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Exercise and Health: Dose and Response, Considering Both Ends of the Curve

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ABSTRACT

Over the past 60 years, an enormous body of data has demonstrated that exercise is good for health. Recently, however, there has been concern that repetitive intense exercise may have deleterious cardiovascular effects. To evaluate this possibility, I have reviewed the health response to exercise, with particular attention to the body's minimum daily requirement and to the maximum amount that is safe and effective.
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KEYWORDS: Moderate exercise; Health; Strenuous exercise; Heart

The benefits associated with regular exercise include substantial protection against heart attack, stroke, hypertension, peripheral artery disease, diabetes, obesity, erectile dysfunction, sarcopenia, osteoporosis, depression, dementia, and common malignancies such as breast and colon cancers. Regular exercise enhances the quality of life, slows the physiological consequences of aging, and promotes longevity.

Although these benefits have been widely publicized, only a minority of Americans exercise regularly. There are many explanations for our national sloth. One is that despite hundreds of studies published over the past 60 years, exercise continues to generate controversy. The latest uncertainty results from a number of papers that report intense exercise may do more harm than good. In a sense, the controversy pits Mae West against William Shakespeare; the iconic sex symbol is purported to have said that too much of a good thing is … wonderful, while the Bard takes the opposite view, saying "Wisely and slow. They stumble that run fast."[1]

How much exercise is best for health? And can extreme exercise undermine health benefits and produce a "U-shaped curve" of cardiovascular risk? To approach these questions, I'll review select developments that have molded our understanding of exercise and health over the past 6 decades.

FIRST STEPS

Scientific information about exercise and health rests on the work of Jeremy N. Morris and Ralph S. Paffenbarger, 2 giants of epidemiology and public health. Working in the UK, Morris and his colleagues studied transport workers, postal workers, and civil servants.[2,3] In the US, Paffenbarger and his colleagues studied longshoreman and college alumni.[4,5] Investigations in these diverse populations found that regular exercise was associated with a substantially reduced risk of heart attack and cardiovascular death, as well as a lower all-cause mortality rate.[6,7]

Morris and Paffenbarger pose contrasting personal histories that relate to the question of whether very high levels of exercise might undo the benefits of moderate physical activity. Morris began walking in childhood and continued until shortly before his death at age 99 years. Despite a strong family history of premature coronary artery disease, Paffenbarger was sedentary until age 45 years, when he began exercising because his own work demonstrated that exercise is beneficial even if started in mid or late life. Over the next 26 years, he completed an astounding 151 marathons and ultramarathons, including 5 grueling Western States 100-Mile Endurance Runs. However, severe coronary artery disease that required quadruple bypass surgery forced Paffenbarger to retire from running at age 71; he died of

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heart failure 13 years later. So would Paffenbarger have been better off running less or walking like Morris? It's impossible to know, but I will discuss relevant studies later in this review.

PAFFENBARGER'S PLATEAU

Paffenbarger's many contributions did not raise concern that high-intensity exercise might produce cardiac damage, but his work did suggest that the health benefits of exercise plateau at moderate levels of physical activity. The Figure, taken from his 1978 study of 16,936 male Harvard graduates, plots the risk of myocardial infarction as a function of the total weekly energy expenditure in kilocalories (kcal). Risk declined progressively up to an exercise level up about 2000-3000 kcal per week; beyond that, benefit plateaued. Although total energy output was the major determinant of protection, participation in vigorous sports enhanced benefit to a modest degree.

A weekly energy output of 2000-3000 kcal corresponds to approximately 25 miles a week of walking or jogging and is similar to the widely cited goal of 10,000 steps a day and to most current exercise guidelines. Morris' London bus conductors got their exercise climbing the stairs on double-decker buses, and Paffenbarger's alumni walked city blocks, climbed stairs, and did yard work as well as playing sports. But what about the enthusiasm for aerobics and running that swept America in the 1970s and 1980s?

CLINICAL SIGNIFICANCE

- Regular exercise is necessary for optimal health.
- Exercising for as little as 15-20 minutes a day is beneficial.
- Benefits plateau beyond 45-60 minutes of daily moderate exercise such as walking.
- More prolonged and intense exercise can be safe with simple precautions.

THE AEROBICS REVOLUTION

In 1968, Kenneth H. Cooper developed a simple way to assess an individual's oxygen uptake.[8] In subsequent research, he and others demonstrated that repetitive exercise training in the "aerobic zone" produces a major increase in maximum oxygen uptake and work capacity. Important

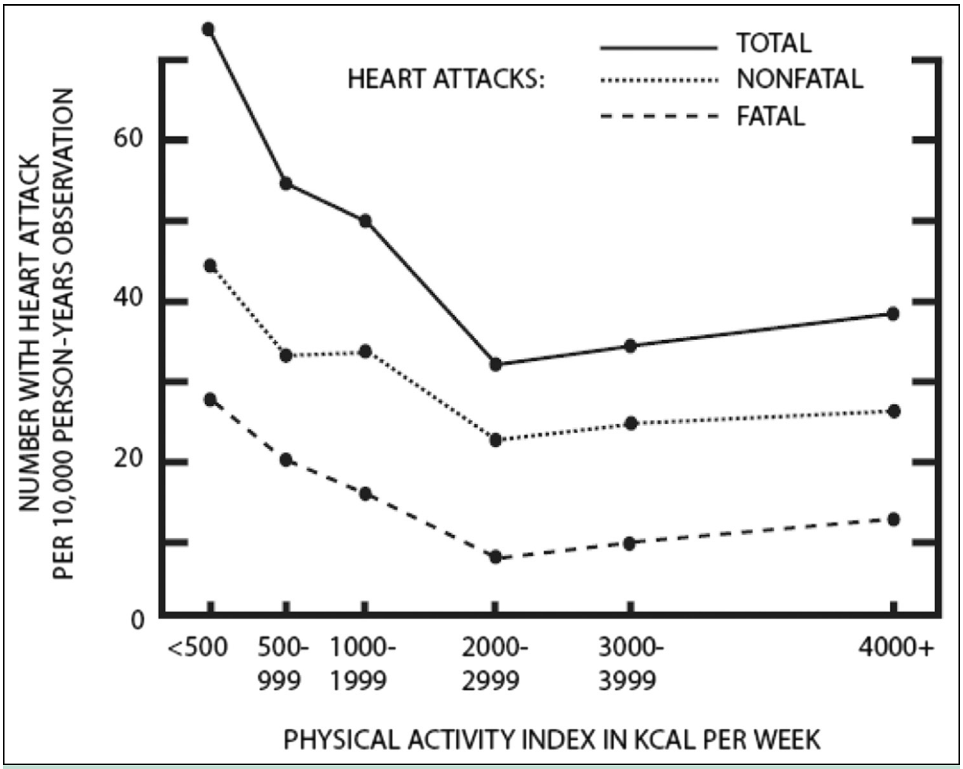

Figure The risk of heart attack as a function of weekly exercise in 16,936 male alumni of Harvard College. As compared with sedentary men, those who expended 2000-3000 kcal/week in exercise enjoyed a 36% lower risk of myocardial infarction. Higher levels of total exercise did not confer additional protection, but strenuous sports enhanced the effect of total energy expenditure to a modest degree. Source: Paffenbarger RS, Wing AL, Hyde RT. Physical activity as an index of heart attack risk in college alumni. *Am J Epidemiol.* 1978;108:161-175 (p 166).[5]

studies at the Cooper Institute in Dallas, Texas and other centers showed that maximum oxygen uptake ("aerobic fitness") was a marker for cardiovascular risk and a predictor of athletic performance, especially in endurance events.

Aerobic fitness rapidly became a standard goal of exercise training. In general, the aerobic doctrine calls for exercising at intensity sufficient to raise the heart rate to 60%-90% of maximum as measured by exercise testing or predicted from a formula based on age. To attain fitness, the doctrine calls for sustaining this intensity for at least 20-30 consecutive minutes and repeating the workout 3 or more times a week.

Aerobic training works; it increases exercise capacity, reduces cardiovascular risk factors, and lowers the risk of many chronic diseases. Heart-rate-based exercise training is still the gold standard for fitness nearly 50 years after the first of Cooper's many books[9] changed the way Americans think about fitness. The same principle of using heart rate to monitor the intensity of endurance exercise has been adapted to the cardiac rehabilitation programs that have been so successful in improving the physical and mental function of patients with ischemic heart disease while also reducing their risk of angina and myocardial infarction.[10]

NO PAIN, BIG GAINS

The successful applications of aerobic training are highly visible, but its limitations are less apparent. Aerobic exercise is hard. While the aerobics doctrine has inspired many people, it has discouraged many, many more.

The aerobics doctrine inspired me to become a runner, but despite my best efforts I was only able to motivate a small minority of my primary care patients to participate in aerobic exercise. I discovered that I loved to run, but my patients didn't.

The aerobics doctrine sets maximum oxygen uptake and aerobic fitness as its primary goals. But Morris' transport workers and Paffenbarger's college alumni earned major health benefits without sustained workouts at elevated heart rates.

For aerobic fitness and endurance sports, aerobic training is a near-necessity. But physical activity can enhance health and reduce the risk of disease without raising the heart rate to the aerobic zone or sustaining that intensity for long periods of time. To update the medical benefits of moderate exercise, I collected 22 studies that evaluated how moderate physical activity affects the risk of heart attack, stroke, and the all-cause of mortality rate.[11] Only one of these studies was a randomized clinical trial, but collectively they evaluated over 320,000 men and women aged 20-93 years from the US, Europe, and Asia. Modest activity, in some cases as little as 1 hour of walking or gardening per week, was associated with major benefits fully comparable to the health benefits linked to aerobic fitness.

These studies and many others convince me that the first steps are indeed the most important. The best form of exercise is the kind that will be done. Most of my patients didn't take kindly to running, but I was able to persuade many to walk.

PHEIDIPPIDES REDUX?

Moderate-intensity daily activities can improve health and reduce the risk of disease. So can intense exercise—but is intense exercise safe? Are today's marathon runners risking the fate of Pheidippides, the cautionary Greek messenger who collapsed and died after running some 24 miles across the Plain of Marathon in 490 BC?

Despite the man-bites-dog publicity that announces the death of an athlete during competition, these tragic events are actually quite uncommon. Males are at higher risk than females in all age groups. Among young athletes, about two-thirds of these deaths are due to trauma and other nonmedical causes[12] such as drug abuse and heatstroke; hypertrophic cardiomyopathy and congenital anomalies of the coronary circulation account for most of the cardiac deaths.[13] Among National Collegiate Athletic Association athletes, the incidence of sudden cardiac death is 1:43,770 participants per year.[12] In older athletes, unsuspected atherosclerotic coronary artery disease is the leading cause of cardiac events during exertion.[14] Exercise can trigger events through mechanisms such as plaque rupture and ischemia-induced arrhythmias. The overall risk is low, amounting to 0.3-2.7 events per 10,000 exercise-hours in men.[15]

Long-distance running has been the major worry about cardiac problems during exertion, but events are uncommon.[16] In a study of 10.9 million participants in American marathons and half-marathons between 2000 and 2010, the risk of cardiac arrest was 0.54 per 100,000 participants.[17]

Exercise can both provoke and protect against primary cardiac arrest. This apparent paradox is explained by a 1984 study.[18] Sedentary men were 56 times more likely to have a cardiac arrest during exercise than at other times. Habitually active men had a much lower risk during exercise, but they were still 5 times more likely to have a cardiac arrest during exercise than at other times. However, men who exercise regularly had a 60% lower overall risk of cardiac arrest than did sedentary men.

THE ATHLETE'S HEART

Repetitive vigorous exercise produces structural and functional changes in muscles, including the skeletal muscles that move the body through space and the cardiac muscle that powers exercise. The cardiac adaptations to exercise include increased left ventricular (LV) wall thickness[19]; this is more prominent in athletes who focus on isometric training such as weightlifting than in endurance athlete such as runners. LV end-diastolic diameter also is increased, but unlike the LV of patients with hypertension and aortic stenosis, the LV of athletes has normal systolic and diastolic function.

The structural changes in cardiac muscle result from physiological cardiac remodeling, which is reflected in electrocardiographic patterns that may mimic pathological left ventricular hypertrophy and other abnormalities. Sinus bradycardia is common in endurance athletes, particularly distance runners. The risk of atrial fibrillation is increased in these individuals[20]; other arrhythmias are less common.

Although the athlete's heart may be confused with a diseased heart, generally it is considered a benign condition with an excellent prognosis. Indeed, the athlete's heart can attain and sustain a higher cardiac output during maximal effort than the healthy heart of an untrained individual. But even if exercise training produces a strong heart, could repetitive, intense exertion produce cardiac damage?

EVIDENCE THAT LESS IS MORE

Laboratory experiments with the "marathon rat" show that over a long period of time, intense, prolonged daily running can produce pathological remodeling, myocardial fibrosis, impaired ventricular function, and arrhythmias, both in previously healthy[21] and hypertensive[22] animals.

A study of 60 nonelite runners who completed the Boston Marathon in 2004 and 2005 raises that possibility.[23] Echocardiography was performed before and 20 minutes after the race, and serum levels of biomarkers were measured at both times. The research reported elevated levels of troponin T and N-terminal pro-brain natriuretic peptide, as well as decreased right and left ventricular function. The changes in serum markers and cardiac performance were most marked in the runners with the least training before the marathon.

Although the study suggests that marathon running may produce myocardial injury, especially in inadequately conditioned athletes, it did not include any follow-up data to address the all-important questions of whether the damage is transient or sustained and whether repetitive injury can produce cumulative damage with adverse consequences.

In patients with coronary artery disease, individuals who exercised intensely 2 to 4 times a week had roughly one-quarter the risk of cardiovascular and all-cause mortality as sedentary patients. However, risk rose in patients who perform strenuous activity daily, resulting in a reverse J-shaped association between physical activity and prognosis.[24]

In a 9-year study of about 1.1 million women who were free of vascular disease at baseline,[25] women who reported moderate or strenuous physical activity even once a week enjoyed protection from vascular events as compared with inactive women; women who performed moderate or strenuous activity 2-3 times a week had somewhat greater reductions in risk. However, women who reported strenuous activity daily experienced less protection; sedentary women had the highest risk of all.

The Copenhagen Heart Study of 1098 healthy joggers and 3950 healthy nonjoggers reported that jogging at a slow pace for 1-2.4 hours per week was optimal.[26] The mortality rate was lowest for light joggers (hazard ratio 0.22 as compared with nonjoggers), followed by moderate joggers (hazard ratio 0.66); the mortality rate for strenuous joggers did not differ from that of sedentary individuals.

A 15-year study of 55,137 American adults reported that runners enjoyed a 30%-45% lower risk of all-cause and cardiovascular mortality and a 3-year life expectancy benefit as compared with nonrunners.[27] Even running for 5 to 10 minutes a day at a pace over 10 minutes a mile was beneficial. Protection was maximal at about 150 minutes of running per week, with a slight increase in the mortality rate above 176 minutes per week.

A study that compared 108 apparently healthy male marathon runners aged 50 years and above with 864 healthy but less active men found that although the marathoners had lower Framingham risk scores, they had a higher prevalence of coronary artery calcification as detected by electron beam computed tomography as well as subclinical myocardial damage as detected by cardiac magnetic resonance imaging.[28]

EVIDENCE EXONERATING STRENUOUS EXERCISE

Unlike their results with runners,[26] the Copenhagen Heart Study of bikers[29] reported a significant inverse association between the intensity of cycling and the all-cause and coronary artery disease death rates.

High-level exercise can be safe in select patients with coronary artery disease. In a study of 2377 heart attack survivors, some protection was evident at levels equivalent to jogging or walking just 0.6-1 miles per day.[30] Benefit increased progressively up to a 63% reduction in cardiovascular mortality at levels equivalent to running 4 miles a day. Beyond that, benefit decreased, but the risk of cardiovascular mortality still remained below that of sedentary patients. While this argues against very strenuous exercise in cardiac patients, a cardiac rehabilitation program reported that both intense and moderate exercise were safe.[31]

In a general population without known heart disease, high-level activity appears to produce a greater gain in life expectancy (3.7 years for men, 3.5 years for women) than low-level exercise (1.3 years for both men and women).[32] The "high levels" of exercise in the study do not exceed current guidelines, but a study of 35,402 male runners reported that men who exceeded current guidelines by running more than 5.5 miles a day had a lower risk of incident coronary artery disease than men who averaged shorter runs.[33]

A study of healthy seniors found "committed-level" exercise (4-5 sessions per week throughout adulthood) and "competitive-level" exercise (6-7 sessions per week) prevented the decrease in LV compliance and distensibility normally associated with aging, while lower doses of exercise do not have this benefit.[34] These findings correspond to the observation that the risk of developing heart failure was inversely related to the dose of leisure-time physical activity in a population of 39,805 men and women.[35]

A reduced risk of cardiovascular disease is the most prominent benefit of regular exercise, but a 22-year study of

44,551 men reported that physical activity also was associated with a reduced risk of major chronic diseases.[36] In this study, vigorous exercise was slightly more beneficial than moderate exercise, reducing cardiovascular risk by an additional 4%.

Elite athletes offer the opportunity to evaluate the effects of truly extraordinary levels of exercise. A study of 114 young Olympic endurance athletes reported that high levels of uninterrupted endurance training for as long as 17 years was not associated with adverse effects on LV function or morphology or with the occurrence of cardiovascular events[37]; left atrial dimension showed a mild increase, perhaps explaining the increased risk of atrial fibrillation in vigorous runners.[20] Former athletes whose events required intense cardiovascular training (such as running, rowing, and cycling) to compete in Olympic Games between 1896 and 1936 had mortality rates that were similar to those of athletes whose events (such as golf and cricket) did not require intense cardiovascular training.[38] Olympic medalists in endurance events had a survival of advantage over medalists in power events.[39]

Although these studies are reassuring, the most convincing evidence that high levels of exercise can be safe and beneficial comes from 2 new studies that evaluated the impact of exercise throughout the dose-response curve. The first tracked 661,137 men and women from the US and Sweden.[40] The researchers used 150 minutes of moderate or 75 minutes of vigorous exercise per week as the recommended minimum amount of physical activity. As compared with sedentary individuals, those who performed less than the minimum recommended amount enjoyed a 20% lower risk of death during a follow-up that averaged 14 years. Levels 2 times the minimum were associated with a 31% lower risk, levels 2-3 times the minimum with a 37% lower risk, and levels 3-5 times the minimum with a 39% lower risk. More extensive exercise did not earn additional survival benefits, but there was no evidence of diminished benefit, much less harm, even at levels 10 or more times the minimum.

The second new study evaluated 204,542 Australians ages 45 to 75 years.[41] Over a follow-up that averaged 6.5 years, there was an inverse relationship between the amount of moderate-to-vigorous activity per week and all-cause mortality. As compared with sedentary individuals, those who performed 10-149 minutes of exercise per week exhibited a 34% reduction in mortality; 150-299 exercise minutes per week was associated with a 47% reduction in mortality, and levels of 300 minutes or higher with a 54% lower mortality rate. In all categories, intense exercise was somewhat more beneficial than similar amounts of moderate exercise. No harm was reported even with the largest amounts of intense exercise.

OVER THE LONG RUN

How much exercise is best for health? There is no single answer; when it comes to exercise, one size does not fit all.

People exercise for one of 3 reasons: for health, for recreation, or for competition. For health, the most dangerous activity is sitting. Current US guidelines for exercise call for all physically able adults to perform at least 150 minutes of moderate or 75 minutes of vigorous exercise per week; levels twice as high are considered optimal.[42] These are wise and appropriate goals, but they have not succeeded in motivating the people who need exercise the most to get off the couch. One reason is the persistent belief that continuous, heart-rate-raising, "aerobic" exercise is necessary for benefit, which leads many people to assume that lower levels of activity are a waste of time. Nothing could be further from the truth.

As little as 15 minutes of moderate exercise a day is extremely beneficial, reducing all-cause mortality rates by 14% and adding 3 years to life expectancy.[43] For starters, we should ask our sedentary patients to walk just a mile a day. Increasing that to 2-3 miles a day (roughly 35 to 60 minutes a day), will bring people into compliance with current guidelines, but the first mile provides the most bang for the buck. Averaging 3-4 miles a day provides some additional health benefit, but the incremental gain is quite modest; beyond that, the only potential health reward for additional exercise is weight control. For optimal results, we should encourage motivated people to incorporate 2-3 sessions of modest strength training into their weekly exercise plan; older people would also benefit from exercises for flexibility and balance.

To empower patients to take those critical first steps, we should stress that the intensity or pace of exercise is less important than the total amount of activity; fast or slow, just do it. Similarly, small aliquots of activity are as helpful as continuous exercise. And although I recommend daily activity, bundling a week's exercise into 2-4 sessions will also work nicely.

Because walking is natural, convenient, inexpensive, and safe, it is a useful benchmark, but any physical activity, from gardening to climbing stairs, will help. I came to this realization the hard way. While I was under the sway of the aerobics doctrine, I smugly told patients that golf is the perfect way to ruin a 4 mile walk—only to learn that walking the course just 2-3 times a week is actually quite beneficial.[44]

As people move from exercising for health to exercising for recreation and competition, intensity and aerobic fitness do matter. And as we approach the right-hand end of the dose-response curve, we have to ask if repetitive, prolonged, intense exercise may have unintended consequences on cardiovascular health. Although more research is needed, current evidence suggests that high-level exercise is safe for most people. The risk of musculoskeletal injuries increases with increasing exercise intensity,[45] but long-term runners have less disability than sedentary controls.[46] As the intensity, frequency, and duration of exercise increase, common-sense precautions become increasingly important; these include warm-ups and cool-downs, good equipment and technique, appropriate medical care, and, above all, listening for signals of bodily distress.

Studies of prolonged, intense, repetitive exercise are limited by the relatively small number of subjects who are available for research. Of necessity, all long-term studies of exercise and health are observational; they can establish correlations but not causation. Additional limitations include potential problems of self-selection, reverse causation, disparate methods for evaluating the amount and intensity of exercise, and confounding variables such as genetics, education and social class, diet, environmental exposures, stress, and training techniques as well as traditional cardiac risk factors.

THE FINISH LINE

Regular exercise is the most effective way to prevent disease; exercise also can help treat many of the chronic illnesses that plague America.[47] Exercise is necessary for optimal health, and for health, moderate exercise is sufficient.

We know much more about the minimum daily requirement for exercise than about the maximum safe limit. But we do know that each individual does have a limit, which increases with proper training but decreases with age and when illness or injury intervenes. Individuals who choose to push toward their limit should do so with informed consent, knowing that some experts worry they may risk cardiac damage, while others believe intense exercise may attenuate the health benefits of more moderate exercise.

Walking, jogging, and running will all promote good health, but no one should mistake health as the reason to run a marathon. Still, there are valid personal reasons for high-level exercise; if marathon running seems right for you, just be sure to do it right.

Edward Stanley, the Earl of Derby, got it right in 1873 when he said that those who think they have not time for bodily exercise will sooner or later have to find time for illness.

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