CHAPTER

9

Cardiovascular Diseases and Physical Activity

The association between physical activity and health, vitality, and longevity has been recognized since antiquity. Over 2,500 years ago, the Greek physician Hippocrates (460–377 BC) succinctly and accurately summed up the benefits of exercise and physical activity as follows:

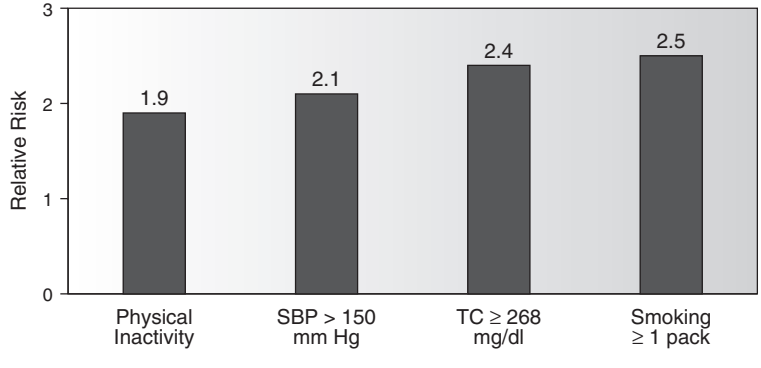
> Speaking generally, all parts of the body which have a function, if used in moderation and exercised in labors to which each is accustomed, become thereby healthy and well developed and age slowly; but if unused and left idle, they become liable to disease, defective in growth, and age quickly.

The quest to define the role of physical activity in human health, disease, and mortality began in the early 1950s. In their landmark study, Morris and coworkers reported that those with physically demanding occupations (London mail carriers and double-decker bus conductors) had approximately 50% lower rates of CHD when compared to the more sedentary bus drivers and desk clerks.[1] Despite the fact that the investigators did not control for confounding factors such as body weight, blood pressure, and blood cholesterol, which are likely to be more abnormal in the sedentary cohort, these findings stimulated worldwide interest in the relationship between physical activity and cardiovascular mortality.

Subsequent leisure time physical activity studies and occupational studies from variety of industries included postal, railroad, and farm workers; employees of utility companies; civil servants; longshoremen; police officers and firefighters; all designed to examine the physical activity–mortality relationship. Most of these studies reported that the most active individuals had one third to three fourths fewer cardiovascular events and deaths when compared to the least active.[2]

A most influential review regarding physical activity and coronary heart disease was by Powell and coworkers in 1987.[3] To assess the relationship between physical activity and mortality, the authors identified 121 studies and carefully evaluated the quality of each. Of the 121 studies, 43 were found to be well-conducted and were included in the final analysis (meta-analysis). Their conclusion was that physical activity is inversely related to the risk of coronary heart disease (CHD). The association was independent of other confounding factors and was as robust as that of established risk factors such as smoking, hypercholesterolemia, and hypertension (**Figure 9.1**).

Figure 9.1 Relative risk for CAD. Note that physical inactivity carries a similar risk with the established coronary factors.



Source: Modified from Powell, et al. *Ann Review Public Health* 1987;8:253–287.

This chapter presents the most influential studies examining the association between physical activity, fitness and cardiovascular disease, and all-cause mortality. In addition, potential mechanisms of exercise-related protection against cardiovascular disease are discussed.

OCCUPATIONAL AND LEISURE TIME PHYSICAL ACTIVITY STUDIES

Occupational and leisure time activity studies utilized questionnaires to assess the physical activity habits of the participants. Despite the subjective nature of such surveys, the overall findings of these studies support a graded reduction in mortality risk with increased level of physical activity. This association is similar for men and women regardless of age. Several of these studies are discussed in some detail because of their unique aspects.

The study by Paffenbarger and Hale[4] followed 6,351 longshoremen for 22 years. The unique feature of this study is that the level of energy output for each participant was estimated based on the energy requirements of 49 longshoring jobs. Accordingly, workers who loaded and unloaded ships were classified as heavy activity, clerks as light activity, and those in between as moderate activity workers. The age-adjusted coronary death rate was 70% higher in the moderate activity and 80% higher in the light activity work group. Because there was little difference in the death rates between moderate and heavy activity workers, the investigators suggested the existence of a protective threshold of physical activity or caloric expenditure.[4]

Fatal and non-fatal coronary events were assessed in 5,288 men and 5,229 women who lived in 58 Israeli settlements called kibbutzim.[5] Participants were classified as physically active or sedentary based on data collected by a physical activity questionnaire. One unique aspect of this study is that these kibbutzim provided communal dining facilities and similar medical care for a relatively homogeneous group. Thus, many of the confounding factors present in epidemiologic studies were eliminated. In addition, risk factors were similar in between physically active and sedentary groups. The other unique aspect is that the study provided information on a large number of women.

The investigators reported that the 15-year relative risk value for fatal and non-fatal coronary events was 2.5 times higher in men engaged in sedentary occupations compared to the men who performed with more physically demanding jobs. For women, the risk was 3.1 times greater for the corresponding occupations.[5]

Not all studies came to similar conclusions. In a Finnish study, the rate of coronary heart disease mortality was greater among lumberjacks compared to less active farmers of the same region.[6] However, this finding must be interpreted with caution for two reasons. Although farmers were less active than lumberjacks, they were not sedentary. Thus, the study compared highly active (lumberjacks) to somewhat less active (farmers) individuals. This along with the higher fat consumption and smoking rates among lumberjacks is likely to have attenuated the positive effects of physical activity in the lumberjacks and showed more favorable outcomes for the farmers.

The landmark epidemiologic work by Paffenbarger and associates provided persuasive evidence on the association between physical activity and mortality. In 1978, the same investigators assessed the association between leisure time physical activity and heart attacks in 16,963 Harvard alumni who entered Harvard between 1916 and 1950 and responded to a questionnaire.[7] The cohorts were categorized based on weekly caloric expenditure based on leisure time activities, ranging from < 500 to

more than 4,000 kcal/week. The data revealed that the risk of first heart attack was related inversely to the level of energy expenditure during leisure time. A sharp reduction in fatal and non-fatal heart attacks rates with increase in weekly energy expenditure was noted at the energy expenditure of 2,000 kcal per week. Those who expended less than 2,000 kcal per week had a 64% higher risk for a heart attack.

Another important finding of this study was that the reduction in risk was only evident if physical activity was maintained throughout the study participant's life. Those who played varsity sports but did not maintain a physically active lifestyle had a higher mortality rate compared to those who maintained a physically active lifestyle in adulthood. Conversely, those who avoided athletics in college but subsequently took up a more active lifestyle also had similarly low rates of mortality.[7]

In the next two reports that followed on the same cohort,[8,9] the investigators reported a consistent, inverse, and graded trend towards a lower all-cause mortality rate; as physical activity-related caloric expenditure increased form 500 to 2,000 kcal per week, the mortality rate decreased. More specifically, the mortality risk for men whose weekly energy expenditure from leisure time activities total 2,000 kcal or more had about 25% to 33% lower mortality rate compared to those with a caloric expenditure of less than 2,000 kcal per week. Paffenbarger et al. speculated that physical activity accounted for approximately 1 to 2 years of additional life. An interesting observation of the study was that the mortality risk tended to increase slightly in those expending more than 3,500 kcal per week.[8] This is equivalent to about 30 to 35 miles of jogging per week.

In the more recent study, Paffenbarger et al.[9] examined the relative risk of death based on different types of physical activity that included walking (miles/week), stair-climbing (floors), and playing sports in 10,269 Harvard alumni over a 9-year period. The inverse and graded association between mortality risk and volume of physical activity was again evident and in accord with their previous findings. In addition, and particularly noteworthy, was the 30% to 40% reduction in mortality risk, evident in those individuals engaging in moderate-to-vigorous activity levels (≥ 4.5 METs; see Chapter 2) with only minimal additional benefits achieved by engaging in activities of greater intensity. The reduction was similar when physical activity was expressed as kilocalories per week (the sum of walking, stair climbing, and sports participation), suggesting that a 40% reduction in mortality occurs by engaging in modest levels of activity (1,000 to 2,000 kcal/week, equivalent to three to five 1-hour sessions of activity).

Collectively, the findings of these studies[4,7,9] provided evidence in support of an exercise intensity threshold of about 5 to 6 METs and an exercise volume threshold somewhere between 1,000 and 2,000 kcal per week for a significant reduction in mortality risk. Furthermore, the findings suggest that most of the benefits occur at moderate exercise volumes and moderate intensities.

Similar results have been reported from large studies that have followed cohorts for coronary heart disease (CHD) morbidity and mortality in the range of 10 to 20 years among British civil servants, U.S. railroad workers, San Francisco longshoremen, nurses, physicians, other healthcare workers, and other cohorts. The findings of these studies are summarized in two comprehensive reviews.[10,11]

Clearly, the accumulated epidemiological evidence provided strong support for the existence of a strong inverse relationship between physical exercise and risk of CHD. As stated by Paffenbarger and Hyde, ". . . the questions to be addressed are not whether exercise is a real element for cardiovascular health, but what kind of exercise is needed, and how much, i.e., with what frequency, intensity, timing, and duration.

An understanding of the ways and means by which exercise alters coronary heart disease risk is only beginning to emerge, but there is wide acceptance that its benefits are vitally needed in the sedentary Western world."[12]

According to a recent review that included 44 observational studies from 1966 to 2000,[13] the collective findings support the following: First, there is strong evidence of an inverse linear dose-response relationship between volume of physical activity and all-cause mortality. Second, an exercise volume threshold can be defined beyond which a significant reduction in mortality risk occurs. This threshold appears to be at a caloric expenditure of approximately 1,000 kcal per week for an average reduction of 20% to 30% in mortality risk. Further reductions in risk are observed with higher volumes of energy expenditure. Third, the independent contribution of the exercise components of intensity, duration, and frequency to the reduction of mortality risk was not clear. The authors emphasized the need for more research to better understand the contribution of each component.[13] Indeed, efforts to define the intensity, duration, frequency, volume, and type of exercise necessary for cardiovascular health and longevity continue. Although progress has been made, much more work is needed.

The influence of genetic factors in the reduction of the mortality risk cannot be dismissed. Furthermore, the argument can be made that it is not the physical activity that provides protection but the genetic composition of these individuals.

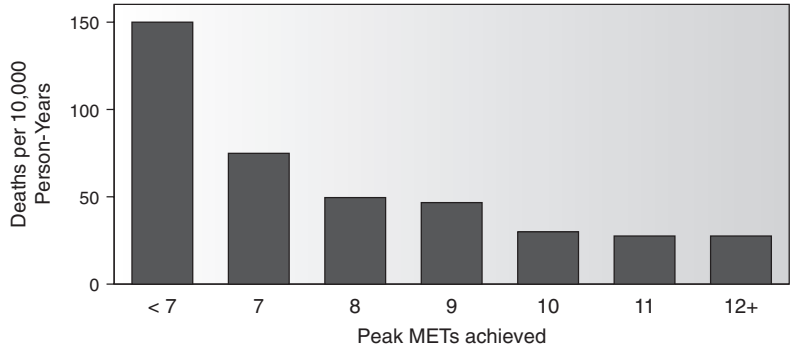
In this regard, the independent association of physical activity and mortality and the influence of genetic and other familial factors were assessed in a cohort of same-sex twins born in Finland before 1958 and with both alive in 1967.[14] In 1975, healthy men (n = 7,925) and healthy women (n = 7,977) responded to a questionnaire on physical activity, occupation, smoking habits, body weight, alcohol use, and physician-diagnosed diseases. Individuals who reported engaging in brisk walk for a mean duration of 30 minutes, at least six times per month were classified as physically active. Those who reported no leisure time activity were classified as sedentary. The remaining individuals were classified as occasional exercisers. When compared to the sedentary twins, the adjusted risk of mortality was 33% lower among the twins who exercised occasionally and 44% lower among the physically active twins. The investigators concluded that physical activity is associated with lower mortality independent of genetic and other confounding factors.

Epidemiological evidence supports a strong inverse relationship between physical exercise and coronary heart disease risk.

Physical Fitness Studies

Physical activity questionnaires provide valuable information and are useful in assessing physical activity levels. However, by nature, they are not objective. A shift from assessing physical activity by questionnaires to a more objective assessment was provided by Steve Blair and his co-investigators in their landmark study.[15] The investigators assessed physical fitness of 10,224 men and 3,120 women by a maximal exercise test at the Institute of Aerobic Research. The cohort was grouped into five fitness categories based on the MET level achieved and were followed for a period of over 8 years. After adjusting for age, blood pressure, smoking habits, fasting blood glucose levels, and family history of coronary heart disease, there was an inverse, strong, and graded association between physical fitness and cardiovascular and all-cause mortality for both men and women. The most striking finding of the study was that the major reduction in mortality risk occurred when moving from the least fit (< 7

Figure 9.2 Age-adjusted all-cause mortality in men according to exercise capacity.



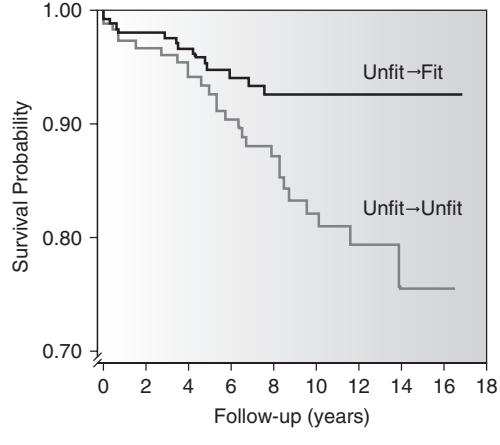
Source: From Blair, et al. *JAMA* 1989;262:2395–2401.

METs) to the next fit category of 7 METs. The risk continued to decline with higher fitness levels and appears to plateau at approximately 9 to 10 METs for women and men, respectively (**Figure 9.2**). The investigators emphasized that the MET levels of 7 to 10 achieved for optimal health benefits are attainable by a brisk walk of 30 to 60 minutes each day.

Despite the objectivity of the maximal exercise test and its greater accuracy in the classification of fitness categories, it still represents a single baseline assessment of fitness. With a single exposure assessment at baseline, it is difficult to discount the influence of genetic factors, underlying diseases, and other confounding variables on the association between fitness and mortality. For example, the low exercise capacity at baseline and the cause of death within the follow-up period of the study may be due to underlying disease and not the low fitness level. In this case, the mortality risk for the low fitness categories will be overinflated and the association spurious.

To address this issue, Blair and coworkers controlled for some of these confounding variables by assessing the fitness of the cohort with two maximal exercise tests. The investigators reported that men who were unfit at both examinations had the highest mortality rate. Those who increased their physical activity and moved from the unfit to fit category within the first and subsequent examinations had a 44% reduction in adjusted mortality risk when compared to men who remained unfit at both examinations (**Figure 9.3**). In addition, the

Figure 9.3 Survival curves for fit and unfit men. A 44% reduction in adjusted mortality risk was noted in the unfit who became fit compared to the unfit men who stayed unfit.



Source: From Blair, et al. *JAMA* 1995;273:1093–1097.

investigators estimate a 7.9% reduction in mortality risk for every minute increase in the peak treadmill exercise time between examinations.[16] This finding also provides evidence to support that the association between fitness and mortality is independent and beyond genetic factors.

The inverse association between physical activity and mortality remains robust after statistical adjustments of potential confounders. However, the impact of physical activity within groups in the presence of known risk factors such as hypertension, diabetes, or smoking has not been assessed. In this regard, Blair and coworkers[17] assessed the impact of fitness within groups who possess specific risk factors. The cohort consisted of 25,241 men and 7,080 women with baseline evaluations that included a maximal exercise test. Low, moderate, and high-fit categories were established based on the peak exercise time.

The findings of this study lead to three principal conclusions. First, an inverse and graded association between fitness and mortality was evident and consistent within the various subgroups examined. For men who smoked, had high blood cholesterol and elevated systolic blood pressure, or were unhealthy, the adjusted all-cause mortality rates were 17% to 39% lower if they were moderately fit compared to low fit. For the fit men, the risk was 32% to 50% lower.

Second, moderate and high fitness levels appear to provide protection against the cumulative detrimental effect of multiple risk factors. For example, the death rates in high-fit individuals with two or three risk factors (smoking, high blood cholesterol, or elevated systolic blood pressure) were significantly lower (15%) when compared to low-fit individuals with no risk factors.

Third, the relative risk for all-cause and cardiovascular mortality due to physical inactivity was similar to those of cigarette smoking and elevated cholesterol levels.

Although the physical activity–mortality relationship was well established by now, information on the intensity, duration, and type of physical activity was still speculative. To address these questions, Lakka and coworkers[18] directly assessed the maximal oxygen uptake by a standardized exercise test. In addition, they collected information by questionnaires on the leisure time physical activity habits of 1,453 healthy men. The cohort was followed for an average of 4.9 years and myocardial infarctions were recorded.

The association between the risk of myocardial infarction and both leisure time physical activity and oxygen uptake was inverse and graded. After adjusting for a number of coronary risk factors, men with an oxygen uptake of more that 34 ml/kg/min (the highest one third of the cohort) had a 55% lower risk of myocardial infarction compared to the risk of the least fit man (the lowest one third). Similarly, men engaging in leisure time activity for more than 2 hours per week had a 60% lower risk than the least fit men. The investigators also reported that a mean intensity of about 6 METs may be the threshold for a reduction in risk.

The unique aspect of this study is that both oxygen uptake and leisure time activity were assessed. Because oxygen uptake was directly measured and not estimated, fitness level is more accurately assessed. Collectively, the oxygen consumption of 34 ml/kg/min, the hours of physical activity per week, and the very similar decrease in risk (55% and 60%) support the contention that physical activity of moderate intensity (about 6 METs as stated by the investigators) is required for risk reduction.

Similar findings were reported in a study of 1,960 middle-aged, Norwegian men whose physical fitness was assessed at baseline by an exercise tolerance test using a bicycle ergometer. During a 16-year follow-up period, the relative risk for cardiovascular mortality was

inversely related to physical fitness. Once again, the major reduction in mortality risk (41%) occurred when moving from the least fit (quintile 1) to the next fit category (quintile 2). The risk continued to decline with higher fitness levels reaching 55% and 59% for quintiles 3 and 4, respectively.[19]

The independent effects of exercise type and intensity on the risk for coronary heart disease were assessed in a large cohort of 44,452 men enrolled in the Health Professionals' Follow-up Study.[20] The MET level for each activity performed was calculated and the cohort was categorized into fitness quintiles based on the MET-hours per week of total physical activity.

The findings of this study support an inverse and graded association between the risk of coronary heart disease and the weekly volume of exercise or physical activity. In this regard, the findings of the study are in accord with previous findings and strengthen the contention that physical activity is protective against premature heart disease. In addition, the study provided information on the type, volume, and intensity of several physical activities and their respective efficacy on coronary heart disease risk reduction. It is also important to mention that this was the first study that provided evidence on the efficacy of weight training or resistance training on coronary heart disease risk reduction. The risk reduction achieved by weight training was similar to that observed by brisk walking and rowing, and approximately half of that observed by running. These findings are summarized in **Table 9.1**.

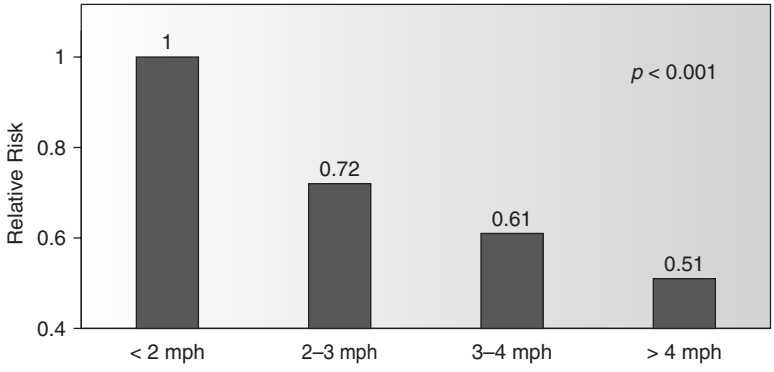
Because walking was the most frequent form of exercise (58% of men reported walking at least 1 hour per week), the investigators examined the independent effects of intensity and duration of walking on the risk for coronary heart disease. They found that walking pace (intensity) was inversely related to the risk of coronary heart disease independent of walking volume (**Figure 9.4**). A 4% reduction in coronary risk was observed for every 1-MET increase in exercise intensity. The duration of walking was also inversely related to the risk. However, the much stronger association between intensity and risk suggests that walking intensity has a stronger effect on risk reduction than duration.

Evidence supports that both exercise intensity and duration are associated with a reduction in mortality risk. However, the stronger association between intensity and risk suggests that additional health benefits may be possible with relatively higher exercise intensities. There is also limited evidence that weight training may be as effective in lowering mortality risk as aerobic exercise.

Table 9.1 Activity Performed and Coronary Heart Disease Relative Risk Reduction in Men

Activity Performed per Week	Relative Risk Reduction
Running ≥ 1 hour	42%
Rowing ≥ 1 hour	18%
Brisk walk ≥ 30 minutes	18%
Weight training ≥ 30 minutes	23%

Figure 9.4 Adjusted risk for coronary heart disease according to walking pace.



Source: Modified from Tanasescu M, et al. *JAMA* 2002;288:1994–2000.

Quantifying the Dose-Response Association

Recently, several more studies have reported a more precise quantification of the dose (amount of exercise or degree of fitness) and response (mortality risk-reduction) relationship by expressing exercise capacity in the context of survival benefit per MET (**Table 9.2**). These studies present the change in mortality risk for each 1-MET increase in exercise capacity assessed by a maximal exercise test. The reduction in mortality risk per 1-MET increase in exercise capacity ranges between 10% and 25%.[16,21–27] This is evident in both men and women. There is also evidence to suggest that the strength of exercise capacity in predicting risk of mortality may even be greater among women than men.[22,28]

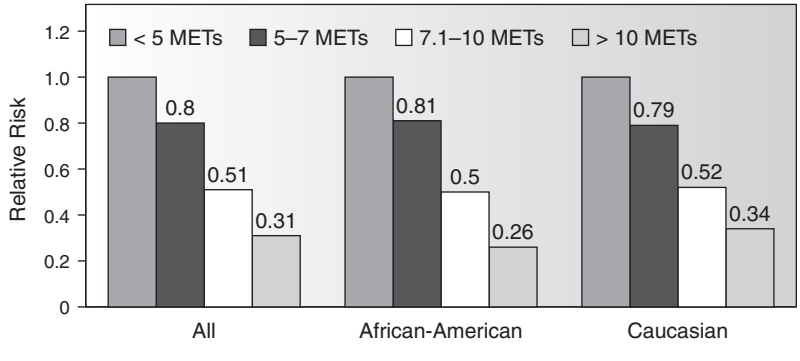
Information on the association between physical activity, exercise capacity, and mortality among African Americans is lacking. It is well-documented that the age-adjusted all-cause mortality rates in African Americans are as much as 60% higher when compared to American Caucasians. To address this issue, Kokkinos et al.[27] assessed the association between exercise capacity and mortality risk in 6,749 African-American and 8,911 Caucasian men. The investigators found exercise capacity to be a more powerful predictor of risk for all-cause mortality than established risk factors (smoking, dyslipidemia, diabetes, and hypertension) among both African Americans and Caucasians after adjusting for cardiac medications. The risk for mortality was 13% lower for every 1-MET increase in exercise capacity for the entire cohort, with similar reductions observed for those with and without CVD.

In addition, when fitness groups were considered, the relative risk for all-cause mortality was approximately 20% lower in those with an exercise capacity of 5 to 7 METs (moderate fit category) when compared to those achieving < 5 METs. The mortality risk was 50% lower for those with an exercise capacity of 7.1 to 10 METs and 70% lower for those with an exercise capacity of more than 10 METs. This gradient for a reduction in mortality with increasing fitness was similar in African Americans and Caucasians in the entire cohort (**Figure 9.5**) and in individuals with and without CVD (**Figures 9.6** and **9.7**). These findings are very

Table 9.2 Survival Benefit per 1-MET Increase in Studies Using Maximal Exercise Testing as a Measure of Fitness

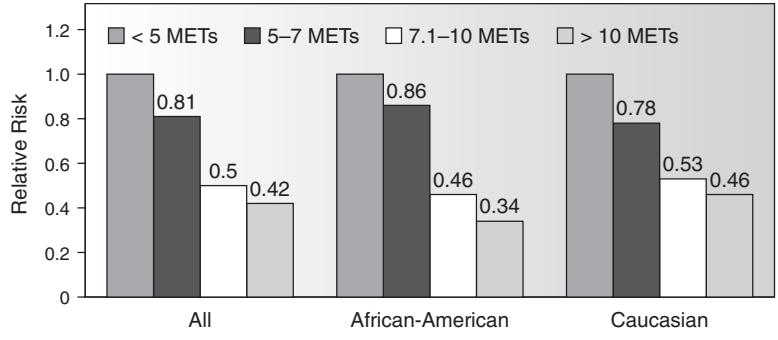
Study	Cohort	N	Mortality Risk Reduction/MET Increase
Blair et al.[16]	Men	9,777	~16%
Dorn et al.[22]	Cardiac rehabilitation	651	8%–14%
Goraya et al.[23]	- Younger	2,593	14%
	- Elderly	514	18%
Myers et al.[26]	Middle-aged men with and without coronary heart disease test	6,213	12%
Gulati et al.[28]	Healthy women	5,721	17%
Mora et al.[24]	Women in the Lipid Research Clinics Trial	2,994	20%
Balady et al.[21]	Framingham Offspring Study:		13%
	- Men	1,431	
	- Women	1,612	
Myers et al.[25]	For every 1,000 kcal/week adulthood activity	6,213	20%
Kokkinos et al.[27]	Middle-aged men with and without coronary heart disease referred for an exercise treadmill test	15,660	13%

Figure 9.5 Adjusted risk for all-cause mortality in African Americans and Caucasians.



Source: Adapted from Kokkinos, et al. *Circulation* 2008;117:614–622.

Figure 9.6 Adjusted risk for all-cause mortality in African Americans and Caucasians with CVD.



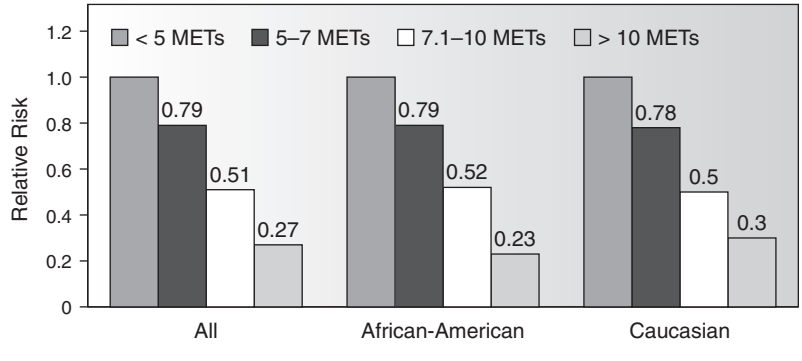
Source: Adapted from Kokkinos, et al. *Circulation* 2008;117:614–622.

similar to the mortality rate reduction reported by Myers et al.[26] in men with and without CVD. Because the cohort of the two studies[26,27] consisted of veterans with very similar health care (the Veterans Affairs Health Care System ensures equal access to care independent of a patient's financial status), the findings strengthen the evidence that higher exercise capacity is associated with lower cardiovascular and all-cause mortality regardless of factors related to socioeconomic strata.

A more precise quantification of the dose (amount of exercise or degree of fitness) and response (mortality risk-reduction) relationship revealed a 10% to 25% reduction in mortality risk for each 1-MET increase in exercise capacity.

These findings have significant public health implications. Mortality risk can be cut in half by just engaging in brisk walk for 2 to 3 hours per week or 30 minutes per session 4 to 5 days

Figure 9.7 Adjusted risk for all-cause mortality in African Americans and Caucasians with no CVD.



Source: Adapted from Kokkinos, et al. *Circulation* 2008;117:614–622.

per week. This was shown for both African Americans and Caucasians with and without heart disease (see Figures 9.5 to 9.7). Collectively, the findings of the aforementioned studies support the concept that exercise capacity should be given as much attention by clinicians as other major risk factors.

Physical Activity and Mortality in Women

Most of the information on the association between physical activity, fitness, and mortality risk has been derived from studies on men. Extrapolating from the findings of the studies on men and the few studies that included women, the health benefits of exercise are likely to be similar for women. These assumptions were substantiated by a number of relatively large studies published since the late 1990s.

In a study of 10,224 men and 3,120 women, Blair et al.[15] reported similarly lower all-cause and cardiovascular disease mortality rates with increased fitness in men and women. These findings were strengthened by their more recent study that included a substantially larger cohort of women (n = 7,080).[17] In addition to the inverse and graded association between physical fitness and mortality, these data revealed differences between men and women, suggesting that the influence of physical activity or fitness on mortality rates may be different in women and men.

First, physical fitness seems to offer a greater degree of protection in women with high blood pressure than men. The reduced risk of mortality in hypertensive but high-fit women was 81% lower when compared to low-fit women. In men, the risk reduction for the comparable groups was only 32%. For the same group comparisons, the risk reduction for elevated blood cholesterol was 50% in men and 23% in women.

Second, the protection against the cumulative detrimental effect of multiple risk factors appears greater for women than men. For example, the death rates in high-fit individuals with two or three risk factors (smoking, high blood cholesterol, or elevated systolic blood pressure) were 15% men and 50% in women when compared to low-fit individuals with no risk factors.

In one of the earlier and largest studies on postmenopausal women (The Iowa Women's Health Study), 40,417 women responded to a survey that included questions related to health habits such as smoking, diet, alcohol consumption, anthropometry, medical history, and leisure time physical activity.[29] Women were classified in three categories (low, moderate and high-fit) based on the frequency and intensity of activity. Physical activities were classified as moderate (those requiring ≤ 6 METs) or vigorous (> 6 METs). Women who participated in moderate activities more than four times per week and those who participated in vigorous activities two or more times per week comprised the high-fit category (n = 9,919). Those who reported vigorous activity once a week or moderate activity one to four times a week comprised the moderate-fit category (n = 10,987). The remaining women comprised low-fit category (n = 19,940). The follow-up period was approximately 7 years.

After adjusting for confounding factors, the investigators reported that high levels of physical activity were associated with decreased risk of mortality.[29] The adjusted risk of mortality was 34% and 48% lower in the moderate- and high-fit women, respectively. Because women who are ill tend to be less active and are likely to die at a higher rate, the mortality rate in the low-fit category may be inflated. To control for this factor, the investigators excluded from the analysis all women who died of cancer or heart disease within the first 3 years of follow-up. When the analysis was repeated, the results did not change substantially.

Another important finding of this study is that the risk appears to be significantly reduced even in those who participated in moderate physical activity once per week to a few per month. This is similar to the findings reported in the Finnish Twin Study.[14] It also supports previous findings of a threshold requirement of about 6 METs for a significant reduction in mortality risk.[18] However, it is in contrast to other studies that reported more vigorous and greater volume of physical activity required for significant risk reduction.[7]

Two reports from the Nurses' Health Study[30,31] provided valuable information on the association between intensity, duration, frequency, and volume of physical activity necessary to reduce the risk of cardiovascular events in women.

The Nurses' Health Study, initiated in 1976, was designed to examine the association between total physical activity (walking and vigorous exercise) and the incidence of cardiovascular events in women. The first study[31] assessed the association between physical activity and the risk of coronary heart disease. The cohort consisted of 72,488 middle-aged women nurses, 40 to 65 years of age, free of cancer and cardiovascular disease at the time of entry into the study who completed a detailed questionnaire about their physical activity habits. Each physical activity (walking, biking, jogging, aerobics, etc.) was expressed in METs and then the total activity level was expressed as MET-hours per week. Five physical activity categories were established as presented in **Table 9.3**. The follow-up period was 8 years.

The large size of the cohort and the long-term follow-up allowed the investigators to address several important questions including the exercise intensity, duration, and volume on the risk for coronary events. By excluding the women who died within the first 2 years of follow-up, the possible overestimation of the mortality rate within the low-fit categories as a result of illness and not low fitness was minimized.

Table 9.3 Relative Risk of Coronary Events According to Weekly Physical Activity (MET-hr/week)

Fitness Category	1	2	3	4	5	*P* value for Trend
(MET-hr/wk)	0–2.0	2.1–4.6	4.7–10.4	10.5–21.7	> 23.7	
Age-adjusted relative risk	1.0	0.77 (0.62–0.96)	0.65 (0.51–0.95)	0.54 (0.50–0.93)	0.46 (0.33–0.67)	< 0.001
Multivariate	1.0	0.83 (0.71–0.95)	0.72 (0.62–0.84)	0.63 (0.54–0.74)	0.55 (0.47–0.65)	< 0.001
Multivariate Excluding first 2 years	1.0	0.89 (0.75–1.04)	0.81 (0.68–0.97)	0.78 (0.66–0.93)	0.72 (0.59–0.87)	< 0.001

Source: Adapted from Manson JE, et al. *N Engl J Med* 1999;341:650–658.
Numbers in parentheses indicate the confidence interval.

A graded reduction in the relative risk of coronary events with increase in the MET-hours per week was noted (see Table 9.3). The association between physical activity and mortality risk was somewhat weaker (mortality risk reduction was attenuated), but still significant, when women who died within the first 2 years of follow-up were excluded (see Table 9.3).

The investigators then sought to assess the attenuating potential effects established risk factors may have on the association between physical activity and coronary events. Thus, the cohort was stratified based on smoking habits, obesity (BMI), and parental history of premature myocardial infarction. For each respective subgroup, physical activity was inversely related to the risk of coronary events in all strata with no substantial differences in the impact of physical activity in the lowering risk (**Figure 9.8**). These findings support that physical activity has a similar attenuating effect on the risk for coronary events even when amplified by the presence of cardiovascular risk factors.

Walking and Coronary Risk Reduction

Approximately 60% of the women in the cohort engaged in at least 1 hour of walking per week and only 26% engaged in vigorous activities requiring ≥ 6 METs and defined vigorous exercise. Thus, the investigators assessed the association between walking and risk of coronary events by excluding the women who reported engaging in vigorous activity. An inverse association was again noted between walking hours per week and the risk for coronary. Women who walked between 1 to 2.9 hours per week at a brisk pace (≤ 20 minutes/mile), the equivalent of 3.9 to 9.9 MET-hours per week had a 30% lower relative risk of coronary events when compared to the sedentary group (no walk). The risk for the women who walked for 3 or more hours per week (≥ 10 MET hr/wk) was 35% lower.

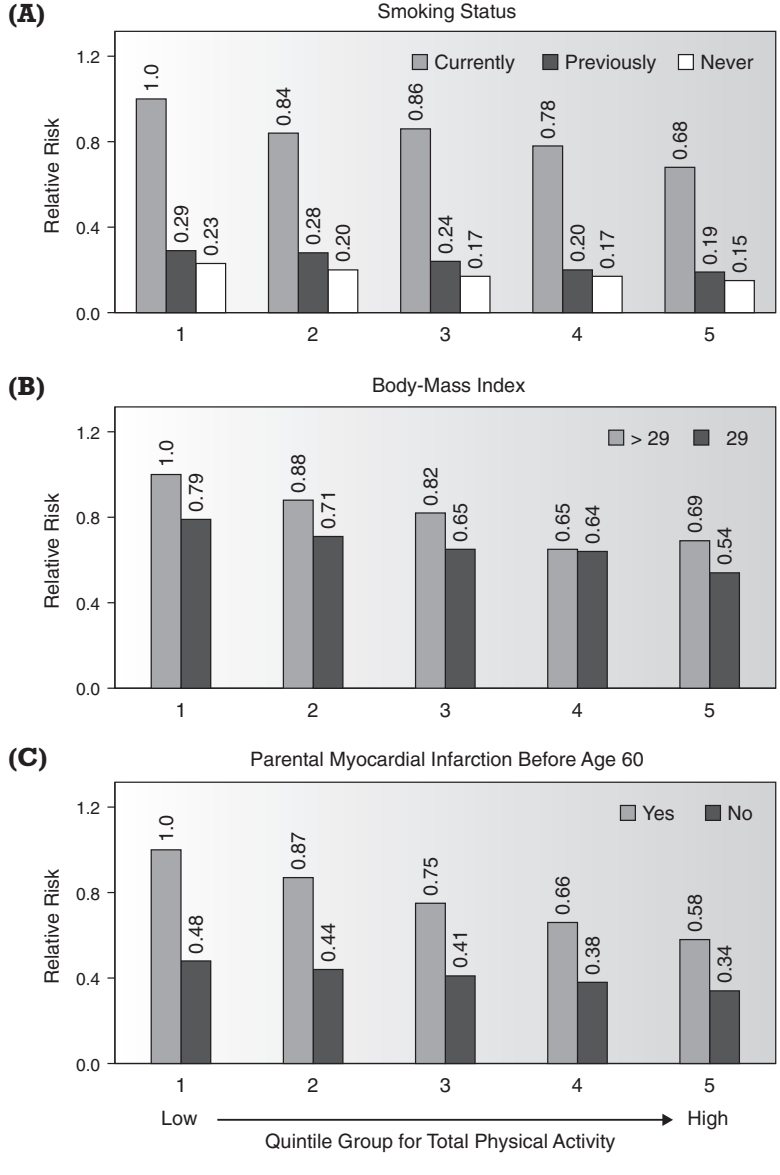
The investigators then sought to determine if walking pace or exercise intensity was an important determinant of risk of coronary events. In a multiple analyses, walking pace emerged as an independent predictor of risk. The multivariate relative risk for women who walked at an average pace of 2.0 to 2.9 miles per hour (20–30 minutes/mile), was 25% lower risk when compared to women who walked at an easy pace (< 2.0 miles/hour). The risk of those who walked briskly or very briskly was 36% (**Figure 9.9**).

A significant reduction in risk (30%–35%) was also observed when walking more than 60 minutes per week (**Figure 9.10**).

When the investigators examined the combined effect of walking and more vigorous exercise to the coronary event risk reduction, they observed that women who engaged in both walking and vigorous exercise had a greater risk reduction than those participating in either type of activity alone. When the effects of walking and vigorous exercise were examined separately, both were effective in lowering risk. A 14% reduction in risk was noted for every 5 MET-hours per week spent on walking (the equivalent of 1.5 hours of brisk walk per week). For every 5 MET-hours per week spent in vigorous exercise (the equivalent of 45 minutes per week of vigorous activities), the risk was lowered by 6%. This suggests that the exercise duration is more effective in lowering the risk for coronary events than exercise intensity.

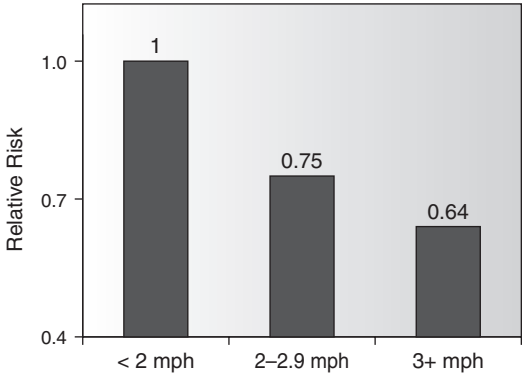
In the second report of the Women's Health Study, the investigators assessed the association between physical activity and the risk for cardiovascular disease.[30] The cohort consisted of mostly the same cohort as in the previous

Figure 9.8 Multivariate relative risk of coronary events (nonfatal myocardial infarction or death from coronary causes) according to quintile group for total physical activity within subgroups defined according to smoking status (A), body-mass index (B), and presence or absence of a parental history of premature myocardial infarction (C). For each risk factor, the reference group is the category at highest risk. Relative risks have been adjusted for the variables in the full multivariate model.



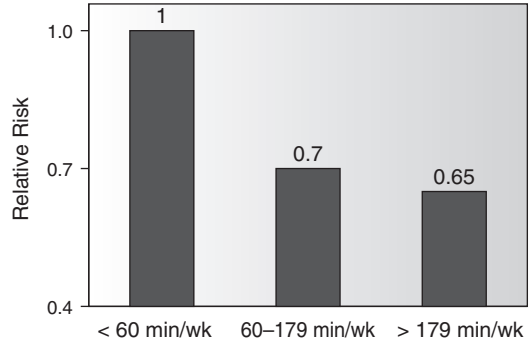
Source: From Manson JE, et al. *N Engl J Med* 1999;341:650–658.

Figure 9.9 Relative risk for coronary events in women (n = 72,488) and walking pace.



Source: Adapted from Manson JE, et al. *N Engl J Med* 1999;341:650–658.

Figure 9.10 Relative risk for coronary events in women (n = 72,488) and minutes of walking at a pace of 3 or more miles per hour.



Source: Modified from Manson JE, et al. *N Engl J Med* 1999;341:650–658.

study, but slightly larger (n = 73,743) and older (50–79 years of age) and all postmenopausal women.

During the 3.2 years of follow-up, a strong inverse association was noted between the total exercise (MET-hours per week) and the age-adjusted risk of coronary heart disease. Similarly, the age-adjusted risk for cardiovascular disease declined as MET-hours per week increased (**Table 9.4**).

Table 9.4 Relative Risk for Cardiovascular Disease According to Fitness Categories

Fitness Category	1	2	3	4	5	*P* value for Trend
(MET-hr/wk)	0–2.4	2.5–7.2	7.3–13.4	13.5–23.3	≥ 23.4	
CHD Age-Adjusted Relative Risk	1.0	0.73 (0.53–0.99)	0.69 (0.51–0.95)	0.68 (0.50–0.93)	0.47 (0.33–0.67)	< 0.001
CVD Age-Adjusted Relative Risk	1.0	0.83 (0.71–0.95)	0.72 (0.62–0.84)	0.63 (0.54–0.74)	0.55 (0.47–0.65)	< 0.001
Multivariate Relative Risk	1.0	0.89 (0.75–1.04)	0.81 (0.68–0.97)	0.78 (0.66–0.93)	0.72 (0.59–0.87)	< 0.001

Source: Adapted from Manson JE, et al. *N Engl J Med* 2002;347:716–725. Numbers in parentheses indicate confidence intervals.

Walking Versus Vigorous Activity and Cardiovascular Risk

In the second report of the Women's Health Study,[30] investigators also assessed the independent effects of intensity and volume of physical activity on the reduction of cardiovascular mortality risk. Similar to the previous study, an inverse association was observed between the coronary heart disease and cardiovascular disease mortality with the increase in the MET-hours per week accumulated during brisk walk. More specifically, when compared to the sedentary women, the reduction in risk ranged from approximately 30% to 40% when engaging in either walking or more vigorous exercise for at least 2.5 hours per week (**Table 9.5**).

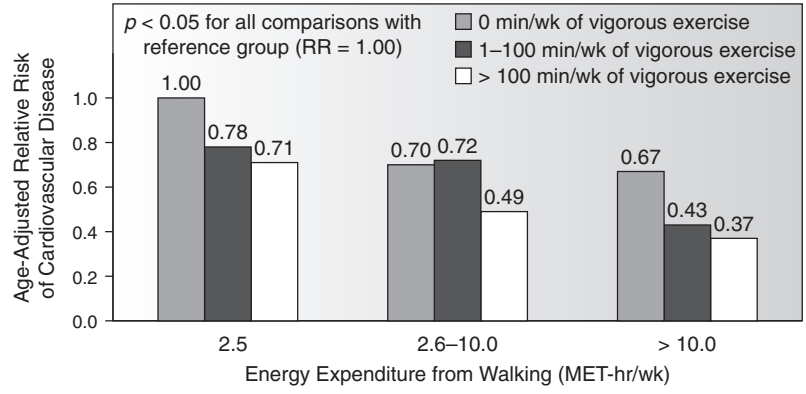
The reduction in cardiovascular risk was greater (63%) for women engaging in both walking and vigorous exercise, suggesting that the exercise intensity may have an independent effect on risk reduction (**Figure 9.11**). This is supported further by the inverse relationship between walking pace and risk reduction. It also appears that an intensity threshold emerges at the approximate walking pace of 2 to 3 miles per hour. When compared to the women who never or rarely walked, those who walked at the pace of 2 to 3 miles per hour (20 to 30 minutes per mile); 3 to 4 miles per hour (equivalent

Table 9.5 Relative Risk for Cardiovascular Disease According to Energy Expenditure by Walking and Vigorous Exercise

Walking	**1**	**2**	**3**	**4**	**5**	***P* value for Trend**
(MET-hr/wk)	0	0.1–2.5	2.6–5.0	5.1–10.0	> 10.0	
CHD	1.0	0.71	0.60	0.54	0.61	< 0.004
Age-Adjusted Relative Risk		(0.53–0.96)	(0.44–0.83)	(0.39–0.76)	(0.44–0.84)	
CVD	1.0	0.88	0.70	0.66	0.58	< 0.001
Age-Adjusted Relative Risk		(0.77–1.01)	(0.60–0.81)	(0.57–0.77)	(0.49–0.68)	
Multivariate Relative Risk	1.0	0.91	0.82	0.75	0.68	< 0.001
		(0.78–1.07)	(0.69–0.97)	(0.63–0.89)	(0.56–0.82)	
Vigorous Exercise						***P* value**
Minutes/week	0	1–60	61–100	101–150	> 150	
CHD	1.0	1.12	0.56	0.73	0.58	0.008
Age-Adjusted Relative Risk		(0.79–1.6)	(0.32–0.98)	(0.43–1.25)	(0.34–0.99)	
CVD	1.0	0.87	0.73	0.69	0.60	< 0.001
Age-Adjusted Relative Risk		(0.72–1.04)	(0.58–0.92)	(0.53–0.89)	(0.47–0.76)	
Multivariate Relative Risk	1.0	0.91	0.81	0.85	0.76	0.01
		(0.73–1.12)	(0.63–1.06)	(0.64–1.13)	(0.58–1.0)	

Source: Adapted from Manson JE, et al. *N Engl J Med* 2002;347:716–725. Numbers in parentheses indicate confidence intervals.

Figure 9.11 Relative risk of CVD according to walking and vigorous activity.



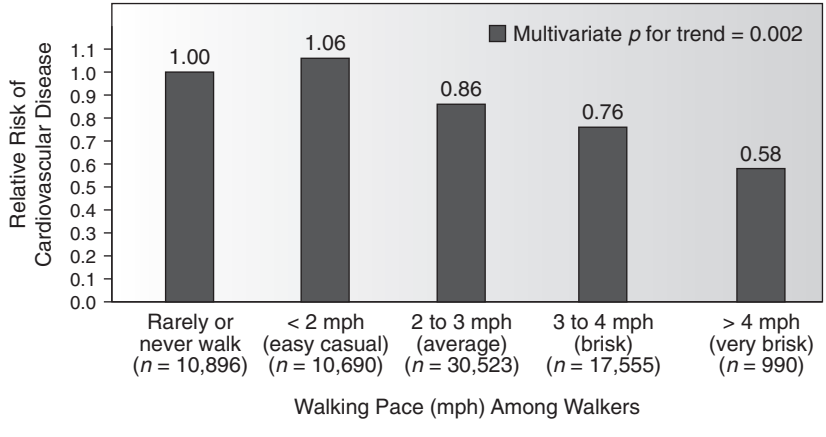
Source: Data from Manson JE, et al. *N Engl J Med* 1999;341:650–658.

to a brisk walk), and more than 4 miles per hour (very brisk walk) had a 14%, 24%, and 42% relative reduction risk of cardiovascular disease (**Figure 9.12**).

Once again, the large size of the cohort allowed the investigators to address several important questions, including the exercise intensity, duration, and volume on the risk for cardiovascular events. In addition, the cohort included a sizable number of African-American women (n = 5,661) allowing the opportunity for much needed information in this subgroup.

For the entire cohort, the graded reduction in the relative risk for coronary heart disease and cardiovascular events with an increase in the MET-hours per week was evident for total physical activity or walking alone (see Table 9.5). The risk reduction was similar for Caucasian

Figure 9.12 Relative risk of CVD according to walking pace.



Source: Adapted from Manson JE, et al. *N Engl J Med* 1999;341:650–658.

and African-American women and for different age brackets for total physical activity (**Figure 9.13**) or walking alone (**Figure 9.14**). Similarly, when the cohort was categorized by body mass index (BMI), fitness was also inversely related to the cardiovascular mortality for each subgroup (see Figures 9.13 and 9.14).

In summary, the two reports from the Women's Health Study provided the following information:

1. Both walking and more vigorous forms of exercise are associated with an inverse and graded reduction in the risk for coronary heart disease and cardiovascular disease.
2. The association is evident in lean and obese Caucasian and African-American women of different ages.
3. The exercise duration for a substantial risk reduction in cardiovascular disease and coronary heart disease appears to be approximately 1.5 to 2.5 hours per week.
4. The exercise intensity for similar risk reduction appears to be at the walking pace of approximately 20–30 minutes per mile.

Two other studies examined changes in physical activity status and the mortality risk in women.[32,33] The cohort of the first study consisted of 1,405 Swedish women aged 38 to 60 years who were initially free of major diseases at baseline. Occupational and leisure-time physical activity data from the baseline and 6-year follow-up examinations were evaluated in relation to all-cause mortality.

Moderate levels of leisure time and occupational physical activity were associated with 44% and 72% lower mortality risk respectively, when compared to sedentary women. An insignificant reduction was also observed with higher occupational or leisure activity levels. The investigators concluded that decreases in physical activity as well as low initial levels are strong risk factors for mortality in women. The effects and predictive value of physical activity persist for several years.[33]

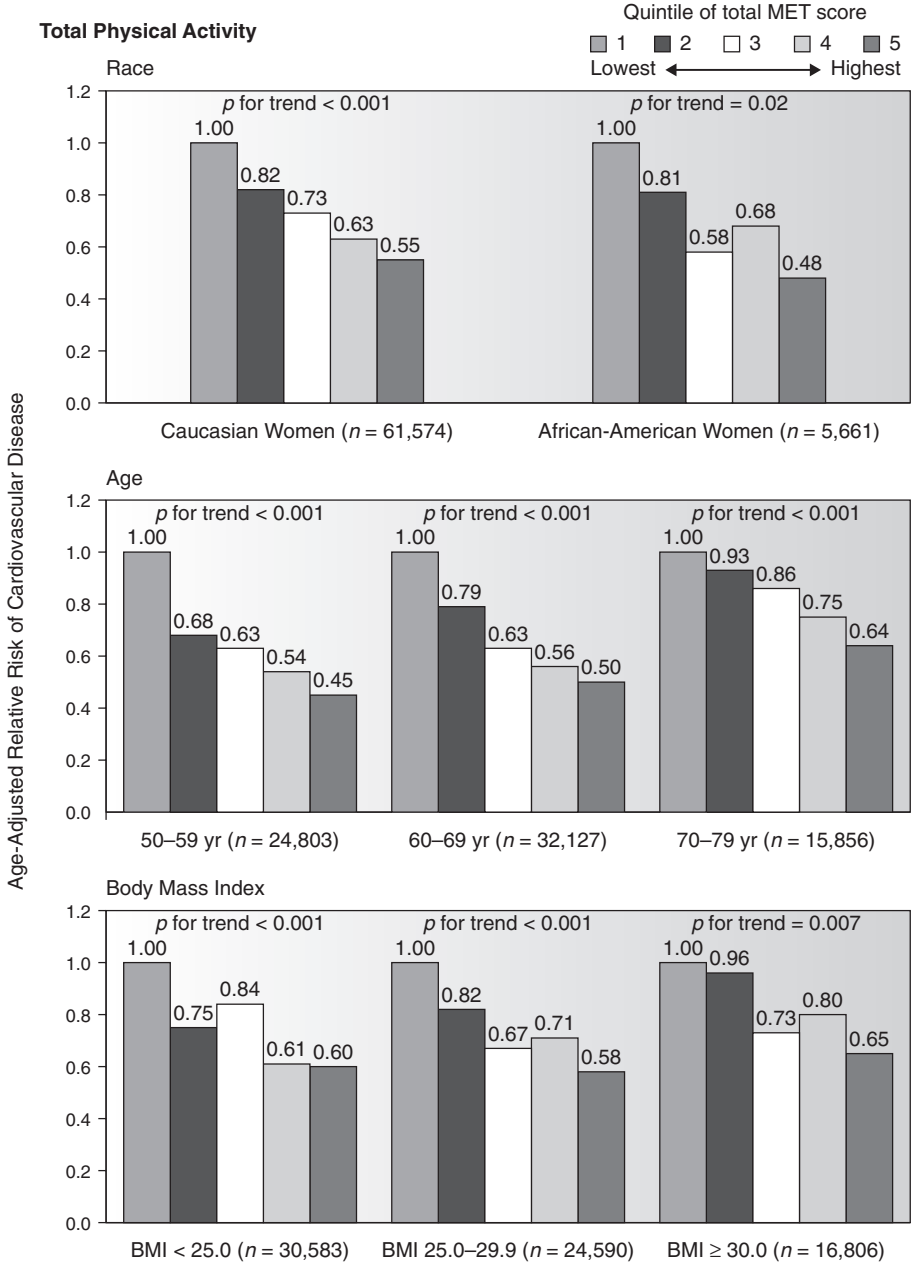
A more recent study[32] examined the relationship of changes in physical activity and mortality among older women. This is a prospective study conducted at four U.S. research centers (Baltimore, MD; Portland, OR; Minneapolis, MN; and Monongahela Valley, PA). The cohort consisted of 7,553 Caucasian women aged 65 years or older who were assessed at baseline (1986–1988) and at a follow-up visit (1992–1994) and followed for about 6 years.

The all-familiar inverse and graded association between increased physical activity and mortality (all-cause and cardiovascular) also was evident in this study. The adjusted all-cause and cardiovascular mortality rate for physically active women who expanded approximately 1,000 to 1,900 kcal per week was approximately 40% lower when compared to the sedentary women. In addition, the following findings are noteworthy:[32]

- Sedentary women who became physically active between baseline and follow-up had a 48% and 36% lower all-cause and cardiovascular mortality rate, respectively, when compared to sedentary women who were sedentary at both visits.
- Women who were physically active at both visits also had 32% lower all-cause mortality and cardiovascular mortality than sedentary women.
- The associations between changes in physical activity and reduced mortality were similar in women with and without chronic diseases but tended to be weaker among women aged at least 75 years and among those with poor health status.

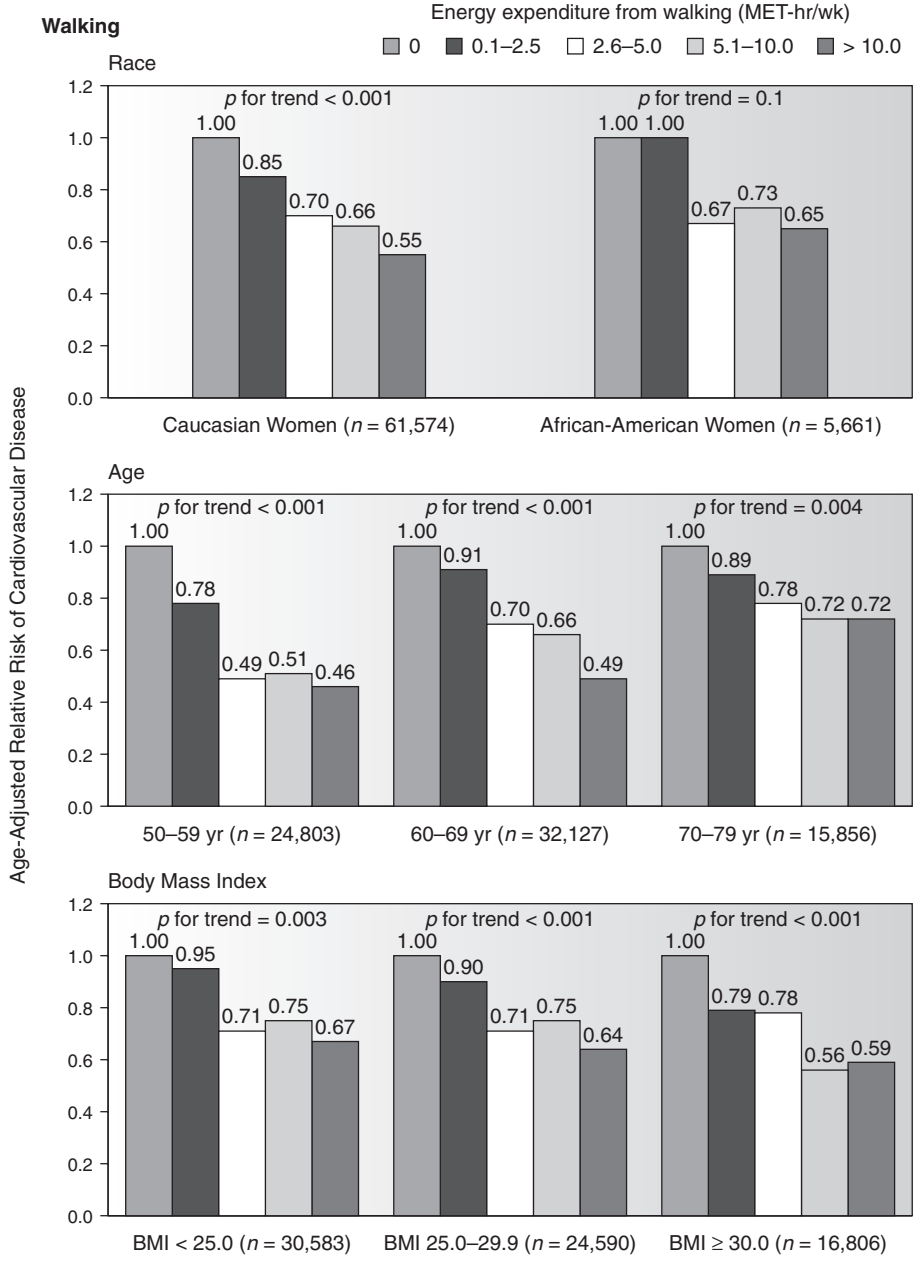
The investigators concluded that increasing and maintaining physical activity levels could lengthen life for older women. The effects appear to be less powerful in women aged at least 75 years and those with poor health status.

Figure 9.13 Relative risk for CVD in women according to total physical activity, by race, age, and BMI.



Source: Adapted from Manson JE, et al. *N Engl J Med* 2002;347:716–725.

Figure 9.14 Age-adjusted relative risk for CVD in women according to energy expenditure from walking.



Source: Adapted from Manson JE, et al. *N Engl J Med* 2002;347:716–725.

Two studies in women expressed the mortality risk reduction per 1-MET increase in exercise capacity.[24,28] In both studies, exercise capacity was assessed by exercise stress test. In the study by Gulati et al.[28], the larger of the two, the adjusted mortality risk was 17% lower for each 1-MET increase in exercise capacity. This was a relatively greater reduction than has been reported in men, prompting investigators to speculate that exercise capacity may have an even greater capacity in predicting risk of mortality among women than men.

Similar findings were reported by the Lipid Research Clinic's prevalence study, where nearly 3,000 asymptomatic women were followed for up to 20 years.[24] The age-adjusted risk for cardiovascular death for every 1-MET decrement in exercise capacity was 20% higher.

Studies examining the association between physical activity and mortality in women have yielded similar exercise-related health benefits with those observed in men. There is also some evidence to support a greater dose-response association between exercise and mortality risk reduction for women compared to men. In addition, the recently large studies in women have helped to better define associations between mortality risk and exercise intensity, duration, and frequency.

Physical Activity and Stroke

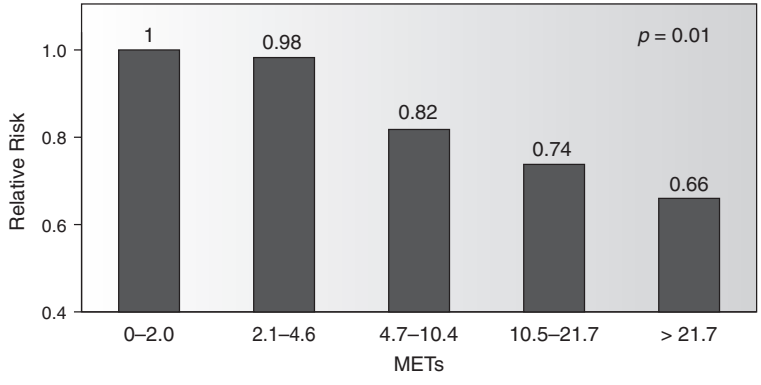
According to the 1996 *U.S. Surgeon General's Report on Physical Activity and Health*, the relationship between exercise and stroke is inconclusive.[34] Since that report, several large studies have been conducted. Their findings strengthen the suggestion of previous studies that physical activity may protect people against strokes.[35]

The findings from the Physicians' Health Study showed a 14% lower the total risk of stroke among men participating in vigorous exercise five or more times a week.[36] Similarly, in the Harvard Alumni Study total stroke risk in men who were highly physically active was 18% lower when compared to sedentary group.[37] The Northern Manhattan Study (NOMAS) that included Caucasian, African American, and Hispanics, both men and women showed a decrease in ischemic stroke risk associated with physical activity levels across all racial/ethnic and age groups and for each gender.[38] Similarly, in the Atherosclerosis Risk in Communities (ARIC) cohort, physical activity was related to lower risk of ischemic stroke.[39]

In a Japanese cohort of 73,265 men and women, the risk of stroke death in the highest category of walking and sports participation was reduced by 29% and 20%, respectively.[40] Moderate and high levels of leisure-time activity were associated with significant trends toward lower risk of stroke in a study of 4,721 men and women in Finland. A smaller but still significant benefit also was observed with occupational activity.[41]

In the Nurses' Health Study, the risk of total stroke was graded inversely with the level of fitness.[42] The risk was 18%, 26%, and 34% lower for the three highest physical activity categories respectively (**Figure 9.15**). Walking pace and METs were also associated with lower risk in a dose-response manner, independent of the number of hours spent walking (**Figure 9.16**). This finding supports that exercise intensity has an independent effect on risk reduction. Another important finding of the study is that sedentary women who became active in middle to late adulthood had approximately 20% reduction in risk adjusted risk for stroke. This finding suggests that the health benefits of increased physical activity are not attenuated by age. More importantly, the health benefits can be realized even if the individual has been sedentary for some time. However, it is strongly recommended that individuals who have been sedentary for a

Figure 9.15 Relative risk of stroke in women according to total physical activity reported in MET-hours/week.



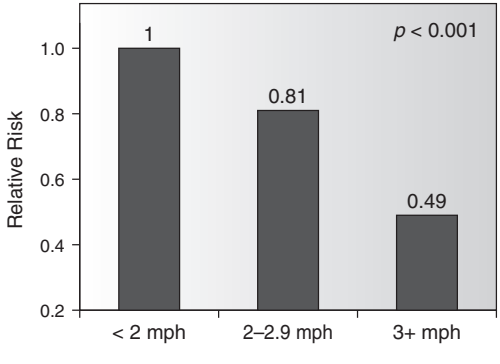
Source: Data from Hu F, et al. *JAMA* 2000;283:2961–2967.

long time consult with a physician prior to embarking on an exercise program.

The association between physical activity and stroke mortality in middle-aged men from the Seven Countries Study (the Corfu cohort), was assessed after taking into account the presence of left ventricular hypertrophy (LVH).[43] The investigators reported that the adoption of even a moderate physically active lifestyle was associated with a significant reduction in the risk of stroke among men with and without LVH. The impact of physical activity on stroke mortality can be appreciated further by the finding that the risk of stroke in physically active men with LVH was 49% lower than the risk observed in sedentary men without LVH. This finding is of particular interest, because LVH is now considered an independent predictor of coronary heart disease and stroke.[44–46]

Finally, the findings of a meta-analysis of 31 observational studies conducted mainly in the United States and Europe support that moderate and high levels of leisure-time and occupational physical activity protected against total stroke, hemorrhagic stroke, and ischemic stroke.[47]

Figure 9.16 Relative risk of stroke in women according to walking pace



Source: Data from Hu F, et al. *JAMA* 2000;283:2961–2967.

Studies investigating the association between physical activity and stroke are relatively few and their findings are not as compelling as those regarding physical activity and heart diseases. However, most studies support that moderate and high levels of leisure-time and occupational physical activity protected against total stroke. Furthermore, the evidence is likely to strengthen as more studies become available.

Chronic Heart Failure and Exercise Training

Exercise training studies overwhelmingly support that individuals with heart failure can exercise safely when exercise is carefully tailored to their needs and capacity.

Prior to the 1980s, exercise or physical activity was not recommended for individuals with heart failure. The prevailing thinking was that physical exertion would cause further deterioration of the already compromised cardiac function. This notion was challenged by some in the early 1980s. Since then, a systematic scrutiny on the safety and efficacy of exercise as a therapeutic modality for CHF patients was pursued.

The findings of early studies were encouraging. Despite the relatively intense exercise programs (80%–90% of peak oxygen consumption for 50–60 minutes per session), the relatively small number of patients, and lack of a control group in some, significant improvements in exercise capacity and no major complications in patients with moderate or severe left ventricular dysfunction were reported.[48–51]

These findings provided the incentive for several carefully designed, randomized studies, using more moderate exercise intensities. Overwhelmingly, theses studies supported previous findings. Significant improvements in exercise capacity and peak oxygen consumption were shown after just 8 weeks of stationary bicycle exercise.[52,53] A similar program resulted in improvements in exercise capacity, peak oxygen consumption, left ventricular function, and quality of life.[54–56] Several studies used longer training periods at similar intensities. These studies also yielded significant improvements both in exercise capacity and peak oxygen consumption.[57–61] Finally, the safety and efficacy of exercise training for the heart failure patient was confirmed by a relatively large, randomized trial (Chronic Heart Failure and Graded Exercise Study)[62] and a more recent meta analysis comprised of 13 studies that included aerobic and weight training of 2,387 heart failure patients.[63]

However, exercise implementation in individuals with heart failure was not fully endorsed, especially in patients with heart failure that resulted from a major heart attack. Clinical and experimental evidence suggests that progressive left ventricular dilation occurs in the pathogenesis of CHF, particularly after myocardial infarction.[64] This stretching, thinning, and expanding of the affected myocardium are influenced by several factors including ventricular wall stress.[65–68] Because ventricular wall stress increases during physical exercise, the thinking was that this increased stress may facilitate the remodeling process, exacerbate symptoms, and lead to progressive deterioration of cardiac function. Indeed, the findings of two studies supported that such a remodeling process of the myocardium occurs as a result of exercise.[69,70] However, the exercise programs implemented in these studies were too demanding even for healthy individuals. The programs consisted of morning and evening exercise, five times per week for 4 weeks.

Subsequent well-designed studies that were relatively large and had long training periods revealed that the ejection fraction must be considered when exercise programs are designed for heart failure individuals.[71,72] In a study of 93 individuals who suffered a heart attack, the investigators found no deterioration of ventricular function or changes in ventricular cavity dimensions and significant improvement in ejection fraction after 6 months of exercise training in patients with normal ventricular function and ejection fraction > 40%. Conversely, individuals with initial ejection fraction

< 40% and ventricular dilation had more significant ventricular enlargement, with increased infarct size, and more pronounced distortion in the shape of the ventricle. However, this was evident in both the exercise and no exercise groups. In fact, the exercise group tended to have less ventricular dilation and a substantial increase in ejection fraction from 35% to 39%. Although these findings were not statistically significant, they suggest that exercise training is not responsible for the increased deterioration in myocardial function observed in HF patients with relatively low EF. In fact, exercise may lessen the deterioration of left ventricular function over time.[72] Similar benefits were reported in patients with reduced ventricular function (EF of 26% to 38%) who exercised daily for 2 months at moderate intensities. The program resulted in a 26% increase in exercise capacity and no deleterious effects on left ventricular volume, function, or myocardial wall thinning regardless of the size of the infarct area.[71]

Despite the efficacy and safety of moderate to high exercise intensities, the use of lower exercise intensities may be preferred for several reasons: (1) Low and moderate intensity exercise carry a relatively low risk for cardiac complications and musculoskeletal injuries; (2) patients are more likely to participate and sustain a lower than higher intensity exercise; and (3) physicians may feel more comfortable advising patients to pursue a low-intensity versus a high-intensity exercise program.

The efficacy of low-intensity exercise training for the CHF patient has been demonstrated by several studies. These studies found that improvements in peak oxygen uptake and peak workload were comparable to those reported with much higher exercise intensities. Additionally, the relatively lower left ventricular wall stress during low exercise intensities decreases the risk for left ventricular enlargement that may occur in heart failure individuals.[73,74]

Relatively small exercise training studies provide strong evidence that exercise capacity and cardiac function improve with carefully conducted exercise programs. The limited evidence suggesting that exercise training also can reduce the risk of mortality in individuals with heart failure is encouraging but this theory awaits the confirmation of large clinical trials.

MECHANISMS FOR IMPROVEMENT BY EXERCISE TRAINING

The mechanisms for such improvements are not fully understood. The reduction in cardiac output was originally thought to be the determining factor in the exercise capacity of the CHF patient. However, indices of resting cardiac function such as left ventricular ejection fraction and hemodynamic measurements are poorly correlated with peak exercise performance or maximal oxygen consumption.[75,76] Attention shifted to changes in skeletal muscle and vascular pathophysiology to explain the impaired exercise tolerance in such patients. Skeletal muscle atrophy is a common phenomenon in CHF patients occurring early in the course of the disease.[77,78] Improvements in exercise capacity following muscle strength gains[78–80] and positive correlations between muscle mass and peak oxygen uptake in CHF patients[78] support that muscle atrophy may be involve at least in part in the poor exercise capacity of heart failure patients.

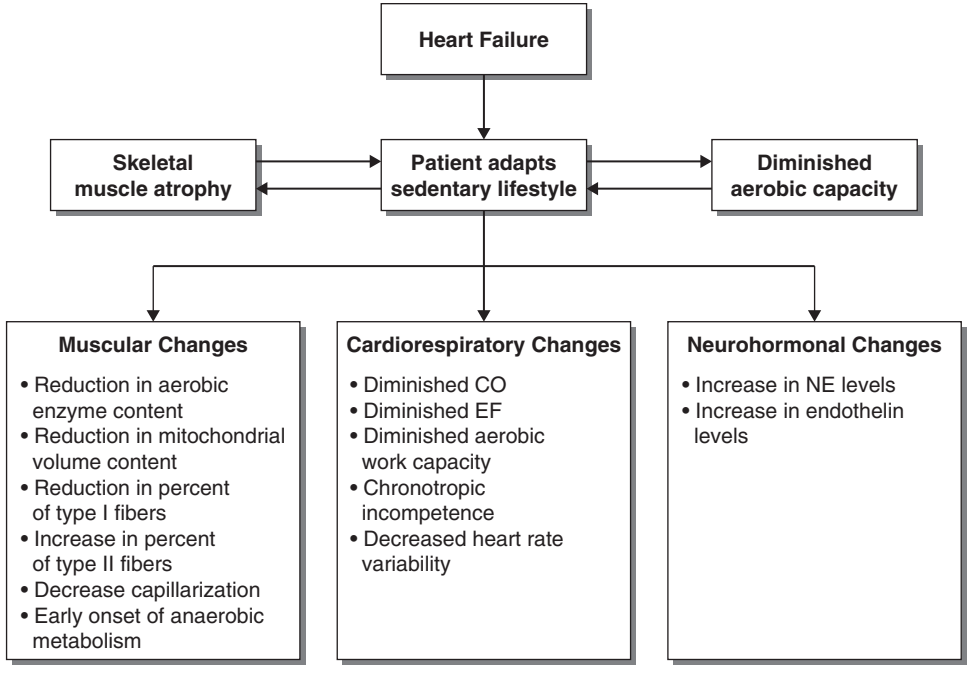
In a recent study, Hambrecht et al.[81] noted significant improvements in endothelial-

mediated vasodilation of the peripheral vasculature, peripheral blood flow, and peak $\dot{V}O_2$ following 24 weeks of moderate-intensity aerobic exercise training. These favorable findings are attributed to the increased formation and release of endothelial relaxing factors in response to increased shear stress induced by pulsatile blood flow. Similarly, endothelial function was improved after 4 weeks of handgrip exercise. Collectively, these findings suggest that long-term physical training restores impaired endothelial function,[81,82] reverses the neurohormonal activation, and ameliorate the autonomic derangement observed in CHF patients.[51,53] It is now generally accepted that physical work capacity in these patients is determined by the interaction of cardiovascular and musculoskeletal and hormonal factors (**Figure 9.17**).

Exercise Training and Mortality in Heart Failure

Encouraging findings on the rate of CHF progression, morbidity, and mortality have been

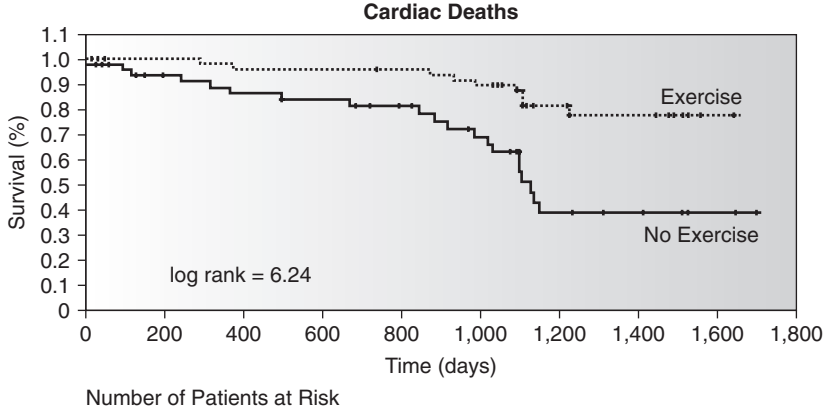
Figure 9.17 Schematic representation of muscular, cardiorespiratory, and neurohormonal changes in heart failure. Patients with heart failure are likely to adopt a sedentary lifestyle. Consequently, there is a deterioration of skeletal muscle and aerobic capacity, fostering an even more sedentary lifestyle and thus further deterioration of muscular and cardiorespiratory functions.



reported by a small randomized and well-controlled trial.[83] Belardinelli et al. randomized 99 middle-aged patients with stable CHF (88 males and 11 women) with EF ≤ 40% into exercise and no exercise groups. After 14 months of aerobic training, the exercise group had lower total and cardiac mortality and hospital readmission for heart failure (**Figure 9.18**). In addition, the quality of life improved in the exercise group. The findings of a meta-analysis of nine randomized trials totaling 801 patients also support a significant reduction in mortality and hospital admissions are significantly reduced after exercise training in HF patients.[84]

Until recently, the impact of exercise training on clinical outcomes in patients with heart failure had not been studied extensively. The findings of a large trial (n = 2,331) on exercise and heart failure (HF-ACTION trial) that were recently published support that exercise reduced all-cause mortality and hospitalization by 11% in patients assigned to the exercise group compared to those in the non-exercise group.[85] Although this can be viewed as a modest reduction, several factors should be considered. First, the 11% reduction was in addition to the reduction achieved by the state-of-the-art medical/device management of heart failure patients. Second, in addition to heart failure, a substantial number of the participants in this study had several comorbidities that made their capacity and ability to exercise on a regular basis very difficult. Consequently, the volume of exercise for these individuals was severely compromised. When the investigators examined those who were able to exercise, the findings were more impressive. More specifically, the average reduction in all-cause mortality and hospitalization was 16% and up to 27% for cardiovascular disease mortality and heart failure hospitalization.[85]

Figure 9.18 Exercise training and mortality in heart failure patients.



Number of Patients at Risk

No Exercise	49	46	43	42	41	37	29	29	29	29
Exercise	50	50	48	48	48	45	42	41	41	41

Source: From Belardinelli R, et al. *Circulation* 99:1173–1182.

Conclusions

- The current literature overwhelmingly supports that carefully designed exercise programs are well tolerated and beneficial to patients with stable heart failure.
- Exercise of low to moderate intensity should be preferred because it is equally beneficial, carries a lower risk for muscular and cardiovascular complications, and is better tolerated by the patients than high intensity exercise.
- Both the cardiovascular and muscular systems are inextricably linked in the pathophysiology of CHF. Improvements observed in exercise capacity following exercise training may be the cumulative result of hemodynamic, histological, and biochemical changes.
- Improvement in work performance following aerobic and strength training exercises are similarly impressive. This suggests that decreased blood flow may be the precursor of all the pernicious manifestations of CHF. Future work in this area should consider exercise programs that enhance both aerobic and anaerobic pathways. The benefits of such exercise programs may be additive and therefore more beneficial to the CHF patient than either exercise mode alone.
- Endothelial dysfunction has been implicated in CHF at least in part due to diminished blood flow. Recent trials support that regular physical activity improves endothelial function and work capacity in CHF patients.
- Carefully designed exercise training programs may be the intervention required to reverse the deleterious effects of endothelial dysfunction. The recently published findings of a large trial (HF-ACTION) support that adequate exercise training increases survival in patients with heart failure.

Low Extremity Arterial Disease and Exercise

As discussed in Chapter 8, the progressive development of atherosclerotic lesions ultimately in the arteries of the lower extremities leads to significant stenosis of the arteries involved. Consequently, blood flow distal to lesions is significantly impaired leading to leg pain, numbness, cold legs or feet, and muscle pain in the thighs, calves, or feet. This is known as *low extremity arterial disease (LEAD)*.

Individuals with this condition lead a sedentary lifestyle. Consequently, the deterioration of cardiorespiratory and muscular functions is accelerated and a decline in the overall health and quality of life for the LEAD patient ensues. In addition, LEAD patients often suffer from comorbidities, including hypertension, diabetes mellitus, dyslipidemia, and coronary artery disease. National health organizations including the American Heart Association, the American College of Sports Medicine, and the Centers for Disease Control and Prevention strongly recommend that increased physical activity alone or as an adjunct to pharmacologic therapy should be implemented for the prevention and management of cardiovascular disease and the aforementioned comorbidities and risk factors.[86,87]

Treatment for intermittent claudication (pain or cramping in legs when walking or exercising) thus should include lifestyle changes for positive modification of the traditional cardiovascular disease risk factors. Exercise training should be an integral part of

Table 9.6 Summary of Select Studies Reporting Improvements in Peak $\dot{V}O_2$ and/or Work Capacity in CHF Patients Following Exercise Training

Reference	*N*	NYHA Class	Improvements
Esani et al.[49]	15	I	Peak $\dot{V}O_2$; work capacity
Sullivan et al.[51]	12	II, III	Peak $\dot{V}O_2$; work capacity
Lee et al.[50]	18	I–IV	Peak $\dot{V}O_2$; work capacity
Coats et al.[52]	11	II, III	Peak $\dot{V}O_2$; work capacity
Coats et al.[53]	17	II, III	Reduction in NE spillover; sympathetic tone withdrawal and increased vagal tone
Belardinelli et al.[54]	55	II, III	Peak $\dot{V}O_2$; work capacity
Belardinelli et al.[55]	46	II, III	Peak $\dot{V}O_2$; work capacity; LV function; quality of life
Belardinelli et al.[56]	43	II, III	Peak $\dot{V}O_2$; work capacity; LV function
Hambrecht et al.[58]	22	II, III	Improvements in aerobic enzyme and mitochondria content; peak $\dot{V}O_2$; work capacity
Wielenga et al.[62]	81	II–III	Exercise time; anaerobic threshold; quality of life
Demopoulos et al.[74]	16	II–IV	Aerobic work; peak $\dot{V}O_2$
Belardinelli et al.[73]	27	II, III	Improvements in aerobic enzymes and mitochondria content
Kiilavuori et al.[61]	20	II–III	Aerobic work capacity; heart rate variability
Koch et al.[79]	25	N/A	Muscle strength; work capacity; quality of life
Minnotti et al.[80]	5	II–III	Forearm muscle strength and endurance
Mancini et al.[78]	8	I–IV	Respiratory muscle endurance and strength
Hambrecht et al.[81]	20	II–III	Endothelial function; peripheral blood flow; work capacity; peak $\dot{V}O_2$
Hornig et al.[82]	19	III	Endothelial function; peripheral blood flow; work capacity; peak $\dot{V}O_2$
Belardinelli et al[83]	99	II–IV	Improved survival, peak $\dot{V}O_2$ and quality of life
Jugdutt et al.[70]	13	15 wks post-MI; not randomized	Deterioration in global and regional ventricular function
Jette et al.[69]	39	10 wks post-MI; EF < 30%	Aerobic work capacity; peak $\dot{V}O_2$; EF improved in some but not all patients and worsened in one
Giannuzi et al.[72]	95	I, II	Aerobic work capacity; peak $\dot{V}O_2$ improved in patients with EF > 40%; no changes in ventricular cavity dimensions; exercise patients with EF < 40% had less deterioration than controls
Dubach et al.[71]	25	N/A	Aerobic work capacity and peak $\dot{V}O_2$ improved; no deterioration in ventricular performance

Source: Data are from Kokkinos, et al. *American Heart Journal* 2000;140:21–28.

such therapeutic approach. An exercise training program of low to moderate intensity can attenuate the deleterious effects of the aforementioned comorbidities associated with LEAD. It is an attractive and conservative alternative therapy for these patients. For example, walking, the preferred form of exercise for LEAD patients, has a relatively low risk–benefit ratio; it is also relevant to daily living, inexpensive, easily implemented to large populations, contributes to the overall health, can be used alone or as an adjunct to pharmacotherapy, and does not interfere with the surgical possibility that may be deemed necessary in the future. In addition, the well-recognized local vasodilatory effects of exercise and the preservation of lean body tissue can only be of benefit to these patients.

Exercise Therapy Findings

The well-known local vasodilation and the consequent increase in blood flow that occurs in the exercising muscle encouraged investigators to assess the possible therapeutic effects of structured exercise programs for LEAD patients. Scientific assessment in patients with mild and moderate claudication began in the 1960s.

Primarily, two exercise training protocols have been used extensively. One requires the patient to walk to the onset of pain (claudication), rest until the pain subsides, and repeat this intermittent walking several times. The other protocol is similar with the exception that the patients walk until near-maximal or maximal claudication is reached.

Without exception, exercise training studies involving LEAD patients yielded substantial and clinically significant improvements in walking distance to the onset of pain or maximal pain.[88–102] A meta-analysis of 21 studies revealed that following exercise rehabilitation, the average walking distance to onset of claudication increased by 179% and the distance to maximal claudication by 122%.[90] Significant increases in peak oxygen uptake along with improvements in maximal and pain-free walking time also have been reported.[91]

There is evidence of a synergistic effect when exercise is combined with pharmacologic therapy. After 6 months of either antiplatelet therapy, exercise therapy, or a combination of antiplatelet therapy plus exercise, walking distance improved in all groups. However, the greatest improvements were observed in the combined therapy group. Pain-free and maximal walking distances increased by 120% and 105% in the combined therapy group, 90% and 86% in the exercise alone group, and only 35% and 38% in the antiplatelet-only group.[98]

Exercise training following reconstructive arterial surgery also merits special attention. In one study, patients were randomized to reconstructive surgery, exercise alone, or reconstructive surgery plus exercise. Performance was assessed at baseline and 48 weeks following intervention. The symptom-free and maximal walking distance in the exercise alone group increased by 179% and 151%, respectively. In the surgery-only group, the increase was 376% in the symptom-free distance and 173% in the maximal walking distance. In the group with a combination of surgery with exercise, symptom-free and maximal walking distance increased by 698% and 263%, respectively.[97]

The findings of the two studies presented (arterial reconstructive surgery and the antiplatelet therapy) support that the implementation of a well-designed exercise program as an adjunct to either therapy can significantly improve the outcome for the LEAD patient. Exercise rehabilitation is now recommended and implemented as the first line of therapy for LEAD patients in stage I and II alone, or in conjunction with medical therapy and after reconstructive arterial surgery in patients with significant hemodynamic improvements.

Without exception, exercise training studies involving LEAD patients have yielded substantial and clinically significant improvements in walking distance to the onset of pain or maximal pain. There is also string evidence of a synergistic effect when exercise is combined with pharmacologic therapy and/or after reconstructive arterial surgery.

Exercise Mode

The mode of exercise for most studies is walking combined with some other forms of leg exercise such as running, cycling, stair climbing, dancing, jumping, and other dynamic and static leg exercises.[90] Two studies used walking alone and two other studies combined and compared walking with resistance (strength) training.[92,100] Walking appears to be superior to other forms of exercise training, especially when the exercise protocol requires that patients perform intermittent bouts of walking to near-maximal or maximal pain.[89] Although both studies reported that resistance training was inferior to walking and no additional benefits to the patient were noted when the walking program was supplemented with resistance training, in some cases, muscle weakness can compromise walking performance. Thus, the possible therapeutic effects of an exercise program that combines aerobic and resistance exercise for the LEAD patient should not be dismissed.

Intensity

The intensity of the exercise programs is not well described in any of the studies. It is estimated that only 16% of patients who do not experience pain at rest can walk a distance of 1,000 meters or more on a flat surface at 4 km/hr or 2.5 miles/hr.[103] Collectively, this information from available studies supports an exercise intensity of approximately 2 to 4 mph walking speed on a flat surface.[104]

Frequency, Duration, and Length of Training

Most evidence supports that exercising three or more sessions per week yields greater improvements in claudication distance when compared with fewer than three times per week.[90] Most studies also support that the exercise duration should be between 30 to 60 minutes per session. Improvements in the onset of claudication pain and maximal claudication pain walking distances are significant in patients exercising 30 or more minutes per session when compared to those exercising less. It thus appears that most improvements in physical performance for LEAD patients occur when exercising for at least 90 minutes per week. However, the interaction between duration and frequency cannot be discerned from the existing literature.

Noticeable improvements in walking distance can be observed even after 4 weeks of training. However, longer training periods are clearly more successful. Greater improvements in walking distances were associated stronger with the length of training lasting 6 months or longer.[90]

Potential Mechanisms

The mechanisms responsible for the exercise-induced improvements in walking distance remain illusive. The compromised blood flow to the lower extremities in LEAD patients and the well-known vasodilation and consequent increase in blood flow in the exercising muscle deserve special attention. However, the decline in physical performance observed in LEAD patients is likely the collective outcome of deterioration on several physiologic systems. Likewise, the exercise-induced improvements

in the functional capacity of these patients are the result of favorable changes in several of these systems.

Potential Mechanisms for the Physical Activity–Related Reduction in Cardiovascular Risk

The mechanisms for the inverse association between physical activity and the risk of cardiovascular disease and cardiovascular mortality are not completely understood. It has been long suspected and is likely that the favorable modification physical activity or exercise exerts on several established cardiovascular risk factors translates to the cardioprotection observed. Evidence for this is provided by a recent prospective study that included 27,055 apparently healthy women.[105] The investigators assessed several metabolic and hemodynamic parameters and inflammatory biomarkers. They also recorded the presence of hypertension and diabetes, and the self-reported physical activity levels of these women. After a mean follow-up period of almost 11 years, the investigators noted a linear decrease in risk for CVD events with higher physical activity levels. The relative risk reductions risk for women who expanded 200 to 599 kcal per week was 27% lower when compared to those expanding less that 200 kcal. The relative risk was 32% and 41% lower for those women who expanded 600 to 1,499, and 1,500 or more kcal/wk, respectively.

The same investigators then assessed the contribution of risk factors to lower risk. Differences in known risk factors explained a large proportion (59.0%) of the observed inverse association. They concluded that the inverse association between physical activity and CVD risk is mediated mostly by known risk factors, particularly inflammatory factors and blood pressure, and to a lesser by lipids, body composition (BMI), and diabetes.

Author's Note

Since the early 1950s, a plethora of scientific evidence has accumulated to support that increased physical activity and exercise lower the risk of cardiovascular disease and overall morbidity and mortality. Study findings are eloquently summarized in a 2002 editorial entitled "Survival of the Fittest."[106] In it, Dr. Gary Balady stated, "During the past 15 years, many long-term epidemiologic studies have shown an unequivocal and robust relation of fitness, physical activity, and exercise to reduced mortality overall and from cardiovascular causes and reduced cardiovascular risk."

Our next challenge is no longer to prove that physical activity or exercise protects against premature death. It isn't even to define the kind of exercise needed, how much, or of what intensity. Although research must continue to define these issues for different populations and diseases, the most compelling challenge is to promote a physically activity lifestyle for people of all ages.

SUMMARY

- Epidemiologic studies support a strong inverse relationship between physical exercise and coronary heart disease risk. This evidence provided the basis to seek answers as to kind of exercise, duration, intensity, and volume needed to reduce the risk of heart disease.
- Physical fitness assessed by a treadmill or bike test allows a more precise quantification of fitness and its association with mortality. The most striking findings of these studies are: (1) the inverse, graded, and independent association between the volume of physical activity and mortality risk; and (2) the relatively low intensity and volume of physical activity required to achieve substantial reduction in mortality risk.

- The exercise components of intensity and duration are also inversely associated with the risk of coronary heart disease independent of exercise volume.
- Some evidence supports that intensity may be more strongly associated with risk reduction. However, it is more likely that a threshold for exercise intensity and duration must be achieved before health benefits are realized.
- A number of observational studies support that moderate and high levels of leisure-time and occupational physical activity protected against total stroke, hemorrhagic stroke, and ischemic stroke.
- Exercise for the heart failure patients was not recommended until recently for the fear that it may worsen the condition. However, well-designed studies that tailored their exercise programs have proven that heart failure patients can tolerate exercise well.
- A number of these small studies provide strong evidence that well-designed exercise training studies yield significant and favorable changes in cardiac function and structure for the heart failure patients.
- Recent evidence from a large randomized trial supports that exercise training reduces hospitalization and mortality in these patients.
- Well-designed exercise programs can be beneficial for individuals with low extremity arterial disease.
- Walking distance can be improved substantially following such programs. Exercise can be used in adjunct to pharmacologic therapy or surgery. Such approaches provide even greater improvements in walking distance for such individuals.
- Recent evidence supports that the cardiovascular risk reduction observed with increased levels of physical activity is mediated by the favorable effects physical activity exerts on several cardiovascular risk factors. More specifically, most of the reduction is mediated by favorable changes in inflammatory factors and blood pressure and to a lesser by lipids, body composition (BMI), and diabetes.

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