Review:
Physical Inactivity: Associated Diseases and Disorders

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Abstract. A sedentary lifestyle is a very serious worldwide problem, especially in North America and Europe. Unfortunately, physical inactivity, which has progressively increased over the past several decades, significantly increases the risk of numerous diseases/disorders, including several forms of cancer, diabetes, hypertension, coronary and cerebrovascular diseases, overweight/obesity, and all-cause mortality, among others. Unless there is a reversal of this sedentary lifestyle, the incidence of these diseases/disorders will increase, life expectancy will decrease, and medical costs will continue to rise.

Key Words: physical inactivity, lifestyle, morbidity, mortality, guidelines

Introduction

Humans are not programmed to be physically inactive. Indeed, the "sedentary death syndrome" is a major risk factor for numerous worldwide diseases and millions of premature deaths each year [1]. Studies have shown that long-lived species are more efficient in cellular maintenance than short-lived species, suggesting that enhancement of the body’s maintenance systems may slow the aging process. Since aging results from the accumulation of cellular damage, interventions in poor lifestyles may prevent damage, promote repair, and thereby increase life expectancy. In fact, about two thirds of the major causes of death are, to a significant degree, lifestyle-related. As noted by Mokdad et al, the major “actual causes of death” are physical inactivity and poor nutrition [2,3]. Although a sedentary lifestyle is important in the pathogenesis of many chronic diseases/disorders, little is known about the mechanisms whereby physical activity decreases their incidence. Since caloric restriction (CR) is the only paradigm that consistently increases the lifespan of flies, worms, mice, rats, etc., a panel of aging experts examined “whether changes in exercise behavior and body composition produces similar changes as those found in dietary restriction and whether these changes can be used to either replace or enhance the beneficial effects of dietary restriction” [4]. Although no definitive conclusions were reached, future research will determine if changes in physical activity and body composition act as CR mimetics.

Physical inactivity results in the so-called “disuse syndrome” (i.e., premature aging, obesity, cardiovascular vulnerability, musculoskeletal fragility, and depression) [5]. Since this reproducible syndrome applies to the young and middle-aged, as well as the elderly, age per se is not completely responsible for many of the diseases/disorders attributed to it. Thus, “illness as we see it has another component that is due neither to disease per se nor to time effects but to disuse, the third dimension” [6]. Indeed, about 15% of the 1.6 million newly diagnosed chronic diseases each year are due to a sedentary lifestyle [7] (Table 1). Moreover, physical activity also improves balance, flexibility, mental health, and overall quality of life. Indeed, “physical inactivity speeds the aging process in many people, whereas increased physical activity slows it down in others” [8]. Thus, the earlier in life one becomes physically active, and remains so, the greater the lifetime benefits.

Physical Activity Guidelines. The 1995 recommended guidelines indicated that at least 30 minutes of moderate intensity physical activity on
most, but preferably all, days of the week would result in significant health benefits [9,10]. However, these guidelines were updated in 2007 [11]. Thus, all healthy adults aged 18 to 65 years need moderate-intensity aerobic (i.e., endurance) physical activity for a minimum of 30 minutes on five days each week or vigorous-intensity aerobic physical activity for a minimum of 20 minutes on three days each week. Although the recommendations for older adults are similar, there are several differences including the following: aerobic intensity should consider the older adult’s aerobic fitness, include activities that maintain or increase flexibility, and balance exercises for those at risk of falls [12]. Moderate intensity is categorized as burning 3.5-7.0 kcal/minute (e.g., walking on even terrain at 3.0-4.5 mph or biking 5.0-9.0 mph). Vigorous intensity is classified as burning 7.0 or more kcal/minute (i.e., race walking at > 5.0 mph; biking > 10.0 mph). To meet current guidelines, individuals must walk a minimum of 3,000 steps in 30 minutes on five days each week. However, three bouts of 1,000 steps in ten minutes each day also meets the recommended goal. More recently, Wen et al prospectively studied 416,175 men and women between 1996 and 2008 [13]. Compare with the inactive group, those who exercised for 15 minutes/day had a 14% reduced risk of all-cause mortality and a 3-year longer life expectancy. Each additional 15 minutes of daily exercise further reduced all-cause mortality by 4% and all-cause cancer mortality by 1%.

Table 1. Physical Inactivity: Associated Diseases/Disorders

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<td>All-cause mortality</td>
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<td>Cancer (colon, breast, prostate, others)</td>
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<td>Dyslipidemia (increased total/LDL cholesterol, decreased HDL cholesterol)</td>
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<td>Metabolic syndrome</td>
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<td>Neurological disorders (functional decline, depression, dementia)</td>
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<td>Osteoporosis (falls, fractures)</td>
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<td>Overweight/obesity</td>
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<td>Sarcopenia</td>
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Gait speed (meters/second) has also been studied with respect to survival in older adults [14]. This analysis of 9 cohort studies involved 34,485 elderly adults with baseline gait speed data and followed for 6 to 21 years. The authors concluded that “…gait speed was associated with survival in older adults.” Unfortunately, at least 26% of American adults are sedentary and more than 50% are not regularly active at the minimum recommended level [15]. The objectives of Healthy People 2010 were that at least 50% of American adults will be regularly involved in moderate to vigorous exercise, since approximately 250,000 premature deaths occur in the U.S. each year as a result of physical inactivity [16]. To evaluate the dose-response relationship between physical activity, various chronic diseases, and all-cause mortality, Lee et al examined the parameters of physical activity dose, volume intensity, duration, and frequency in 44 published studies [17]. Their findings showed the following: (a) there is “clear evidence” that an inverse relationship exists between volume of physical activity and all-cause mortality rates in men, women, younger adults, and older adults; (b) adherence to the current minimal physical activity guidelines is associated with a 20-30% reduction in all-cause mortality; and (c) further risk reductions occur at higher levels of energy expenditure.

Although healthcare providers are strongly encouraged to promote increased physical activity in older people, many do not feel adequately prepared to prescribe a specific exercise program [18]. Indeed, a Center for Disease Control report indicated that only 19% of physicians counseled their patients about exercise [19]. Physical inactivity among children and adolescents is also a major problem. For example, Kimm et al prospectively followed black and white girls for 10 years (ages 9 to 19 years) [20]. The median activity scores for black and white girls were 27.3 and 30.8 metabolic equivalent times (MET)/week at base line, respectively. By year 10
they declined to 0.0 and 11.0 MET/week (100% decline for black girls, 64% decline for white girls). Moreover, one-third of U.S. high school students did not participate in the minimum recommended level of moderate or vigorous physical activity in 2003 [21], and only 55.7% were enrolled in a PE class where only 28.4% attended classes daily [22].

**Physical Inactivity and All-Cause Mortality.**

Life expectancy based on age and sex alone provides limited information since survival is also significantly influenced by health and functional abilities. Indeed, about 65% of the major causes of death are lifestyle-related [2,3]. Although individuals with lower health risks generally live longer than those with higher health risks, there is often concern that increased life expectancy may result in greater disability and increased medical costs. However, the compression-of-morbidity hypothesis suggests that it is possible to reduce lifetime morbidity and thereby increase life expectancy [23]. Indeed, a study of university alumni showed that those with high health risks (e.g., low exercise patterns, smoking, excess body weight) had twice the cumulative disability compared to those with a low health risk after 32 years follow-up [24]. Thus, “not only do persons with better health habits survive longer, but in such persons, disability is postponed and compressed into fewer years at the end of life.”

Television viewing time is associated with biomarkers of cardiometabolic risk, but since its relationship with mortality had not been studied, Dunstan et al examined adult viewing time [25]. After adjustment for important variables, the hazard ratio for each one-hour increment in television viewing time per day was 1.11 for all-cause mortality and 1.18 for cardiovascular mortality. Compared with viewing time of less than two hours/day, the hazard ratios for all-cause mortality were 1.13 for 2-4 hours/day and 1.46 for more than 4 hours/day. For cardiovascular mortality, the corresponding hazard ratios were 1.19 and 1.80.

In an early study, physical activity was compared with all-cause mortality in 16,936 Harvard alumni [26]. After 16 years follow-up, the death rate declined steadily as the expended energy increased. A subsequent prospective study of Harvard alumni showed a graded inverse relationship between total physical activity and all-cause mortality [27]. The third study of this group showed that distance walked and floors climbed were independent predictors of longevity [28].

Blair et al compared the degree of physical fitness with all-cause and cause-specific mortality in men and women over an 8-year period [29]. Here, the age-adjusted all-cause mortality rate declined across physical fitness quintiles from 64/10,000 person-years in the least fit men to 18.6/10,000 in the most fit men (relative risk, 3.4) and 39.5/10,000 person-years to 8.5/10,000 for women (relative risk, 4.7). In a subsequent study, the relationship between changes in physical fitness and mortality risk was evaluated in men [30]. Each man underwent two clinical examinations (mean interval, 4.9 years) to assess any changes in physical fitness as associated with risk of mortality during the follow-up period. The highest age-adjusted all-cause death rate was present in those who were unfit at both examinations; the lowest death rate was in men who were physically fit at both examinations. Moreover, men who improved from unfit to fit between the two examinations also had a lower death rate. In a recent review of physical activity and all-cause mortality in women, the authors concluded that “by adhering to current guidelines for physical activity and expending about 4,200 kJ (about 1,000 kcal) of energy/week, women can postpone mortality” [31].

Since little was known about the mortality risk and physical activity in the elderly, Bijnen and associates evaluated 802 retired Dutch men at baseline [32]. All-cause 10-year mortality in the highest tertile decreased with increasing physical activity (relative risk, 0.77). More intense physical activity was associated with greater decreased mortality. Moreover, walking or bicycling at least 3 times/week for 20 minutes significantly reduced all-cause mortality compared with those who were physically inactive (relative risk, 0.70). More recently, Newman et al evaluated the long-term positive effects of elderly adults at baseline who completed a 400 meter corridor walk [33]. After a mean period of 4.9 years, those unable to complete the walk had a significantly higher mortality risk, incident coronary heart disease, disability, and mobility limitation. Each additional minute of performance time to complete the walk was associated with the following hazard ratios: mortality, 1.29; incident coronary heart disease, 1.20; mobility limitation, 1.52; and disability, 1.52. Those in the lowest
quartile had a significantly higher risk of death than those in the highest quartile. Others evaluated the daily energy expenditure and mortality among high functioning elderly individuals for a mean of 6.15 years [34]. The free-living activity energy expenditure was separated into the following three tertiles: less than 521 kcal/day; 521 to 770 kcal/day; and greater than 770 kcal/day. After adjusting for various confounders, those in the highest tertile energy expenditure group were at a significantly lower all-cause mortality risk than those in the lowest tertile. Indeed, the least active group was three times more likely to die. Benetos and associates evaluated the role of physical activity and other risk factors in older individuals who could potentially reach the age of 80 years for men and 85 years for women [35]. Their data showed a significantly increased probability of reaching these ages if they were involved in regular physical activity. Wang et al added further support for recommending physical activity in older persons [36]. In this 13-year prospective study, runners’ club members 50 years and older were compared with sedentary control subjects. Their findings showed significantly lower disability levels in the runners’ clubs members and the death rate in the control group was 3.3 times greater. A recent meta-analysis of 33 all-cause mortality studies also indicated that better cardiorespiratory fitness (CRF) was associated with a significantly lower risk of all-cause mortality [37].

A recent study also suggested that leisure time physical inactivity might accelerate the aging process [38]. These researchers studied twin volunteers on physical activity level, smoking, and socioeconomic status, as well as determined their leukocyte telomere length. After adjusting for age, sex, BMI, smoking, socioeconomic status and physical activity at work, telomere length was positively associated with leisure time physical activity and thereby possibly slowed the aging process.

**Heart Disease: Primary Prevention.** Heart disease has been the leading cause of death in the U.S. for the past four decades [39]. In 2007, cardiovascular disease (CVD) accounted for 33.6% of all deaths in the U.S.; 2,200 Americans died of CVD each day [40]. Moreover, the myth that heart disease is only a “man’s disease” has been debunked. Indeed, it is the major worldwide cause of death in women since it accounts for one-third of all female deaths. In many countries, including the U.S., more women die of CVD than men [41]. Primary heart disease prevention, a reduction in coronary heart disease (CHD) risk factors in healthy people, results in a four-fold higher reduction in mortality from CHD than secondary prevention (i.e., risk factor reduction in people with established CHD) [42]. Although about 40% of 40 year old adults will develop heart failure during their lifetime, the Physicians’ Health Study indicated that adherence to healthy lifestyle is associated with a significantly lower risk of heart failure [43]. Morris et al reported in the early 1950s that active conductors in the London double-decker buses were protected against CHD compared with the sedentary bus drivers [44,45]. Similarly, postmen were protected from CHD compared with less active government employees. Three decades later, Paffenbarger and associates examined 16,936 Harvard alumni for lifestyle experiences related to CHD and longevity [46]. Those expending 2,000 kcal/week in walking, stair climbing, and sports play were at a 39% lower risk for CHD than the less active alumni and 16% fewer CHD deaths would have occurred if everyone had expended the same amount of energy in some form of exercise. Since that time, there has been a growing interest in using walking speed to assess functional status and motor performance in older people, 3,208 elderly men and women were followed for an average of 5.1 years [47]. Here, persons with low walking speed had a three-fold increased risk of cardiovascular death compared with those who walked faster.

In their study of the association of 400 meters corridor walk performance with the total mortality in elderly individuals, Newman et al also evaluated its effect on incident CHD [33]. Here, inability to complete the walk was associated with a significantly higher risk of incident CHD. Of those who completed the walk, each additional minute was associated with a hazard ratio of 1.2 for incident CHD. Others studied the consequences of different physical activity levels on total life expectancy with and without CHD in both men and women [48]. Compared with low levels of physical activity, moderate and high levels led to 1.3 and 3.7 and 1.1
and 3.5 more years in total life expectancy, respectively, as well as 1.3 and 3.3 more years free of CHD.

Since the role of walking compared with vigorous exercise in the prevention of coronary heart disease remains somewhat controversial, especially among women, healthy postmenopausal women were prospectively studied [49]. The results showed that increasing quintiles of energy expenditure had age-adjusted relative risks for coronary events of 1.00, 0.73, 0.69, 0.68 and 0.47, respectively. To further understand these variables, Duncan et al randomized 492 sedentary adults to 1 of 4 exercise-counseling conditions or to a physician advice comparison group [50]. The duration (30 minutes) and type (walking) of exercise were held constant while exercise intensity and frequency consisted of moderate intensity-low frequency (3-4 days/week) and hard intensity-high frequency (5-7 days/week). After 24 months, participants in the high-intensity exercise group showed significant increases in cardiorespiratory fitness.

Although exercise capacity is an important prognostic factor in people with CHD, it had been uncertain whether it predicts mortality equally well among healthy individuals. To evaluate this, Myers and associates studied 6,713 men referred for treadmill exercise testing [51]. The participants were classified into two groups: 3,679 had an abnormal exercise test result, history of CHD, or both; 2,534 had a normal exercise test result and no history of CHD. The peak exercise capacity, measured in metabolic equivalents (MET), was the strongest predictor of death between both groups. Each MET increase in exercise capacity conferred a 12% improvement in survival.

To evaluate increased physical activity in the frail elderly, Ehsani et al randomly assigned frail octogenarians to a control sedentary group or an exercise group in a 6-month training program followed by 3-months of more intense endurance exercise [52]. Compared with the sedentary group, the exercise group showed a 14% increase in both the peak oxygen consumption and exercise cardiac output. The authors concluded that “although frail octogenarians have a diminished capacity for improvement in aerobic power in response to exercise training, this adaptation is mediated most by an increase in Q (peak exercise cardiac output) during peak effort.”

Heart Disease: Secondary Prevention. Although rest and physical inactivity have been recommend for patients with established CHD for decades, it is important to recognize that recent studies clearly show that the benefits of physical activity and fitness also apply to those with coronary and other vascular diseases. For example, a recent prospective Nurses’ Health Study showed that regular exercise significantly minimizes the risk [53]. Indeed, the absolute risk of sudden cardiac death associated with moderate to vigorous exertion was “exceedingly low.” A prospective study of U.S. male physicians also indicated that habitual vigorous exercise “diminishes the risk of sudden death during vigorous exertion” [54]. The following reports further document the importance of physical activity in patients with established CHD.

A British study involving men with established CHD compared the relative risks of death from cardiovascular disease and all-cause with the level of physical activity [55]. Compared with the inactive or occasionally active group, the relative risks (RR) were as follows: light activity, 0.42; moderate activity, 0.47; and moderately vigorous or vigorous activity, 0.63. In addition, recreational activity of four or more hours/week, moderate or heavy gardening, and regular walking 40 or more minutes/day were also associated with a significant reduction in mortality. Those who were initially sedentary, but began a light or more active program, also lived longer (RR, 0.58). Similarly, Hung et al compared the effect of aerobic training (AT) or combined AT and strength training (CT) on peak aerobic power (VO2 peak), distance walked in 6 minutes, upper and lower extremity maximal strength, and quality of life in elderly women with CHD [56]. The subjects, randomly assigned to AT or CT, exercised 3 days/week for 8 weeks. Both AT and CT improved similarly in VO2 peak, 6 minute walking distance, lower extremity strength, and emotional as well as and global quality of life.

Since the association between long-term outcomes and the number of cardiac rehabilitation sessions attended were unknown, Hammill et al identified 30,161 elderly patients who attended at least one session over a four-year period [57]. After adjustment for several confounders, the results showed the following: those who attended 36 sessions had a 14% lower risk of death and a 12% lower risk of
MI than those who attended 24 sessions; a 22% lower risk of death and a 23% lower risk of MI than those who attended 12 sessions; and a 47% lower risk of death and a 31% lower risk of MI than those who attended one session. In an early meta-analysis of 48 clinical trials involving patients with CHD, exercise-based cardiac rehabilitation decreased all-cause mortality (20%), cardiac mortality (26%), nonfatal MI (21%), coronary artery bypass graft surgery (13%), and percutaneous coronary angioplasty (19%) [58].

Flynn et al tested the effects of exercise training on the health status of individuals with heart failure [59]. This multi-center, randomized controlled trial involved stable outpatients with heart failure, of which 1,172 underwent usual care plus aerobic exercise training consisting of 36 supervised sessions followed by home-based training. The control group only received usual care. The researchers concluded that “exercise training conferred modest but statistically significant improvements in self-reported health status compared with usual care without training.”

**Ischemic Stroke.** In 2008, stroke was the third leading cause of death in the United States [60], and each year an estimated 795,000 people experienced a new or recurrent stroke [61]. However, physical activity has been shown to reduce the risk of ischemic stroke in both women and men. For example, Hu et al examined the association between physical activity and risk of stroke in 72,488 women [62]. After eight years of follow-up, the relative risks for ischemic stroke across increasing metabolic equivalent tasks from lowest to highest quintiles were 1.00, 0.87, 0.83, 0.76, and 0.52. Similarly, Lee and Blair examined the association between cardiorespiratory fitness and stroke mortality in men over a ten year period [63]. After adjustment for age and other risk factors, the high-fit men had a 68% lower risk and moderately-fit men a 63% lower risk of stroke mortality compared with the low-fit men.

More recent studies confirm the importance of physical activity in reducing the risk of ischemic stroke. For example, a prospective cohort of stroke-free older individuals in the Northern Manhattan Study indicated that moderate to heavy physical activity was protective against the risk of ischemic stroke in men, but not women [64]. However, their later study found that increased levels of physical activity were associated with a lower risk of silent brain infarcts in both men and women [65].

**Hypertension.** Aging is accompanied by cardiovascular changes that include a decrease in elasticity and an increase in stiffness of the coronary arteries, which increases the afterload on the left ventricle resulting in systolic hypertension. Unfortunately, hypertension is a major public health problem and appears to be increasing. For example, in a community-based prospective study, Vasan et al evaluated the lifetime risk of developing hypertension in 55- to 65-year-old individuals who were free of hypertension at baseline [66]. The residual lifetime risk for developing hypertension was 90% in both groups. Compared with an earlier period, the risk for hypertension remained unchanged for women, but increased approximately 60% for men.

Since exercise is a cornerstone therapy for the prevention, treatment, and control of hypertension, lifestyle modifications are strongly encouraged. In an early study of 14,998 Harvard male alumni, those who did not engage in vigorous sports play were at a 35% greater risk for hypertension than those who did [67]. Moreover, increased levels of BMI, weight gain since college, history of parental hypertension, and lack of strenuous exercise independently predicted an increased risk. The following year, Blair et al reported on the association of physical fitness with hypertension in men and women over a period of one to twelve years [68]. Those with low levels of physical fitness had a relative risk of 1.52 compared with the highly fit group. As noted by Brennan et al, isolated systolic hypertension is present in most older women [69]. To evaluate the possible effect of lower levels of physical exertion on blood pressure, they studied 109 elderly women, of whom 63.3% were hypertensive. The mean systolic BP was lower among women moving 5 or more hours/day than those moving less than 5 hours/day. Others carried out a similar six-month randomized controlled trial of combined aerobic and resistance training in persons with untreated systolic BP of 130-159 mm Hg or a diastolic BP of 85-99 mm Hg [70]. Although the mean diastolic BP was significantly reduced, the systolic BP
was not, suggesting that “older persons may be resistant to exercise-induced reduction in systolic BP,” perhaps due to “the lack of improvement in aortic stiffness….” Based on current evidence, the American College of Sports Medicine recommends 30 or more minutes of moderate-intensity physical activity for hypertensive people on most, but preferably all, days of the week [71].

**Type 2 Diabetes Mellitus.** Aging is commonly associated with an increased incidence of insulin resistance and type 2 diabetes mellitus. Unfortunately, the number of diagnosed cases in the U.S. rose from 1.5 million in 1958 to 17.9 million in 2007 and as of 2009, 23.6 million Americans had type 2 diabetes [72]. In the U.S., diabetes is currently the seventh most common cause of death. However, since it is also a major risk factor for cardiovascular, cerebrovascular disease, and peripheral vascular diseases, hypertension, and renal disease, its actual cause of death is significantly higher.

Type 2 diabetes constitutes from 92% to 96% of all diabetes cases. For decades, it was termed “late-onset diabetes” since it was uncommon prior to aged 40 years. It was also commonly referred to as the “3-Fs” - female, fat, and forty. However, because of the marked lifestyle changes over the past several decades, the disease is now common in males, adolescents and young adults. Indeed, the major risk factors for type 2 diabetes are abdominal obesity and physical inactivity. Although a familial risk factor is often present, it is significantly less important than lifestyle.

Numerous studies have clearly demonstrated that exercise improves glucose metabolism. To evaluate the effect of lifestyle intervention, the Diabetes Prevention Program Research Group assigned 3,234 non-diabetic middle-aged persons with elevated fasting and post-load plasma glucose concentrations to one of three groups: placebo, metformin, or lifestyle change [73]. After an average follow-up of 2.8 years, lifestyle intervention decreased the incidence by 58% and metformin use by 31%. Moreover, after a median follow-up of 23.1 years, the Physicians Health Study reported that the hazard ratios of inactive men with normal, overweight or obese BMIs were 1.41, 3.14, and 6.57, respectively [74]. Active but overweight and obese men had hazard ratios of 2.39 and 6.22.

In an early study, Pan et al randomized 577 Chinese men and women with impaired glucose tolerance to either a control group or one of three treatment groups: diet only, exercise only, or diet plus exercise [75]. After six years of follow-up, 67.7% of the control group developed diabetes compared with 43.8%, 41.1% and 46.0% in the diet only, exercise only, and diet plus exercise groups, respectively. Similarly, 522 middle-aged overweight/obese Finnish subjects with impaired glucose tolerance were randomly assigned to an intervention group or a control group [76]. Each interventional group member received counseling for reducing weight, improving diet, and increasing physical activity. After 4 years follow-up, the incidence of diabetes was 11% in the intervention group and 23% in the control group.

Hu et al. followed 84,941 female nurses who were free of cardiovascular disease, diabetes, and cancer at baseline for 16 years [77]. They concluded that 91% of the 3,300 new cases of type 2 diabetes were attributable to poor lifestyles. Although overweight/obesity was the single most important risk factor, physical inactivity was the second most important factor. Similar findings were also reported in children [78]. In this study, insulin resistance was evaluated in 9 to 11.5 year-old obese and lean children. As with adults, total and central adiposity were positively associated with increased insulin resistance while physical activity was negatively associated with insulin resistance.

Importantly, diabetic adults 18 years and older who walked at least two hours/week reportedly had a 39% lower all-cause mortality rate and a 34% lower cardiovascular mortality rate compared with sedentary persons [79]. The mortality rates were lowest for individuals who walked three to four hours/week. The authors concluded that “one death per year may be preventable for every 61 people who could be persuaded to walk at least 2 hr/wk.”

**Cancer.** Cancer is the second leading cause of death in the U.S., Canada, and most of Europe. In addition to poor nutrition and tobacco use, physical inactivity is a major risk factor for several cancers. Indeed, “The adoption of an active lifestyle could reduce all-cause cancer rates by as much as 46%” [80]. Although the mechanism(s) whereby regular physical activity may prevent site-specific
cancers is unknown, evidence suggests that components of the innate immune system are involved, as well as a better overall lifestyle, lower body fat, decreased stool transit time, lower estrogen levels, and enhancement of antioxidant enzyme systems [81]. The major cancers associated with physical inactivity are listed in Table 2.

1. Prostate Cancer. Studies of the relationship between physical activity and prostate cancer have been inconsistent. A literature review between 1989 and 2001 identified 13 cohorts of U.S. and international studies, nine of which showed an association between increased physical activity and decreased risk of prostate cancer [82]. Five of 11 case-control studies also indicated that high physical activity levels decreased prostate cancer risk. Of all studies between 1976 and 2002, 16 of the 27 reported a reduced risk in the most active men. More specifically, a recent Chinese case-control study showed that moderate physical activity was inversely associated with prostate cancer risk [83]. There was also a dose-response relationship. However, a population-based case-control Canadian study reported mixed evidence for an association between prostate cancer risk and physical activity [84]. Although occupational activity decreased the risk, only vigorous physical activity decreased the risk.

Nilsen et al prospectively examined the association between physical activity and prostate cancer in 29,110 Norwegian men [85]. After 17 years of follow-up, multivariable analysis showed that exercise frequency and duration were inversely associated with the risk of advanced prostate cancer and cancer death. However, the results of a Health Professionals Follow-up Study showed no association between total prostate cancer and total, vigorous, or non-vigorous physical activity, although in men 65 years and older there was a lower risk in the highest category of vigorous activity for advanced and fatal prostate cancer [86]. Since vigorous activity after diagnosis had been reported to be inversely associated with prostate cancer-specific mortality, Richman et al examined vigorous activity and brisk walking among 1,455 men with clinically localized prostate cancer [87]. After 2,750 person-years, men who walked briskly for 3 hours/week or more had a 57% lower rate of progression than those who walked at an easy pace for less than 3 hours/week.

2. Breast Cancer. Studies clearly demonstrate that increased physical activity reduces the risk of breast cancer. Although the positive effect of exercise applies to both pre- and postmenopausal women, the association is stronger for the latter [88]. Among women of the French E3N cohort, there was a linear decrease in breast cancer risk with increasing amounts of moderate (P < 0.01) and vigorous (P < 0.0001) recreational activities [89]. Moreover, women in the Women’s Contraceptive and Reproductive Experiences Study, which involved both black and white women with newly diagnosed breast cancer, were compared with cancer-free women matched for age, race/ethnicity, and study site [90]. Here, breast cancer risk was significantly decreased with increased levels of lifetime exercise activity in all women. Similarly, John et al conducted a population-based case-control breast cancer study in African Americans, Latinos, and whites to assess the association with a lifetime of moderate and vigorous physical activity [91]. The results showed significant breast cancer risk reductions in both pre- and postmenopausal women and were similar in the three racial/ethnic groups. Interestingly, the Women’s Health Initiative Observational Study of older women reported that those who had engaged in strenuous physical activity three or more times/week and worked up a sweat at age 35 years, had a relative risk for breast cancer of 0.86 compared with women who did not [92]. Thus, “An hour every day of moderate or strenuous activity provides the most benefit.” It should also be noted that obesity, which can be controlled to a significant degree by physical activity, is also a major risk factor for postmenopausal breast cancer [93].

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3. Colorectal Cancer. There is a strong inverse association between risk of colon cancer and physical activity. In a case-control study, data collected on lifetime occupational and recreational physical activity for ages 20, 30, 40, 50 and 60 years from patients with colon cancer were compared with a cancer-free control group [94]. For lifetime physical activity, the multivariate odds ratio for the highest quartile was 0.37. For life-long high exercisers, compared with non-exercisers, the odds ratio was 0.26. Others examined the association between occupational and leisure-time physical activity and colorectal cancer in a cohort of male smokers [95]. After 12 follow-up years, the relative risks for light and moderate/heavy occupational activity were 0.60 and 0.45, respectively. In addition, the relative risk for distal colon cancer in moderate/heavy occupation activity was 0.21. For rectal cancer, the relative risk reductions for light and moderate/heavy occupational activity were 0.71 and 0.50, respectively. Slatterly et al also reported that vigorous physical activity reduced the risk of rectal cancer among both men and women [96]. Although the incidence of colorectal cancer in Japan is among the highest in the world, increased job-related physical activity in males is associated with a significant risk reduction in both distal colon and rectal carcinoma [97]. However, only total and moderate or “hard” non-job physical activity averted a positive affect on rectal cancer. In females, job-related physical activity and moderate or “hard” non-job physical activity were protective only in the distal colon. In a recent review of 52 studies, 37 found a significant association between the level of physical activity and decreased colon cancer [98].

4. Lung Cancer. Population studies of the association between physical activity and lung cancer have yielded inconsistent results. For example, Bak et al examined the relationship between physical activity and risk of lung cancer in a Danish cohort aged 50 to 64 years [99]. After adjustments for smoking, education level, possible occupational exposure to carcinogens, and diet, there was “no convincing protective effect of physical activity on lung cancer risk.” Similarly, a large European study showed “no consistent protective association of physical activity with lung cancer risk” [100]. Other studies, however, have shown that physical activity decreases the risk of lung cancer. For example, an Iowa Women’s Health Study found that women with high physical activity levels were less likely to develop lung cancer than those who were relatively inactive [101]. Similarly, a case-control study of women from the Czech Republic reported an inverse association for lung cancer between smokers and physical exercise [102]. Moreover, researchers of an extensive Norwegian study reported that men who exercise four or more hours each week had a lower lung cancer risk for both small cell and adenocarcinoma than men who did not exercise (relative risk, 0.71) [103]. Furthermore, a sub-cohort of these men in which physical activity was assessed twice, the relative risk for lung cancer was 0.39 for those who were most active at both assessments. Moreover, in a meta-analysis “of all relevant reports published from 1966 through October 2003”, the odds ratios for lung cancer were 0.87 for moderate leisure-time physical activity and 0.70 for high activity [104].

5. Ovarian Cancer. Increased physical activity may lower the risk for ovarian cancer by decreasing circulating sex hormones, ovulation frequency, body fat or chronic inflammation. To investigate this possible association, Hannan et al carried out a prospective cohort study of 27,365 women [105]. Although there was no overall significant association between physical activity and ovarian cancer over the previous year, “the results are suggestive of an inverse association.” However, in the Copenhagen City Heart Study “a highly significant inverse association was seen between vigorous physical activity in leisure-time and cancer of the ovary…” [106]. Similarly, a case-control Canadian study reported that, compared to women in the lowest tertiles of moderate, vigorous and total recreational activity, those in the highest tertiles had a significantly lower risk [107]. In a case-controlled Chinese study, the risk for ovarian cancer also declined with increasing duration of strenuous sports and frequency of “activity-induced sweating among pre-menopausal women…” [108]. In addition, a literature review concluded that “physical activity protects against ovarian, endometrial and post-menopausal breast cancer independently of BMI” [109].
6. Endometrial Cancer. The results of an early population-based case-control study of physical activity at work and outside work showed that non-retired women holding sedentary jobs or with sedentary lifestyles were at a “somewhat increased risk of endometrial cancer” [110]. Similarly, the authors of an early British study concluded that “physically inactive women may be at increased risk of endometrial cancer because they are more likely to be overweight or obese” [111].

More recently Moradi et al reported results from a population-based case-control study in the “entire Swedish female population aged 50-74 years...” [112]. Compared with the lowest levels of physical exercise, there was a significant reduction in endometrial cancer for those in the highest exercise levels. Another population-based case-control study that examined the relationship between endometrial cancer and physical activity from exercise, household activities, and transportation showed the following: exercise participation in both adolescence and adulthood reduced the cancer risk by 40%; postmenopausal women who initiated exercise in adulthood significantly reduced their cancer risk; and reductions in risk were found for household activities and walking for transportation [113]. A review of physical activity and individual cancer risk concluded that “a convincing risk reduction was found for colon cancer and estrogen-dependent malignancies such as breast and endometrial cancer” [114].

Sarcopenia. By the age of 50 years, most humans become aware that they are losing endurance and muscle strength due to a loss of muscle mass and adaptive ability (sarcopenia). The most apparent causes are lack of use, depletion of muscle regeneration stem cells, a decline in anabolic hormones, and decreased physical activity. As a result, muscle strength decreases approximately 50% from age 30 to 80 years [115], and by the seventh and eighth decades of life, maximal voluntary strength is decreased by 20-40% for men and women in both proximal and distal muscles [116]. A recent study evaluated the effects of aging on the functional and morphological properties of cardiac, skeletal, intestinal muscles, and oxidative status in mice to determine whether a moderate lifelong exercise program would be protective against some harmful aging effects [117]. Indeed, moderate treadmill running during murine lifespan reversed all of the aging effects on intestinal, skeletal, and heart muscles. It also prevented the enhancement of lipid peroxidation and sarcopenia.

Raguso et al evaluated the association between physical activity on body composition in healthy elderly men and women [118]. After a 3-year period, increased physical activity was associated with greater muscle mass and less truncal body fat. Exercise not only reverses the age-associated decline in muscle mass, but also muscle strength [119]. After 12 weeks of exercise training, about 40% of the 10-year strength loss and 75% of the muscle mass loss were restored.

When exercise intensity is low, only modest increases in strength are achieved in the elderly. However, progressive resistance training shows similar or even greater strength gains compared with young individuals. For example, after a 12-week progressive training program involving older men, the extensor strength more than doubled, flexor strength more than tripled, and total muscle area increased by 11.4% [120,121]. Strength training also leads to significant improvement in muscle strength in frail individuals aged 90 years and older [122]. After eight weeks of high-intensity resistance training, strength gains averaged 174%, mid-thigh muscle area increased 9%, and mean tandem gait speed improved 48%.

Osteoporosis and Fractures. Osteoporosis, a very common problem in postmenopausal women and the elderly, is associated with a decrease in bone mineral density (BMD) and increased fractures resulting in a high percentage of late-life disability and death. Unfortunately, 20 million Americans have osteoporosis and another million will develop the disease unless preventive action is taken [123]. An estimated 26% of U.S. women 65 years and older and more than 50% 85 years and older have osteoporosis [124]. However, osteoporosis is not just a woman’s disease. Although men are commonly affected, it is not well appreciated by the medical community. In fact, two million American men have osteoporosis compared with eight million women [125]. Moreover, 24% of men 45 years and older will have an osteoporosis-related fracture compared with 47% of women and 31% will die...
within one year compared with 17% of women. Osteoporosis is responsible for over 1.5 million fractures each year in the U.S. resulting in 500,000 hospitalizations, 800,000 emergency room visits, 2.6 million physician visits, 180,000 nursing home admissions, and 12-18 billion dollars in healthcare costs.

Numerous studies have shown that physical activity is an important factor in reducing/preventing osteoporosis. Furthermore, increased physical activity during childhood and adolescence is an important prevention factor. For example, athletically active adolescent females have higher bone mass than their sedentary counterparts [126]. Moreover, weight bearing physical activity during the years of peak bone acquisition (age 12 to 18 years) “appears to have lasting benefits for lumbar spine and proximal femoral aBMD (areal bone mineral density) in postmenopausal women.” Similarly, an Eastern Finland study that compared the walking distance at ages 9 to 11 years with femoral BMD in peri-menopausal women showed that the greater the walking distance, the higher the BMD [127].

Others studied the effect of daily physical activity on the proximal femur in women aged 35-40 years [128]. After 12 months, there was a significant relationship between physical activity and proximal femoral BMD. Similarly, after comparing the BMD of long distance male runners with age-matched healthy controls, the runners had significantly higher BMD at the calcaneus, lower limbs, femoral neck, pelvis, and trabecular lumbar spine [129]. However, a meta-analysis of 10 studies that examined the effect of walking on BMD in men and postmenopausal women indicated that walking only had a significant positive effect on lumbar BMD, but the effect was not significant on the femur or calcaneus [130]. Nevertheless, when combined with a weight-bearing program, the results are more significant. For example, in a 12-month prospective randomized trial, elderly women assigned to the exercise group showed a significant increase in BMD of the Ward’s triangle, improvement in walking speed, and isometric grip strength [131].

Physical Disability. As a person ages, there is a significant increased risk of becoming frail and disabled. In an early study, predictors of disability were compared between 50- to 80-year old members of a runners’ club and a university population [132]. The runners’ club members had significantly better overall health and less disability at baseline and after a six-year follow-up. Predictors of greater subsequent disability were greater baseline disability, medication, pack-years of smoking, and age, as well as increased blood pressure, arthritis, and less physical activity. Similarly, a six-year prospective longitudinal disability study compared older men and women with general community members [133]. The authors concluded that “older persons who engage in vigorous running and other aerobic activities have lower mortality and slower development of disability than do members of the general population.”

To further appreciate the benefits of aerobic exercise on disability and mortality in older persons, Wang et al examined whether regular exercise could compress morbidity into later years of life [134]. Compared with the control group, their findings showed the following: (a) disability levels were significantly lower in the runners’ club members; (b) relative disability was postponed 8.7 years; (c) runners’ club membership and participation in other aerobic activities were protective against mortality; and (d) controls had a 3.3 times higher death rate in every disease category.

Overweight/Obesity. Physical inactivity and obesity are major public health concerns throughout the industrialized world. Indeed, obesity and physical inactivity independently contribute to all-cause and cause-specific mortality among young and middle-aged adults [135]. These researchers compared adiposity with physical activity in predicting mortality over a 24-year period involving 116,564 women who were free of cancer and coronary heart disease at baseline. Compared with physically active lean women, the multivariate relative risks of death were 1.55 for lean inactive women, 1.91 for active obese women, and 2.42 for inactive obese women. Moreover, a BMI greater than 25 and physical activity less than 3.5 hours each week together accounted for 31% of all premature deaths. Since the amount of physical activity needed to prevent long-term weight gain in older persons was unclear, Lee and associates carried out a prospective 15 year study involving 34,079 healthy women.
At the end of the study, the average weight gain was 2.6 kg. However, those who were successful in maintaining normal weight and gaining less than 2.3 kg averaged 60 minutes of daily moderate intensity activity (mostly walking). Menschik et al studied 3,345 adolescents over a five-year period and found that the likelihood of being an overweight young adult was reduced by 48% in those involved in various extracurricular wheel-related activities (i.e., rollerblading, roller skating, skate boarding, or bicycling) more than four times each week [137]. Moreover, each weekday the students who participated in curricular physical education decreased the odds of being overweight adults by 5%; participation in physical education every weekday decreased the odds by 28%.

The HALE project investigated the single and combined effect of the Mediterranean diet, being physically active, moderate alcohol use, and non-smoking on all-cause and cause-specific mortality in elderly Europeans [138]. After 10 years of follow-up, the hazard ratios were as follows: adherence to a Mediterranean diet, 0.77; moderate alcohol use, 0.78; physical activity, 0.63; and non-smoking, 0.65. The combination of these risk factors lowered the all-cause mortality rate to 0.35. Indeed, Mokdad et al noted that combined physical inactivity and obesity/poor diet was the second highest “actual” cause of death in the United States in 1990 and 2000 [2,3].

**Depression and Dementia/Alzheimer’s Disease.**

**Depression.** Depression is reportedly the leading cause of nonfatal medical disability in developed countries among those aged 15 to 44 years [139]. Indeed, depression is the major cause of suicide, the 10th leading cause of death in the U.S. Although aging is strongly associated with functional decline and depression, increased physical activity has been shown to delay these disorders. For example, 158 men and women aged 50 years and older with a major depressive disorder were randomly assigned to a program of aerobic exercise, antidepressants, or combined exercise and medication [140]. Although persons receiving medication alone exhibited the quickest initial response, exercise was equally effective in reducing depression after 15 weeks.

More recently, Lindwall et al investigated the relationship between light and strenuous exercise and depression in elderly Swedish men and women [141]. Here, the inactive elderly had higher depression scores both in terms of light and strenuous exercise. Moreover, those who were continuously active had lower depression scores than both the continuously inactive persons and those who shifted from activity to inactivity during the previous year. Similarly, a Finnish study found that those who exercised at least two to three times each week experienced significantly less depression, anger, cynical distrust, and stress than those exercising less frequently or not at all [142]. Others evaluated the effect of treadmill walking in a group of U.S. men and women with a major depressive episode [143]. Following an interval training pattern, treadmill walking 30 minutes daily for ten days resulted in “a substantial improvement in those with major depressive disorders.”

**Dementia/Alzheimer’s Disease.** Under normal conditions, the production of neurons (i.e., neurogenesis) occurs only in the hippocampus and olfactory systems of the adult brain. Since aging causes changes in the hippocampus, it may lead to cognition decline in the elderly. However, several studies have shown that regular exercise ameliorates some of the deleterious morphological and behavioral consequences in aging mice and thereby increases the potential for neurogenesis [144-147]. Moreover, as in mice, exercise was shown to have a primary effect on dentate gyrus cerebral blood volume, which correlated with cardiopulmonary and cognitive function in humans [148].

Recognizing that increased physical activity may also maintain cognitive function in older adults, Weuve and associates examined the association between regular long-term physical activity, including walking, and cognitive function in 18,766 elderly women [149]. They found that when combining the tests of cognition, verbal memory, category fluency and attention, women in the highest activity quintile had a 20% lower risk of cognitive impairment. Indeed, an American study noted that greater energy expenditure is protective against cognitive impairment in a dose-response manner [150]. However, since low-intensity physical activity, such as walking, had not been evaluated with
regards to dementia, Abbott et al examined this association in men aged 71 to 93 years [151]. After five years of follow-up, those who walked less than 0.25 miles each day experienced a 1.8-fold higher risk for dementia than those who walked two or more miles each day.

Colcombe and associates reported that increased cardiovascular fitness results in increased functioning of the attentional brain network during a cognitively challenging task [152]. Here, highly fit or aeroaobically trained individuals showed greater task-related activity of the prefrontal and parietal cortices compared with low fit or the non-aerobic control group. More recently, they reported a significant increase in brain volume in 50 to 79 year old individuals who participated in aerobic fitness compared with those who participated in the non-aerobic group [153].

Alzheimer’s disease (AD) is the sixth leading cause of death in the U.S. The major risk factors include age, family history, educational level, and the presence of the apolipoprotein E (APOE) genotype e4 [154]. A leading explanation for AD is an increase in cerebral beta-amyloid protein. Importantly, Lazarov et al recently reported that “environmental enrichment” decreases the accumulation of amyloid protein and alters the gene expression changes in a double transgenic mouse model [155]. These genetically modified mice were placed in an “enriched” environment containing exercise equipment and toys, as well as the usual food, water, and bedding material for the control mice. After five months, the brains of the mice housed in the enriched environment showed a significant reduction in amyloid protein, which was primarily related to increased physical activity.

At about this same time, Podewills and associates reported that persons regularly engaged in a variety of physical activities may decrease the risk of developing AD by as much as 50% [156]. Increased physical activity also decreased the risk of all-cause and ischemic dementia. However, physical activity did not affect individuals who carried APOE4, a gene variant that increases the risk for AD. Others also reported that leisure-time physical activity at midlife is associated with a decreased risk of AD [157]. Thus, “regular physical activity may reduce the risk or delay the onset of dementia and AD, especially among genetically susceptible individuals.”

Both physical activity and diet were recently evaluated in a prospective study of two cohorts comprising community-dwelling elders without dementia at baseline [158]. After 14 years, the hazard ratio for “some” physical activity was 0.75 and 0.67 for “much” activity. A literature review of the positive effects of exercise on the aging brain and cognition has been published [159].

Miscellaneous Diseases/Disorders.

Inflammation and Atherosclerosis. Although the pathogenesis of atherosclerosis is incompletely understood, inflammation is a widely accepted mechanism. Since CHD is the number one cause of death in the U.S. and in most other Western countries, and cerebrovascular disease is number three, the prevention or delay of these diseases would not only improve the quality of life but increase longevity. As of 2005, twenty-two prospective epidemiologic studies demonstrated that increased blood levels of high sensitivity C-reactive protein (hs-CRP), a sensitive marker of inflammation, is a strong predictor of future CHD. Other studies also showed that physical activity decreases the inflammatory process. For example, a group of 197 patients with CHD was randomized to either a comprehensive lifestyle program (regular physical activity, low fat diet, smoking cessation) or usual care with routine follow-up for six months [160]. Independent of diet and smoking, physical performance was significantly and inversely correlated with levels of C-reactive protein, interleukin-6, and soluble cell adhesion molecule-1 in patients with CHD “possibly retarding the process of atherosclerosis.”

Immune System. Aging is commonly accompanied by a decrease in immune function, which can lead to an increased incidence of infectious diseases, malignancy, and autoimmune disorders; thus, the immune theory of aging. Since the aging process does not uniformly affect the immune system, a possible explanation may be due, at least in part, to differences in the level of physical activity. Indeed, many studies have shown that moderate exercise training attenuates immunosenescence in the elderly. For example, Chubak et al studied the effects of moderate-intensity exercise on the risk of colds and upper respiratory tract infections in overweight and obese sedentary postmenopausal women [161]. After several months, the risk of colds in
the control group was three times that of the exercisers. Although moderate regular physical activity benefits the immune system by augmenting resistance to infections and some forms of cancer, intense long-term exercise (e.g., marathon runners) apparently has a negative effect. For example, the susceptibility to upper respiratory tract infections (URT1) after chronic physical exercise at various intensities is described with a “J-shaped” curve. In this review, Nieman presented data from several studies indicating that individuals engaging in marathon-type events and/or very heavy training are at increased risk of URT1 [162]. Regular exercise also accelerates wound healing in the elderly. For example, in a group of healthy older men and women, wound healing occurred at a significantly faster rate in the exercise group compared with the sedentary group [163].

Metabolic Syndrome. The metabolic syndrome is a combination of cardio-metabolic risk determinants including central obesity, insulin resistance, glucose intolerance, dyslipidemia, hypertension, hyperinsulinemia, and microalbuminuria. Sisson and associates examined the association of leisure time sedentary behavior (LTSB) and usual occupational/domestic activity with metabolic syndrome and cardiovascular disease (CVD) risk factors in men and women [164]. After four years, the odds of developing the metabolic syndrome were 1.94 in men for four or more LTSB hours/day, compared with one or less hour/day. LTSB of four or more hours/day was also associated with increased waist circumference, low HDL-cholesterol, hypertension, and increased blood glucose in men. In women, high LTSB was only associated with an increased risk of the metabolic syndrome.

Summary
Physical activity clearly leads to increased physical fitness, exercise capacity, and risk reduction of a wide variety of pathological diseases and clinical disorders resulting in lower rates of morbidity, all-cause and cause-specific mortality, and increased life expectancy. More specifically, physical inactivity increases the risk of coronary heart and cerebrovascular diseases, type 2 diabetes mellitus, hypertension, several cancers (e.g., lung, prostate, breast, colon, others), osteoporosis/fractures and dementia, among others. However, even among the very old “not only continuing but also initiating” physical activity is associated with better survival and function [165]. Moreover, since there is a linear relationship between the level of physical activity and health status, children and adolescents should participate daily in 60 minutes or more of moderate to vigorous physical activity that is enjoyable, involves a variety of activities, and is developmentally beneficial.

References
Physical Inactivity: Associated Diseases and Disorders

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