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Physical Activity and the Prevention of Cardiovascular Disease: From Evolution to Epidemiology

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Abstract For most of human history, the environmental demands of survival necessitated prodigious amounts of physical exertion. The avoidance of predators, hunting, gathering, and the literal "chopping wood and carrying water" of daily existence provided a wholesome dose of physical activity that obviated the need for deliberate exercise. Nevertheless, 21st century humans are now immersed within an environment explicitly designed to eliminate physical labor. Over the past century and especially the past 50 years, an accrual of epidemiological evidence has established that the unintended consequence of humankind's predilection for labor-saving contrivances is an epidemic of hypokinetically induced cardiovascular disease, morbidity, and mortality. This review surveys data from observational studies supporting the premise that physical activity, exercise training, and improvements in cardiorespiratory fitness are essential elements in the prevention and treatment of the cardiovascular diseases induced by an environment in which survival no longer obligates physical exertion. (Prog Cardiovasc Dis 2011;53:387-396)

Keywords: Epidemiology; Physical activity; Cardiovascular disease; Cardiorespiratory fitness

Sedentarism, epidemiology, and cardiovascular disease

Modern humans are immersed within an environment explicitly designed to eliminate physical labor. As a result, sedentary lifestyles have become a predominant and pervasive feature of industrialized nations. Concomitant with the rise in sedentarism has been an epidemic of chronic disease and mortality. The confluence of passive transportation, spectator-based entertainment, and a decrement in energy expenditure via occupational and household physical activity (PA) has engendered an increase in hypokinetically induced obesity and cardiovascular disease (CVD). Because human cardiovascular (CV) physiology evolved within an environment that obligated prodigious amounts of energy expenditure via physical exertion,[1] it is not surprising that a lack of PA has induced a host of morbidities.

Over the past 5 decades, a substantial accumulation of epidemiological and experimental data has established a causal relationship between low levels of occupational and/or leisure-time PA (LTPA) (ie, a sedentary lifestyle) and an increased risk of CVD.[2,3] The evidence for the cardioprotective effects of exercise and the importance of PA in primary prevention as well as an empirically supported treatment is now quite extensive. Accordingly, the American Heart Association has concluded that a sedentary lifestyle is a major modifiable risk factor for CVD.[4] Nevertheless, there exists a lack of implementation of PA interventions in the prevention and treatment of CVD.

This review begins with a brief overview of how anthropogenic alterations of the social and physical environments reduced the necessity of physical exertion to the point that the deliberate adoption of a physically

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Abbreviations and Acronyms

BMI = body mass index

CHD = coronary heart disease

CV = cardiovascular

CVD = cardiovascular disease

CRF = cardiorespiratory fitness

ET = exercise training

HTN = hypertension

LTPA = leisure-time physical activity

PA = physical activity

RR = relative risk

SR = self-report

active lifestyle is now essential for health and well-being. A survey of the benefits of PA, exercise training (ET), and cardiorespiratory fitness (CRF) in the prevention of CVD is presented, followed by a review of relevant issues in the implementation and prescription of PA or ET. In 1996, the National Institutes of Health Consensus Statement on Physical Activity and Cardiovascular Health defined PA as "bodily movement produced by skeletal muscle that requires energy expenditure and promotes health benefits."[5] Exercise training is a subset of PA and must be systematic and progressive. *Exercise training* was defined as "planned, structured, and repetitive bodily movement done to improve or maintain one or more components of physical fitness." *Cardiorespiratory fitness*, also known as aerobic fitness, is defined as the capacity to use atmospheric oxygen for cellular energy production via aerobic metabolism. This energy production supports the metabolic demands of all bodily functions as well as the skeletal muscle movements involved in all forms of PA. Cardiorespiratory fitness is an objective measure of habitual PA and, therefore, is a better predictor of overall CVD risk than self-reported PA. Fig 1 illustrates the degree to which the objective measurement of PA via CRF more accurately estimates the cardioprotective effects of PA.[6] Maximal and peak oxygen consumptions are the most often reported measures of CRF.

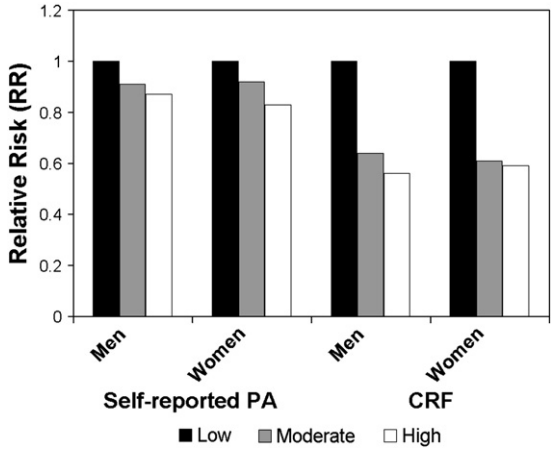

Fig 1. Relative risk of CVD mortality in 31,818 men (1492 deaths; average follow-up, 14.6 years) and 10,555 women (230 deaths; average follow-up, 12.8 years). Self-reported PA substantially underestimates the true cardioprotective effect.[54]

Survival and the evolution of the human CV system

The environmental demands of survival

Homo sapiens evolved in an environment in which survival necessitated significant amounts of physical exertion. Consequently, human CV physiology evolved to meet the demands of that milieu. It was not only an opposable thumb that elevated early humans above other animals but also the unique capacity to expend vast amounts of energy in sustained PA.[1,7] The ability to stalk prey (ie, "persistence hunting") and gather resources over vast distances required a CV system capable of delivering atmospheric oxygen to the working musculature over an enormous range of environmental conditions. Extremes of temperature, altitude, terrain, and other environmental features regularly challenged the physiology of evolving humans.

Humans can maintain top speeds averaging more than 6.0 m/s[8] and can easily cover 10 to 50 km/d. For example, a marathon is just over 42 km (26.2 miles) and is easily traversed by tens of thousand of individuals each year.[9,10] The ability to traverse large distances is a feat that no other primate and few other mammals can perform. Nevertheless, the energetic cost of locomotion for humans is much greater than for most other animals[1] and demands twice the metabolic cost per mile traveled as similar-sized mammals.[11,12] As a result, these environmental demands obligated the adaptation of a CV and musculoskeletal capable of prodigious feats of physical exertion. Over millions of years, these adaptations as well as alterations of the social and natural environment allowed humans to become the dominant species on earth.

The social environment and energy demands of survival

The evolution of human society is inversely related to human energy expenditure[13] and the concomitant demands on the CV and musculoskeletal systems. Although a lone human is remarkably unprepared to survive in the wild, a social milieu obviates much of the physical burden of survival.[13,14] Early social hierarchies allowed for the avoidance of predators and the sharing of hunting and gathering of food. By 7000 BCE, the development of agriculture facilitated the transition from foraging and persistence hunting to a less energetically costly way of life.[15] This period, known as the "Neolithic Revolution" facilitated the ascendancy of *H sapiens* to the top of the food chain.[16] Attendant with this increasing dominance was a dramatic reduction in the energy costs of survival. Nevertheless, humans still toiled long and arduously to survive. As a result, they expended enough energy through

occupational activities (eg, hunting and farming) to sufficiently tax the CV and musculoskeletal systems and forestall many of the chronic illnesses that now befall modern man. For most of human history, the PA necessary for survival was more than enough to support health; and most people died of infectious rather than of chronic diseases. Yet, as human society progressed from persistence hunting to agrarian-based cultures to industrialization, the physical exertion obligated by the environment diminished; and with each transition, the demands on the CV and musculoskeletal systems declined.

Before the 20th century, many of the behaviors, which forestall CVD, were performed out of necessity (eg, occupational PA, activities of daily living, walking, and other forms of active transport). Nevertheless, by the latter half of the 20th century, the unrivaled success of *H sapiens* in shaping their natural and social environments allowed the labors and exertions of earlier humans to be replaced with knowledge-based work and increments in occupational sedentarism and induced the morbidities that modern man now faces.[17] The systematic elimination of physical exertion from daily life and the concomitant rise in chronic disease and CVD mortality demonstrate that the primary prevention and treatment of CVD necessitate deliberate exercise and the adoption of a physically active lifestyle.

The relationship of PA and mortality

> "The only way for a rich man to be healthy is by exercise and abstinence, to live as if he were poor." William J. Temple

Modern epidemiological history: the relationship between PA and health revisited

Early epidemiological evidence

From the Age of Enlightenment (early 18th century) to the 19th century, there were numerous commentaries on the relationship between occupational PA and chronic disease. The health benefits of PA with respect to CVD have been known for over a century.[18,19] Dr. WA Guy of King's College compared the death rates of sedentary workers with those more physically active. Guy[19,20] suggested that "strong exercise is favorable to health" and found that sedentary lifestyles affected women as well as men. In 1846, Dr. Edward Smith[21] suggested that the vigorous PA reduced the mortality of agricultural workers, whereas the sedentary working conditions of tailors contributed to their increased mortality.

Before the 20th century, CVD was relatively rare. It afflicted the affluent and, only rarely, the working classes. William Osler,[18] the celebrated cardiologist who wrote extensively on angina pectoris, stated that, in 7 years of practice at Johns Hopkins Hospital, he witnessed only 4 cases.[22] This fact is interesting in that hospitals at the turn of the century were mainly philanthropic institutions, which treated the poor working classes for infectious diseases.[22] Yet, with the decrement in occupational PA concomitant with the advent of the Industrial Revolution, the prevalence of CVD in the middle/working class began to increase. In 1910, Osler delivered his famous lectures on angina pectoris at the Royal College of Physicians in London and commented on the rising prevalence of CVD in the United States. Within the span of less than 2 decades, he had seen an additional 208 cases.[23]

Occupational PA and CVD

Despite the increasing longevity of the US population in the early 20th century, by the 1930s, an increasing disparity in male-female death rates became apparent. Although longevity was increasing for both men and women, the increase was much greater in women. Eventually, the disparity was explained by 2 major causes of death: coronary heart disease (CHD) and lung cancer.

In 1939, OF Hedley described the relationship between CVD mortality and occupation. Mortality for businessmen and professionals was dramatically higher than manual laborers.[24] Nevertheless, the disparity in mortality was not directly attributed to PA but, instead, was attributed to the emotional and societal factors delineated by Osler and other clinicians.[22] The work of Hedley was followed by the seminal work of Jeremiah Morris, the "Father of Physical Activity Epidemiology."[25]

Morris et al[26] observed a large cohort of London transport workers between the ages of 35 to 64 years during 1949 to 1950. They found that the sedentary bus drivers had higher rates of CVD mortality than their active counterparts, the conductors, who ascended and descended between 500 and 750 steps per day while collecting fares on London's double-decker buses (annual incidence 2.7/1000 vs 1.9/1000, respectively). Morris et al posited that "physically active work" had a cardioprotective effect, which was exhibited primarily by a decrease in sudden cardiac death.

Morris et al[26] continued their line of investigation with other civil servants in various occupations. They found that the cardioprotective effects of PA extended to postmen who walked or cycled while delivering mail. These civil servants had much lower rates of heart disease than the postal clerks (eg, telephone operators) who had sedentary jobs. Interestingly, Morris et al was the first to document a dose response for exercise. Postal workers whose jobs offered at least some PA (eg, counter workers) had lower rates of CVD than those employees who spent most of the workday seated.

Morris et al[26] posited that "men doing physically active work have a lower mortality from CHD in middle age than men in less active work." This hypothesis was met with the cynicism and disbelief that often heralds a paradigm

shift.[26,27] A great deal of the criticism surrounding the work of Morris et al came from the teachings of William Osler who posited that CVD was a result of the psychologic stressors of the employment environment rather than a lack of occupational physical exertion.[28] The hypothesis of Osler was refuted, and much of the criticism faded away when the conductors (and their trade unions) argued that the conductor's job was much more stressful when compared with the drivers. Despite the psychologic turmoil of continuously interacting with passengers, the conductors had lower CVD mortality.[29]

Despite the mounting evidence, the hypothesis of Morris et al[26] regarding the cardioprotective effects of PA was met with a more pedestrian criticism. The prevailing opinion and conventional wisdom of practitioners, clinicians, and researchers were that CVD resulted from hypertension (HTN), hypercholesterolemia, diabetes, and obesity. At that time, the strong inverse relationship between PA and these other risk factors was not established. So, in 1966, Morris et al published a follow-up article using univariate and multivariate analysis to examine the known and suspected factors related to CHD. Not surprisingly, the relationship between occupational PA and CVD was significant. Other risk factors such as HTN and blood lipids were reduced in physically active conductors compared with the sedentary drivers.[30,31] The work of Morris et al work ushered in the age of PA epidemiology and clearly established the relationship between sedentarism, PA, and CVD. The seminal work of Morris et al was paralleled and extended by the investigations of Dr. Ralph Paffenbarger Jr.

In 1951, Paffenbarger and Hale[32] began an observational study of 3000+ San Francisco longshoremen who were 35 to 64 years old. They examined 44,585 man-years over the next 16 years. During that period, there were 888 deaths, of which 291 were CHD fatalities. Paffenbarger and Hale found that the most active workers expended more than 4200 kJ per work shift than the least active. The CVD death rate was significantly lower in the most active compared with sedentary workers: 59 vs 80/10,000 man-years of work.[32]

In 1975, Paffenbarger et al[32] examined "repeated bouts of work activity" in another cohort of 6000+ longshoremen. The group was stratified by kilojoule expenditure per work shift into high (7850 kJ), middle (6200 kJ), and light (3600 kJ) subgroups. When analyzed as work-years, the most active longshoremen had lower age-adjusted rates for CVD compared with the other groups. The death rate for the 3 subgroups (high to low) was 5.6 vs 15.7 vs 19.9/10,000 man-years of work.[32]

Numerous other studies have documented an inverse relationship between occupational PA and overall CVD risk. The association has been replicated in US railroad workers,[33] postal workers,[34] Kibbutz workers,[35] and farm workers.[36] With each empirical undertaking, death from CVD was 2 to 4 times more likely in sedentary workers.

Leisure-time PA and CVD mortality

With the advent of modernization and automation, occupational energy expenditure in farming and industry dropped precipitously. At the beginning of the 20th century, the contribution to total agricultural and industrial energy expenditure from human exertion was roughly 30%. Today, that figure is less than 1%.[37-39] Consequently, the relative contribution to total daily energy expenditure and the concomitant demands placed on the musculoskeletal and CV systems from occupational PA has decreased dramatically. Nevertheless, as work-related PA decreased, LTPA increased. As such, Morris et al[26] hypothesized that PA outside the occupational domain would provide cardioprotective benefits. In 1968, they began a 3-year prospective study of "executive-grade" men in the UK between the ages of 40 and 64 years. These men were employed in various departments of the British government and had little opportunity to engage in PA during their workday. As such, they provided an excellent population to examine the effects of LTPA.[40] Questionnaires were used to gain information on leisure-time activities, social-economic circumstances, health behaviors, and medical history. During the 3-year duration of the study, 232 men had clinical CVD events. The executives who recorded vigorous activities with an energy expenditure of at least 32 kJ/min had a 33% reduction in their relative risk (RR) of a CVD event. The vigorous LTPA was cardioprotective in much the same manner as the occupational exertions of the bus conductors and postmen. The results of Morris et al established that "vigorous activity promotes CV health" and protects against "rapidly fatal heart disease and other first clinical attacks."[40] Morris et al would extend their findings with an 8-year follow-up of a similar cohort. Their results demonstrated that individuals who engaged in vigorous LTPA had a lower rate of fatal CVD events (1.1% vs 2.9%) and nonfatal CVD events (age-adjusted rate of 3.1% vs 6.9%) when compared with sedentary counterparts. These findings were evident from middle age to early old age and extended to men with a variety of risk factors (eg, smoking, familial history, obesity, and HTN). These results allowed the researchers to extend their earlier hypotheses to state that "vigorous exercise is a natural defense of the body, with a protective effect on the aging heart against ischemia and its consequences."[41]

College alumni study

Before his 1975 follow-up of the San Francisco longshoremen, Paffenbarger et al[42] was involved in the creation of the College Alumni Study involving the University of Pennsylvania and Harvard College. Although this investigation examined numerous maladies of the "middle and later ages" (eg, cancer, stroke, HTN,

diabetes, and cancer), it was to become one of the most well-controlled and widely cited studies on the relationship between PA and CVD.[42]

The data on the Harvard cohort were extensive. Detailed entrance records of more than 36,500 male alumni from 1916 to 1950 provided an extensive baseline record. These data included physical examinations and information on athletic participation gained during enrollment. Subsequent questionnaires and surveys regarding exercise and physician-diagnosed diseases added to the enormous database on this cohort. The Harvard alumni office provided lists of deaths, which allowed the determination of the circumstances as well as cause of death. The researchers quantified PA via the attribution of kilojoule-per-minute expenditures for self-reported activities such as walking, stair climbing, and sports. They divided the cohort into low energy expenditure (<8400 kJ/wk) and high energy expenditure (8400 kJ/wk) groups.

In 1978, Paffenbarger et al[43] reported that, in the follow-up period ending in 1972, there were 215 fatal myocardial infarctions of a total of 572 CVD events. An inverse relationship between PA and CVD was established such that those individuals in the low-energy-expenditure group (8400 kJ/wk) had greater than 60% increased risk of CVD regardless of other risk factors (eg, familial history and HTN). The researchers found that low PA energy expenditure increased the RR of CVD by 50%. Yet, when low PA was combined with another risk factor (ie, smoking or HTN), they found that the RR was increased to 2.7. When all 3 risk factors were combined (ie, low PA, smoking, and HTN), the RR increased to an astonishing 7.7. Interestingly, there were no cardioprotective effects from previous PA or sport participation during the participant's college years. The cardioprotective effects of PA cannot be accumulated; an individual has to be presently engaged in PA or ET to experience the benefits of reduced CVD.

The College Alumni Health Study consistently demonstrated a dose-response relationship between PA and CVD mortality. The RR of CVD mortality decreased in a stepwise fashion, as energy expenditure from PA increased from a low 2100 kJ/wk to a maximum 8400 kJ/wk.[43] The relationship with PA and CVD remained strong even after adjustments for conventional risk factors such as familial history of CVD, obesity, tobacco use, HTN, and diabetes.

Over the past few decades, there has been a substantial accrual of epidemiological evidence on the inverse relationship between LTPA and CVD. A recent meta-analysis of prospective cohort studies by Sofi et al[3] reported on results from 26 studies incorporating 513,472 individuals and 20,666 CHD events with follow-ups of 4 to 25 years. Self-reported LTPA was categorized into 3 groups: high, moderate, and low. Using a random effects model, both high and moderate levels of self-reported LTPA were associated with significant reductions in CVD mortality (RR, 0.73 and 0.88, respectively).

Women and CVD

Most of the early reports on the relationship between PA and CVD focused on men, and the few studies of women provided equivocal results. These works had methodological issues in that the early questionnaires were aimed at men and emphasized vigorous activities such as sports. As such, they failed to account for the vastly different patterns of PA exhibited between the sexes by neglecting to account for activities such as child care and household chores. Because women often work in both the public and private (ie, household) domains, the potential for misclassification on PA was great. In more recent studies, women's actual energy expenditure has been shown to be underpredicted by as much as 30%.[44] Interestingly, in the 19th century, Guy[19] found that sedentary single women had higher mortality rates than their married counterparts. Although acknowledging numerous confounders, this may suggest that the chores associated with "hearth and home" provide a wholesome dose of cardioprotective PA.

The nurses' health study

To address the underrepresentation of women in health research, a large prospective public health initiative known as The Nurses' Health Study began in 1976 and followed up more than 100,000 female registered nurses. Questionnaires on lifestyle behaviors, the incidence of CVD morbidity and risk factors allowed the examination of PA and CVD. A report in 1999 examined the association between total PA and CHD events in more than 72,000 nurses who were between the ages of 40 and 65 years in 1986.[45] The results showed a strong inverse gradient between PA energy expenditure and CHD events. When the women were grouped in quintiles from inactive to highly active based on their self-reported PA patterns, the age-adjusted RR of a CHD event decreased in a stepwise fashion by 23%, 35%, 46%, and 54%, respectively. After correcting for a host of risk factors (ie, familial history of CVD, age, tobacco use, hormone replacement therapy, hypercholesterolemia, aspirin therapy, vitamin supplementation, and body mass index [BMI]), the association remained strong with reductions of 12%, 19%, 26%, and 34%, respectively. Manson et al[45] demonstrated that women who walked vigorously for greater than 150 min/wk had a 35% reduction in CHD events compared with those who walked infrequently. The most hopeful finding was that women who became active in middle age had a lower risk of CHD events when compared with women who remained sedentary.[45]

Physical activity or physical fitness?

Self-report PA and objectively measured CRF

A large subset of the evidence on the relationship between PA and CVD has been based on self-report (SR) questionnaires. PA surveys and other SR PA instruments are subject to recall bias, demand characteristics, and social desirability and often fail to account for most energy expended through activities of daily living (eg, standing and walking). The extant literature suggests that some populations (eg, obese, sedentary individuals) often dramatically overestimate their levels of habitual PA. Lichtman et al[46] showed that some obese participants overreported their daily PA by more than 2100 kJ and underreported their daily food intake by more than 4200 kJ.

A comprehensive review of SR PA questionnaires by Shephard[47] in 2003 suggested that despite widespread use, SR PA instruments have limited reliability and poor validity. Researchers often limit evaluations of SR questionnaires to examinations of reliability while ignoring the crucial issue of validity. Although published reliability estimates of 0.50 to 0.70 are common,[48,49] validation studies have revealed that correlations between objective measures of PA (eg, doubly labeled water analyses, accelerometry, and pedometry) and SR PA instruments range from 0.22 to 0.49.[47] This suggests that only 5% to 25% of the variance is accounted for by these SR measures.

Given the inherent limitations of human memory and recall, objective measures of CRF using graded treadmill stress tests provide the most reliable and impressive data on the associations between PA, ET, and the risk of CVD.[6] As demonstrated by numerous studies, the cardioprotective benefits of PA cannot be stored.[43,50,51] As such, CRF provides a valid estimate of recent patterns of PA and, therefore, more accurately reflects the adverse consequences of sedentarism. Although CRF is influenced by many variables such as age, sex, health status, and genes, the primary determinant of CRF is habitual PA and ET. The more sedentary an individual, the lower levels of CRF they will exhibit. Most studies using objectively measured CRF demonstrate a much stronger inverse relationship with CVD than studies using subjectively reported PA. We have demonstrated that objectively measured CRF is a better predictor of CVD risk and all-cause mortality than self-reported PA.[52-54] Our more recent work also demonstrates that CRF is not only a reliable and valid measure of habitual PA but also an accurate diagnostic and prognostic health indicator in clinical settings.[6]

In 1989, we reported on a study of more than 13,000 healthy men and women with more than 8 years of follow-up (a total of 110,482 person-years of observation). We categorized participants by CRF into low, moderate, or high based on graded treadmill performance. The age-adjusted all-cause mortality rates for men increased from a low of 18.6 per 10,000 person-years in the most fit quintile to 64.0 per 10,000 person-years in the least-fit quintile. The corresponding values for women were 8.5 per 10,000 person-years to 39.5 per 10,000 person-years. This strong inverse trend remained after correcting for age, smoking, systolic blood pressure, cholesterol levels, familial history of CVD, and fasting serum glucose levels. Higher levels of CRF appeared to delay all-cause mortality through lower rates of CVD and cancer. Our results clearly demonstrate that a low CRF, presumably due to low levels of PA, leads to increased risk of CVD and premature mortality.[53]

In a subsequent report, we presented the results of a large observational cohort study, which sought to quantify the relationship between CRF and CVD mortality. We examined 25,341 men and 7080 women who had completed preventive medical examinations and a maximal exercise test. The participants were grouped by CRF level into high, moderate, and low CRF groups and stratified by cholesterol levels, tobacco use, blood pressure, and health status. During 211,996 man-years of follow-up, there were 601 deaths; and there were 89 deaths during 52,982 woman-years of follow-up. Among men, low CRF was a strong independent predictor of mortality (RR, 1.52). This was greater than the RR for elevated systolic blood pressure (RR, 1.34) and only slightly less than smoking (RR, 1.65). In women, the only statistically significant independent predictors of mortality were low CRF (RR, 2.10) and smoking (RR, 1.99). Individuals with a high level of fitness exhibited a lower risk of death than low-fit individuals despite any combination of traditional risk factors. These results demonstrate that the cardioprotective effects of CRF are present whether or not other risk factors are present.[55]

Fig 2 presents data on the attributable fractions for all-cause mortality in a large population of women and men in the Aerobics Center Longitudinal Study. An attributable fraction is an estimate of the number of deaths in a population that would have been avoided if a specific risk factor had been absent (eg, if all smokers were nonsmokers or all inactive persons were walking for 30 minutes per day

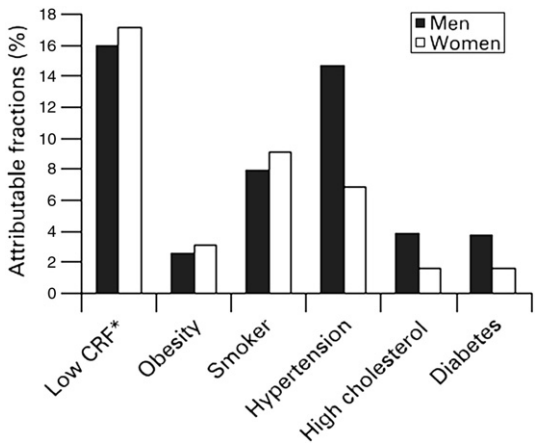

Fig 2. Attributable fractions (%) for all-cause mortality in 40,842 men (3333 deaths) and 12,943 women (491 deaths) in the Aerobics Center Longitudinal Study. The attributable fractions are adjusted for age and each other item in the figure. *Cardiorespiratory fitness determined by a maximal exercise test on a treadmill.[56]

at least 5 days of the week). These estimates depend on the prevalence of that specific risk factor in the population as well as the strength of the association between an exposure and outcome. As Fig 2 depicts, low CRF accounts for approximately 16% of all deaths in both men and women in this population. This fraction is substantially greater than the other risk factors with the exception of HTN in men.[56]

Numerous groups have confirmed the strong association between CRF and CVD mortality. A cohort of 1960 Norwegian men was followed up for a period of up to 16 years by Sandvik et al.[57] The participants were divided into quartiles by CRF. A strong, graded inverse relationship between CRF and CVD risk was demonstrated. The RR of CVD decreased from the most fit to the lowest fit quartiles (0.41, 0.45, and 0.59).[57] Meta-analyses have consistently demonstrated a strong inverse relationship between CRF and several other major health outcomes.[52,58] Individuals in the lowest quintile of fitness have a 3- to 4-fold increase in mortality risk compared with individuals in the highest quintile of fitness. The cardioprotective effects of high levels of CRF are present even for individuals with multiple risk factors (eg, familial history of CVD, HTN, obesity, and chronic illness). Fig 3 illustrates the protective effects of CRF for a large population of men with type 2 diabetes. In this study, Church et al[59] followed up 2316 men for an average of 15.9 years with 179 deaths attributable to CVD. The data clearly show a strong inverse gradient for CVD deaths across fitness categories within each BMI category. The obese men who were moderate/highly fit had less than half the risk of dying than the normal-weight men who were unfit.[59]

Genes, CVD, and changes in CRF

The risk of disease is the result of an interaction of an individual's genetic inheritance and the physical and social environment in which they are immersed across time.[60] As such, genes may provide a "default setting," which determines the trajectory of health parameters. Nevertheless, although genes may predispose an individual to a specific disease trajectory, alterations of the physical and social environments lessen the impact that genes exert in the initiation or progression of disease.[61-63] Genes will explain less of the variation among patients or participants when the environment is modified extensively. This is especially true in the relationship between a genetic predisposition for CVD and alterations in the behavioral environment.

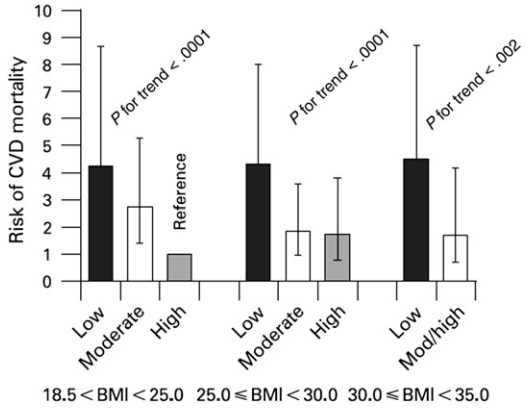

Fig 3. Risk of CVD mortality by CRF and BMI categories; 2316 men with type 2 diabetes at baseline (179 deaths). Risk ratios are adjusted for age and examination year. Black bars indicates low CRF; white bars, moderate CRF (in obese category, the white bar includes both moderate and high CRF; and the gray bar, high CRF). Adapted from Church et al.[59]

The early work of Klissouras[64] suggested that most (>90%) of the performance measures of CRF (eg, peak oxygen intake) were genetically determined. Later work demonstrated that this work was flawed because of limited sample size.[65] The Finnish Twin Study examined the relationship between PA and mortality in a sample of 15,900 participants. The subjects were divided into 3 categories (ie, sedentary, occasional, and conditioned exercisers) based on their patterns of PA. Multivariate analysis demonstrated that the odds ratio adjusted for age and sex was 0.71 in occasional exercisers and 0.57 in conditioned exercisers compared with the sedentary twins. When twins were healthy at baseline but discordant for death (n = 434), the odds ratio for death was 0.66 in occasional exercisers and 0.44 in conditioned exercisers compared with the sedentary twin. The protective effect of PA remained after controlling for other significant predictors of mortality.[66] Subsequent work has demonstrated that heredity plays neither a decisive nor predominant role in the etiology of CVD. After evaluation of data from twin and familial studies, Bouchard et al[67] posit that the genetic contribution to CVD is less than 30%. This suggests a substantial role for modifiable environmental factors such as PA.

Modification of the behavioral environment

The risk of CVD is determined by the confluence of modifiable and nonmodifiable factors including genes, PA, sedentary behaviors, nutrition, health status, and social circumstances. All play a role in the initiation and progression of CVD. Although individuals cannot alter their genotype, lifestyle choices can alter the trajectory of the disease. One of the strongest modifiable determinants of CVD risk is PA. Through the use of regular PA, individuals can improve their CRF and dramatically decrease their risk of CVD mortality.

In 1995, we reported on the relationship between changes in CRF over time and mortality. In a population of 9777 men, alterations in CRF were measured via 2 maximal exercise fitness tests given 5 years apart. The highest rates of all-cause and CVD mortalities were in men who were the least fit in both examinations (122.0/10,000 man-years). The lowest death rate was in men who were physically fit in both examinations (39.6/10,000 man-years). The most important finding was that men who improved their CRF between the initial and subsequent

examinations had a 44% reduction in mortality risk relative to men who were unfit at both examinations. Individuals who demonstrated improvements in CRF had an age-adjusted death rate of 67.7/10,000 man-years. For each minute increase in maximal treadmill time, there was a corresponding 7.9% decrease in the risk of mortality. Improvements in CRF were associated with lower mortality after adjusting for age, health status, and other risk factors.[68]

Numerous other studies have demonstrated that improvements in PA or CRF lead to reductions in mortality or CVD risk factors. As reported earlier, The Nurses' Health Study suggested that women who became active in middle age had a lower risk of CHD events when compared with their sedentary counterparts.[45] Paffenbarger et al[69] showed that initiating moderately vigorous sports activity was independently associated with lower rates of death from CVD among middle-aged and older men.[69] Several studies have demonstrated that moderate improvements in CRF or work capacity have been shown to delay the initiation and slow the progression of CVD.[70] Niebauer et al[70] assessed the long-term effects of physical exercise and other lifestyle changes on the progression of CVD. They randomized 113 male patients with CHD to an intervention group (n = 56) or a control group (n = 57). After 6 years of follow-up, there was a 28% increase in the physical work capacity of the intervention group, with no change in the control group. Coronary stenoses progressed at a slower rate in the exercise group. Patients with delayed progression expended an average of 7464 ± 1607 kJ/wk via ET (approximately 30 minutes of moderate aerobic exercise per day).[70]

As demonstrated, PA interacts with several risk factors (eg, obesity and diabetes) such that overall risk is reduced when CRF is improved. For example, Li et al demonstrated that PA attenuates the genetic potential to obesity. The European Prospective Investigation of Cancer (EPIC)-Norfolk Prospective population study of nearly 20,000 men and women determined that PA reduced the risk of obesity in the genetically predisposed by 40% (Li et al, 2010). The reduction in risk was seen even at the lowest levels of PA (ie, transitioning from a sedentary to a standing occupation improved risk). Given that sedentary behavior is an independent risk factor for CVD,[71] physicians should encourage their sedentary patients to adopt even modest levels of PA. The displacement of sedentary behavior with any form of PA (eg, standing) confers benefit.[72]

The cause and effect relationship between PA and CVD

The noted English statistician Sir Bradford Hill[73] posited a set of criteria that, if satisfied, would establish a casual relationship. His paradigm included several criteria: a temporal relationship (ie, cause must precede effect), the strength of the association, a dose-response relationship, biological plausibility, and other relevant factors. In 1987, investigators from the Centers for Disease Control and Prevention reviewed more than 40 studies in an attempt to test the relationship between PA and CVD using the paradigm of Hill.[2,37] Nearly 70% of the studies reported a statistically significant relationship with the RR associated with sedentarism ranging from 1.5 to 2.4 with a median of 1.9. Interestingly, the methodologically stronger studies consistently reported in the higher range. This RR is comparable with other traditional CVD risk factors such as HTN (RR, 2.1), cigarette smoking (RR, 2.5), and hypercholesterolemia (RR, 2.4).[37] The dose response, first published by Morris et al[26,27] in 1953, was demonstrated by the vast majority of studies with increasing inactivity leading to increased mortality. Experimental studies on rodents and humans elucidated the biological mechanisms and, therefore, the plausibility of the posited relationship including metabolic (eg, lipid and carbohydrate metabolism), vascular (eg, endothelial function), and central factors such as enhanced regulation of autonomic outflow (eg, sympathetic and/or vagal tone). Several other reviews and meta-analyses have provided a plethora of evidence to support the hypothesis that PA delays the onset of CVD and decreases CVD severity and mortality.[74-76]

Summary

Modern humans are immersed within an environment explicitly designed to eliminate physical labor. As a result, hypersedentary behaviors have become a predominant and pervasive feature of modern life. The adverse effects of this ever-increasing sedentarism on public health have become ever more obvious as chronic diseases and premature mortality have gained ascendancy. The decrement in the quality of life due to the vast spectrum of functional limitations associated with a sedentary lifestyle (eg, erectile dysfunction, gait and balance disturbances, and frailty) induces an ever-increasing allostatic burden in addition to increments in CVD mortality.

The evidence base, which began with Hippocrates and continues to accrue via modern epidemiological studies, demonstrates a strong, inverse relationship between PA and chronic diseases, especially CVD. The health benefits and cardioprotective effects of PA and ET are irrefutable. Reduced mortality and improvements in metabolic function, body composition, hemodynamics, musculoskeletal, and psychologic functioning are a few of the myriad benefits of increased PA and ET. Even small increments in PA via reductions in sedentary behavior are beneficial, given that each is an independent risk factor for CVD.[75] Because even modest improvements in CRF have health benefits, considerable gains in public health may be obtained by encouraging the least-fit individuals to become more active.[77] Nevertheless, despite the vast amount of evidence supporting the use of PA and ET in the primary prevention and treatment of CVD, these essential tools are underused and poorly implemented. This reality represents a challenge for physicians.

Before the latter half of 20th century, the role of the physician was that of a clinician and not that of an educator or counselor. The severity of the onset of most infectious diseases combined with the limited duration and brevity of treatment allowed physicians to have limited contact with patients and dispense medication rather than information. The patient rarely needed to know the etiology of the disease or the mechanisms of the cure. As the predominant cause of morbidity and mortality transitioned from infectious agents to lifestyle behaviors, the role of the physician has become that of an advocate, educator, and counselor: a dispenser of information rather than just medication. It may be that health outcomes in the 21st century will be determined more by persistence and perspiration on the part of the patient than by the prescription of pharmacologic agents by a physician. The greatest barriers to reductions in CVD will be overcome by the acknowledgment that a patent's lifestyle is the ultimate determinant of health.

To address the problem of sedentarism, the American College of Sports Medicine and the American Medical Association initiated "Exercise is Medicine," a comprehensive program that seeks to make PA level a vital sign in the primary prevention and treatment of disease (http://www.exerciseismedicine.org/about.htm). In addition, the US Department of Health & Human Services' national PA guidelines are a comprehensive plan for implementing the best available science into the lives of patients as well as the general public: http://www.health.gov/paguidelines/guidelines/default.aspx.

Humans evolved in an environment in which survival obligated physical exertion. If human society is to continue to evolve, 21st century humans must adapt to an environment in which health, well-being, and continued survival obligates the adoption of a physically active lifestyle.

Statement of Conflict of Interest

All authors declare that there are no conflicts of interest.

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