical activity per week) was $\approx 50\%$ lower than among those who were physically inactive.⁸⁷ Although such an association does not demonstrate cause and effect, this and similar reports strongly suggest that a relationship exists between physical activity levels and obesity, in which comparatively sedentary individuals are more likely to be obese compared with those who are physically active.

Despite relatively modest weight reductions associated with structured programs of physical activity, findings from large epidemiological studies support the concept that a reduced risk of cardiovascular disease and all-cause mortality

occurs among more active individuals regardless of weight loss. In a large follow-up from the ACLS ($n=25\,714$), higher fitness levels were associated with lower risk of mortality in normal-weight, overweight, and obese men.⁸⁸ Compared with other risk factors (total cholesterol, hypertension, and smoking), having a low fitness level carried similarly heightened risks in each weight category for both cardiovascular and all-cause mortality. In a subsequent study from the ACLS among older subjects (>60 years), higher waist circumference was associated with higher mortality, but this association was not significant after adjustment for fitness.⁸⁹ Fitness strongly predicted mortality independent of measures of body dimensions. These investigators suggested that it is as important for clinicians to assess the fitness status of an overweight or obese patient as it is to evaluate BP, inquire about smoking habits, and measure fasting plasma glucose and lipid levels.

Similarly, in the Nurses' Health Study ($n=116\,564$), higher levels of physical activity in women were associated with reduced mortality risk across all categories of body weight.⁹⁰ After adjustment for age, smoking status, parental history of CHD, menopause, hormonal use, and alcohol consumption, higher levels of physical activity reduced mortality risk but did not eliminate the high risk associated with obesity. Regardless of weight category, the relative risk for cardiovascular and all-cause mortality was significantly higher in women whose physical activity level was <1 h/wk. In a subsequent study from the Nurses' Health Study, being physically active moderately 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.⁹¹ Other prospective studies performed over the last decade have assessed the independent and joint associations between fitness, physical activity patterns, and outcomes. In each of these studies, the highest mortality risks were observed in subjects who were obese, unfit, or comparatively sedentary. When stratified within a given category of body dimensions (body mass index, waist circumference, or weight),

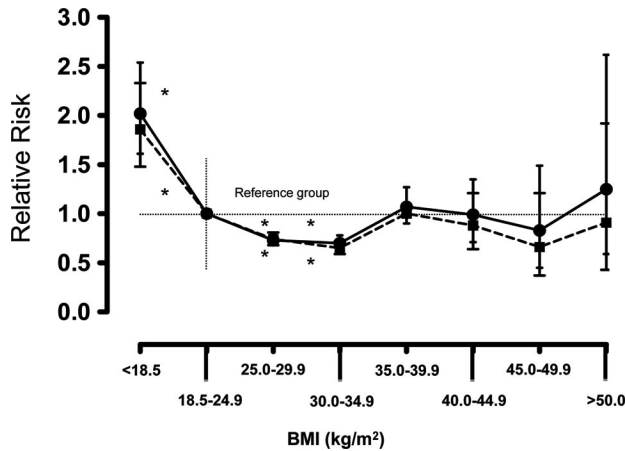


Figure 4. Mortality risk by body mass index (BMI) category in middle-aged men adjusted for age, ethnicity, cardiovascular disease, and risk factors (solid line) and with additional adjustment for fitness (dashed line). *Different from reference group ($P < 0.001$). Adapted from McAuley et al.⁹⁸ with permission of the publisher. © 2010, Mayo Foundation for Medical Education and Research.

subjects who are more physically active or fit consistently have a lower risk for adverse outcomes compared with those who are inactive or unfit. Higher levels of physical activity attenuate the mortality risk in all categories of adiposity, and both physical inactivity and excess weight are independently associated with the risk of cardiovascular disease.^{92,93}

As mentioned above, modest weight reductions have been associated with structured programs of physical activity. Because of the high prevalence of overweight and obesity among patients referred for cardiac rehabilitation (estimated to be $>80\%$ ⁹⁴), there has been recent interest in high-calorie-expenditure exercise. A recent trial demonstrated that patients randomized to an intensive counseling and exercise program designed to achieve an energy expenditure of 3000 to 3500 kcal/wk experienced double the weight loss of those in the standard cardiac rehabilitation group (8.2 ± 4 versus 3.7 ± 5 kg), a greater reduction in waist circumference, reduced insulin resistance, improved blood lipids, and lower prevalence of the metabolic syndrome (59% versus 31%).⁹⁵ Recent epidemiological findings have also drawn attention to an inverse association between body mass index and mortality in some populations, often termed the *obesity paradox*.⁹⁶⁻⁹⁸ In a recent report from the Veterans Affairs database, this inverse association was attenuated when fitness levels were considered (Figure 4).⁹⁸ This finding suggests that individuals within the lowest body mass index category may have had undefined chronic illness, resulting in weight loss and poor exercise capacity.⁹⁷ In this case, the inverse association may be fostered by unidentifiable confounding factors (such as subclinical disease) or an as yet unknown relationship not associated with chronic illness.

Inflammation

It is widely recognized that atherosclerosis is largely an inflammatory process. The “response to injury” hypothesis as a cause of atherosclerosis suggests that damage to the arterial endothelium initiated by a pathogen leads to immune re-

sponses that interact with metabolic risk factors to propagate an arterial lesion, eventually progressing to an atherosclerotic plaque. Circulating immune cells are recruited to the inflamed vessel by interacting with adhesion molecules and other proteins associated with the body’s immune response. Inflammation particularly occurs in areas where plaque is unstable. It is thought that as many as 70% of myocardial infarctions occur in areas of “vulnerable plaque.”⁹⁹ A number of blood markers have been identified that are associated with inflammation, most notably white blood cell count, C-reactive protein (CRP), homocysteine, fibrinogen, and other proteins involved in the immune response.

The most widely studied inflammatory blood marker is CRP.¹⁰⁰ In a recent follow-up study, elevated levels of CRP were associated with a higher risk of myocardial infarction, stroke, and mortality in both healthy individuals and patients with existing cardiovascular disease.¹⁰¹ The relationship between CRP and cardiovascular risk has consistently been shown to be independent of traditional risk factors such as smoking, hypertension, and lipid disorders. Others observed that CRP added markedly to the prognostic power of traditional risk factors and had twice the predictive value for cardiovascular events as low-density lipoprotein and HDL cholesterol.¹⁰² In the Physicians’ Health Study, the highest risk quartile for CRP was associated with a nearly 3-fold risk of sudden cardiac death compared with subjects in the lowest quartile for CRP.¹⁰³ In addition, several recent studies have shown that higher CRP levels and other inflammatory markers are associated with risk factors that define the metabolic syndrome (abnormal blood glucose, obesity, low HDL cholesterol, high triglycerides, hypertension).^{100,104,105}

Physical Fitness and Inflammation

Early epidemiological studies reported lower CRP levels in subjects with normal body weight, those who were most physically active, or both compared with overweight or inactive individuals. Several recent studies have focused on the association between inflammatory markers and fitness assessed by maximal exercise testing. Among 722 men in the ACLS, CRP levels were inversely related to fitness, with a nearly 80% reduction in CRP in the most-fit test group compared with the least-fit group.¹⁰⁶ A similarly strong and inverse trend was observed among 1640 men undergoing exercise testing as part of a preventive medicine evaluation.¹⁰⁴ The effect of fitness was strongest among subjects with the metabolic syndrome, suggesting that the benefits of fitness may be most pronounced among individuals with insulin resistance. In a Japanese cohort of 2722 adults, CRP was proportionately higher as peak VO_2 was lower. CRP increased in accordance with the number of cardiovascular risk factors present.¹⁰⁷ Collectively, the findings of epidemiological studies have been highly consistent in support of an inverse association between CRP, other inflammatory markers, and fitness. The recent recognition that fitness is a more powerful predictor of survival than traditional risk factors and other exercise test variables^{8,108} has been explained in part by the strong inverse association between fitness and inflammatory markers.

Physical Activity and Inflammation

Acute exercise induces a transient inflammatory response, including heightened CRP concentration. This is most likely due to joint and muscle inflammation after vigorous activity. However, regular, sustained exercise has been shown to suppress inflammation. This has been observed by studying inflammatory markers and physical activity patterns cross-sectionally and also by measuring CRP before and after periods of training. Among runners studied before and after 9 months of training in preparation for a marathon, mean CRP decreased by 31%.¹⁰⁹ A strong and independent association between higher physical activity patterns and level of CRP was also observed in 3638 middle-aged or older healthy men. Those who engaged in physical activity ≥ 5 times per week had 37% lower CRP levels than those who performed activity roughly once a week or less.¹¹⁰ In a more generalized follow-up from the National Health and Nutrition Examination Survey III, CRP levels from 13 748 adults were analyzed; the most active subjects had CRP levels nearly 50% lower than those of sedentary subjects.¹¹¹ CRP levels have shown similar improvements in response to 3 months of cardiac rehabilitation.¹¹² Some reports suggest that CRP and other inflammatory markers are lower only among subjects who engage in relatively vigorous activities (jogging and aerobic classes) compared with those participating in less demanding activities.¹¹³ However, others have reported markedly reduced CRP levels among those engaging in both larger and smaller volumes of physical activity compared with those who are sedentary.¹¹⁴

The mechanisms underlying more favorable levels of inflammatory markers in the blood among individuals with higher levels of fitness or physical activity have not been clearly established, but several mechanisms have been proposed. Higher physical activity patterns and fitness are associated with lower levels of body fat and low-density lipoprotein cholesterol, both of which have been suggested to be noninfectious triggers for elevated CRP.^{100,115} It has also been suggested that physical activity can reduce inflammation by improving insulin resistance because several inflammatory markers are higher among insulin-resistant subjects.¹¹⁶ By promoting weight loss, circulating insulin levels are reduced, leading to a reduction in CRP. Physical activity also improves endothelial function, and endothelial cells are known to increase production of interleukins, important proteins involved in directing the immune response.¹¹⁷

Thrombosis

Thrombosis plays a significant role in the pathogenesis of acute myocardial infarction, unstable angina, and sudden cardiac death, and therefore this issue has long been the topic of studies in the context of acute and chronic exercise. A number of hemostatic changes occur with exercise that involve blood platelets, coagulation factors, and fibrinolysis. Thrombin, a protein that has multiple catalyzing effects that promote clotting, activates platelets and other proteins in the "coagulation cascade," leading to enhanced fibrin generation and clot formation. Both acute and chronic exercise regimens influence these markers of blood homeostasis. Because acute exercise is thought to increase platelet aggregation, concerns have been raised regarding exercise as a potential trigger for

thrombosis-related cardiac events.^{118,119} However, such events are rare during exercise, and the precise role of the coagulation cascade in triggering cardiac events with acute exercise is unclear.¹¹⁹ For example, acute exercise increases some clotting factors (particularly factor VIII and von Willebrand factor), and this has been associated with a reduction in clotting time, but it is unclear whether this leads to significant thrombin generation and/or fibrin formation.^{120,121} Many of these changes disappear quickly during recovery from exercise, although other factors may take as long as 48 hours to return to baseline levels.¹²² There is considerable interindividual variability in the response to acute exercise, and these responses are dependent on exercise intensity, suppressed by β -blockade, enhanced by catecholamine responses, and more pronounced among patients with coronary artery disease.^{118,119,121}

In contrast to acute exercise, both higher physical activity patterns and structured exercise programs have an inhibitory effect on thrombogenic factors and enhance blood fibrinolytic potential.^{119,123–127} These changes have been demonstrated in both healthy subjects and patients with cardiovascular disease and occur across a broad range of factors involved in the coagulation cascade.^{119,123–127} For example, platelet aggregation has been shown to be reduced after a low to moderate period of exercise training in overweight, hypertensive men¹²⁸ and other high-risk groups.¹¹⁹ Although cross-sectional studies have consistently shown that plasma fibrinogen is lower among more active subjects,^{119,123,129} controlled training studies on the effects of fibrinogen have been mixed.^{119,130,131} Nevertheless, the findings of most studies suggest that regular exercise has a significant impact on the coagulation cascade and may be a factor underlying the reduction in cardiovascular risk among physically active individuals.

Exercise Prescription for Health Benefits

Exercise should be tailored to meet an individual patient's needs and abilities. This is especially true for special populations such as elderly, overweight or obese, hypertensive, and diabetic individuals. The current recommendations from the American Heart Association and the American College of Sports Medicine for middle-aged adults and older individuals are as follows: Exercise should be primarily aerobic, supplemented by muscle-strengthening activities. The exercise intensity should be moderate (eg, 40% to 59% of VO_2 reserve or heart rate reserve or brisk walking at 15 to 20 minutes per mile) for most individuals and at even lower intensities for those unable to sustain such walking speeds. Moderate- and vigorous-intensity (jogging) activities can be combined for younger individuals or those able to sustain such intensities. The exercise duration should consist of ≥ 30 minutes of continuous or accumulated physical activity on most, and preferably all, days of the week. A gradual increase in the minimum exercise volume is recommended to maximize health benefits. In addition, a minimum of 2 days per week of light weight-resistance exercises involving the major muscle groups and designed to maintain or increase muscular strength and endurance is encouraged.^{27,35,50,51}

High-Intensity Interval Training

In recent years, several studies have shown significant improvements in metabolic and cardiovascular parameters uti-

lizing high-intensity aerobic interval training in both young healthy adults and heart failure patients. More importantly, interval training proved more benefit than traditional continuous exercise programs in several metabolic, muscular, and cardiovascular parameters. Such training consists of multiple short bouts of activity (usually 3 to 4 minutes in duration), followed by approximately equal periods of low-intensity activity. The intensity is usually >85% of peak oxygen uptake or peak heart rate.

Compared with traditional continuous exercise programs, interval training has resulted in marked improvements in skeletal muscle capacity for fatty acid oxidation in young women,¹³² increases in muscle oxidative capacity in young men,¹³³ and resting BP reduction in middle-aged and older individuals¹³⁴ and has improved the cardiovascular risk profile in rats with the metabolic syndrome.¹³⁵

Intuitively, high-intensity training raises safety concerns, especially in older individuals and those with heart disease. In this regard, a recent study performed in heart failure patients is noteworthy.¹³⁶ Elderly patients with stable postinfarction heart failure (ejection fraction <40%) receiving optimal medical therapy were randomized to either a moderate continuous exercise program at 70% of peak heart rate, interval training at 95% of peak heart rate, or a control group. After 12 weeks, the high-intensity interval training resulted in greater improvements in aerobic capacity, mitochondrial function, and skeletal muscle flow-mediated dilation. High-intensity interval training induced reverse LV remodeling and improved cardiac function (including higher ejection fraction and reductions in end-systolic and end-diastolic volumes). The program was also well tolerated, and quality of life improved. Although these findings must be confirmed by larger studies, the concept of high-intensity aerobic interval training may have important clinical implications in training stable cardiac patients in rehabilitation programs.

Future Directions

Decades of epidemiological studies and recent national health surveys have demonstrated an enormous public health impact of physical inactivity. The escalating sedentary lifestyle in the United States and throughout the world reflects a global epidemic that warrants greater attention from policy makers, healthcare professionals, and healthcare systems. Although the focus of the current discussion is on cardiovascular disease, physical activity has a significant impact in the prevention and therapy of many other chronic diseases, alone or as an adjunct to medication and other therapies. In short, physical activity remains the “best buy in public health” today.²⁸ However, the fact remains that a small percentage of people in the Western world perform even the minimal recommended exercise. Therefore, physicians, allied health professionals, and others should make efforts to persuade policy makers that investments in both proven strategies and further research are critical to better integrate the value of physical activity into the healthcare paradigm. In the interim, healthcare professionals can invest the extra moment it takes to discuss physical activity with their patients. High-intensity interval training shows promise for more pronounced physiological changes and health benefits within relatively short lengths of

training. The implementation of such exercise training, especially for some populations, should be examined further. Finally, fitness status assessed by exercise testing should play a more integral part in the cardiovascular risk paradigm.

Disclosures

None.

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