Physical Activity and Cardiovascular Health

Lessons Learned From Epidemiological Studies Across Age, Gender, and Race/Ethnicity

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In 1953, Morris et al.1–2 published the findings from a study showing that bus conductors in London, who spent their working hours walking the length of the buses as well as climbing up and down the stairs of the English double-decker buses to collect fares, experienced half the coronary heart disease (CHD) mortality rates of their driver counterparts, who spent their day sitting behind the wheel. Investigators hypothesized that it was the physical activity of work that protected the conductors from developing CHD, at the same time realizing that other factors may also play a role because the conductors were smaller in size, as evidenced by their smaller uniform sizes. Thus was born the field of “physical activity epidemiology”: formal epidemiological investigations into the associations of physical activity with many health outcomes.4

Since the initial observations of Morris et al, many other studies have been conducted, yielding similar results: Active people have lower rates of CHD and cardiovascular disease (CVD) than inactive ones.5–7 These findings have been supported by plausible biological mechanisms, which are detailed in other articles in this review series. The collective body of evidence led the American Heart Association in 1992 to recognize physical inactivity as a risk factor for CHD and CVD and led the Surgeon General in 1996 to conclude that “regular physical activity or cardiorespiratory fitness decreases the risk of CVD … and CHD.”9 The basis for these conclusions was derived primarily from studies in men and in white populations; for example, in a 1990 meta-analysis of physical activity in the prevention of CHD that included 33 studies, women were subjects in 5 studies, and racial/ethnic minorities were the focus of 2 studies.

In 2008, the federal government issued its first-ever physical activity guidelines for Americans10 based on a comprehensive and systematic review of studies published since the 1996 Surgeon General’s report on physical activity and health.9 Many of these studies now included women, and several also included substantial numbers of racial/ethnic minorities as subjects. The purpose of this review is to summarize the current state of knowledge about physical activity and cardiovascular health on the basis of epidemiological studies included in the systematic evidence review of the 2008 Physical Activity Guidelines for Americans (hereafter referred to as the 2008 Guidelines) and supplemented by recent studies published after the review. In particular, 3 specific questions are addressed, with reference to age, gender, and racial/ethnic subgroups where applicable:

1. What is the magnitude of the association between physical activity and CHD/CVD?
2. Is there a dose-response relation between physical activity and CHD/CVD? If so, what is the shape of the dose-response curve?
3. Can physical activity ameliorate the increased risk of CHD/CVD associated with adiposity?

Magnitude of the Association

There is substantial evidence, all from observational epidemiological studies, to support an inverse relationship between physical activity and CHD/CVD risk.5–7 For the purpose of this review, we will focus on the findings from prospective cohort studies because this study design represents the strongest observational study design, minimizing the potential for bias from recall of physical activity. In these studies, investigators typically have defined CHD as including myocardial infarction, revascularization procedures, and angina and have defined CVD as including CHD, cerebrovascular disease, and cardiovascular death.

The systematic evidence review behind the 2008 Guidelines summarized 30 prospective cohort studies published between 1995 and 2007, all using self-reported data on physical activity, to examine the association with CHD risk (Table).2 These studies were conducted in a several countries including the United States (14 studies),12–25 the United Kingdom (5),26–30 Finland (4),31–34 Sweden (3),35–37 Canada (2),38,39 Israel (1),40 and Norway (1).41 In total, these studies included >141 000 men and >263 000 women in gender-specific analyses and >50 000 subjects in analyses of both genders combined. However, few of the reviewed studies focused on older (≥65 years) or minority subjects. Only 2 studies were conducted in which the median age of participants was ≥65 years,18,22 and...
another 2 studies included >10% nonwhite subjects in their investigations.12–14

In the systematic evidence review supporting the 2008 Guidelines, the expert panel concluded that compared with the least active subjects, the most active men and women had median risk reductions of ≈30% to 35% for developing CHD. The amount of physical activity currently recommended, at least 150 min/wk of moderate-intensity aerobic physical activity or 75 min/wk of vigorous-intensity aerobic physical activity, is clearly associated with reduced risk. Furthermore, the available data also suggest that this does not represent a minimum threshold level for risk reduction. In fact, some data suggest that especially among those with very low levels of physical activity or who are unfit, even smaller amounts of physical activity may be associated with CHD/CVD risk, supporting a “some is good; more is better” message (see additional discussion under “Dose-Response Relation” below).

With regard to CVD, a similar picture was observed in data from prospective cohort studies (Table). The systematic evidence review supporting the 2008 Guidelines summarized the findings from 20 prospective cohort studies on this topic that were published between 1995 and 2007. The magnitude of the inverse association with CVD was generally similar to that observed for CHD. These studies of CVD were conducted in the United States (7 studies),19,42–47 Finland (3),48,49 the United Kingdom (3),50,51 Germany (2),52,53 Sweden (2),54,55 Norway (1),41 Canada (1),38 and China (1).56 These studies included >68 000 men and >347 000 women in gender-specific analyses and >88 000 men and women in analyses that combined both genders. As with the CHD studies, only 2 studies were conducted in which the median age of participants was ≥65 years;42,46 and 5 studies included populations with >10% nonwhite subjects.42,45–47,56

Since the systematic evidence review behind the 2008 Guidelines was published, 4 additional prospective cohort studies have been published.57–60 These recent studies report results that are in agreement with the aforementioned findings. The median risk reduction observed in the 4 studies for CHD/CVD, comparing most active with least active subjects, was ≈40% (range, 25% to 50%).

Because the inverse association of physical activity and CHD/CVD risk is observed from data derived only from observational studies and not from randomized controlled trials, these data cannot prove a causal relation. However, the available evidence strongly supports a causal relationship between increased activity and decreased risk of disease. Most importantly, plausible biological mechanisms, demonstrated in randomized clinical trials, exist, which are discussed in other articles in this review. Second, the findings from these studies, published in many countries throughout the world, overall showed consistent inverse associations between physical activity and CHD/CVD risk. Third, bias due to decreased physical activity from ill health (ie, a spurious inverse relation, with ill health causing decreased physical activity rather than physical activity causing lower mortality rates) is unlikely because many studies excluded subjects with CVD and cancer, major causes of ill-health, at baseline. Additionally, many of the studies had long follow-up periods, thus diluting the bias from ill health decreasing physical activity because with longer years of follow-up, more of the ill subjects die.

Fourth, although misclassification of physical activity likely existed because all of the studies used self-reported physical activity, because of the prospective nature of the study design, this misclassification is most likely random and thus would tend to attenuate observed findings toward the null. The prospective cohort study design also prevents recall bias (ie, participants could not be influenced by the presence of disease because they reported their physical activity before the onset of disease). Finally, the vast majority of the observational studies attempted to account for the clustering of physical activity with other healthy lifestyle habits by statistically adjusting for several potential confounders, including age, gender, race, education, smoking, alcohol, diet, personal and family medical history, and reproductive variables in women. In fact, several of the studies may indeed have “overcontrolled” their analyses, accounting for potential intermediate, beneficial effects of physical activity, such as body mass index, hypertension, dyslipidemia, and diabetes mellitus. Thus, by controlling for the beneficial effects of physical activity on CVD risk factors, the reported risk reductions between
physical activity and the development of CHD/CVD likely are underestimated.

**Differences by Age?**

Most of the studies of physical activity and CHD/CVD risk included in the systematic evidence review behind the 2008 Guidelines were conducted in middle-aged adults, with the median or mean ages of subjects primarily in the range of 45 to 60 years. The median or mean ages of subjects at baseline exceeded 60 years in only 8 studies,\(^{14,17,18,23,32,43,45,61}\) and in most of these studies, the average age was in the range of 60 to 69 years. These data suggest that physical activity is also inversely related to CHD/CVD risk among subjects older than 60 years.

For example, in the Harvard Alumni Study,\(^ {18}\) in which the mean age of men at the start of the study was 66 years, those expending \(\geq 16,800\) kJ/wk (4000 kcal/wk) in physical activity experienced a multivariate relative risk of 0.62 (0.41 to 0.96) for CHD (ie, risk reduction of 38\% [4\% to 59\%]) compared with those expending \(<4200\) kJ/wk (1000 kcal/wk). Among women in the Women’s Health Initiative,\(^ {45}\) the age-adjusted relative risks of CVD, comparing the most active with the least active quintile in 3 age groups of 50 to 59, 60 to 69, and 70 to 79 years, were 0.45, 0.50, and 0.64, respectively. Among older community-dwelling men and women in Washington state,\(^ {61}\) where the average age was 70 to 74 years, walking \(>4\) h/wk was associated with a 31\% (10\% to 52\%) reduction in risk of hospitalization from CVD in both men and women.

A recent publication from the Rancho Bernardo study, published after the 2008 Guidelines review, included 50- to 90-year-old individuals (56\% of subjects were aged \(\geq 70\) years) and investigated the association of walking and leisure-time physical activity with CHD.\(^ {58}\) Self-reported exercise occurring at least 3 times a week was associated with a multivariate hazard ratio of 0.49 (0.31 to 0.77) for CHD mortality compared with a lesser frequency of exercise. Thus, these data support an inverse relation between physical activity and CHD/CVD risk among older men and women (with data primarily available on those in their 60s and 70s) of a magnitude at least similar to that seen for younger individuals.

**Differences by Gender?**

Many of the studies in the systematic evidence review supporting the 2008 Guidelines included samples of women only (13 studies) or samples of both men and women (5 studies). In addition, all of the 4 recently published studies included women, with 2 being studies of women only.\(^ {57,60}\) The inverse association between physical activity and risk of developing CHD/CVD is present in both men and women, and, as shown in Figures 1 and 2, is similar, if not more pronounced, in women compared with men. The median risk reduction in women was 40\%* when most active women were compared with least active women, whereas that in men was 30\%†.

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*References 12, 15–17, 20, 24, 25, 31, 32, 34, 35, 38, 41.
†References 12–15, 17–19, 22, 23, 26, 28, 30–34, 36.
Although the magnitude of association appears stronger in women than in men, comparisons across gender are limited by the fact that the different studies used varied questionnaires for assessing physical activity and different categorizations (eg, by amount of energy expended, intensity of activities, duration, or frequency) of physical activity for analyses. Because women are less active than men and because comparisons typically are performed relative to the least active group studied, the categories of physical activity used in analyses (eg, total energy expended) may represent different amounts and intensities of physical activity in women than in men.

Differences by Race/Ethnic Group?
Relatively few studies have examined the relationship of physical activity and CHD/CVD risk in nonwhite populations. Seven of the studies in this review included >10% racial/ethnic minorities among subjects or were conducted among Japanese Americans or Chinese women in Shanghai.

The data from these studies indicate that the inverse association between physical activity and CHD risk was observed only among nonblack men and women but not among black subjects. The investigators suggested that possible reasons for the lack of association in the latter group included small sample size, lack of range of physical activity among black subjects, and a physical activity questionnaire that had not been specifically validated for the black population.

Dose-Response Relation
The expert panel conducting the systematic evidence review behind the 2008 Guidelines concluded the following: “Greater amounts of activity appear to provide greater benefit but the shapes of any dose-response relations have not been well defined.” The concept of “dose” in physical activity studies has been applied variously to the total volume of energy expended or the intensity, duration, or frequency of physical activity, with most data available on the total volume.

As discussed above, the difficulty in combining data across studies in trying to define a dose-response relation arises from different questionnaires used across the various studies to assess physical activity in 1 or more of these domains of activity (leisure-time, household, occupation, and commuting activity), with most assessing primarily leisure-time physical activity. In analyses, the studies classified subjects by different classification schemes, such as by energy expended or intensity, duration, and frequency of activity.

Nonetheless, the panel attempted to define 3 groups of different doses of physical activity and concluded that compared with men and women having low amounts or intensity
of physical activity, on average, those with moderate amounts or intensity of physical activity had ~20% to 25% reduced risk of CHD and those with high amounts or intensity had ≈30% to 35% risk reductions (Figure 3). Although the available data do not allow for a specific and clear definition of what constitutes a “moderate” or “high” amount of physical activity, these data are consistent with the 2008 federal physical activity guidelines, which recommend at least 150 min/wk of moderate- or 75 min/wk of vigorous-intensity aerobic physical activity for “substantial health benefits” and 300 min/wk of moderate- or 150 min/wk of vigorous-intensity aerobic physical activity for “additional and more extensive health benefits.”

In the 4 new studies published since the 2008 Guidelines review, similar inverse dose-response associations were observed. The median risk reductions in these 4 studies for CHD/CVD when moderate and low amounts of physical activity were compared were ~20% (range, 17% to 33% reduction), and they were 40% (range, 25% to 50% reduction) when high and low amounts of activity were compared.57–60

To provide a more detailed picture of the doses of physical activity, we provide data from 2 exemplar studies, 1 in men and 1 in women. In the Harvard Alumni Study, which followed >7000 men for 6 years, physical activity was estimated from self-reported walking, climbing stairs, and participation in sports or recreational activities.18 On the basis of these activities, investigators estimated the total energy expenditure per week and classified men into those expending <1000, 1000 to 1999, 2000 to 2999, 3000 to 3999, and ≥4000 kcal/wk. After adjustment for age, smoking, parental history of premature mortality, alcohol, diet, and the intensity and duration of activities, the hazard ratios for CHD across these categories were 1.00, 0.80, 0.80, 0.74, and 0.62, respectively, with P for trend <0.05 (Figure 4). The shape of this curve in men appears curvilinear (ie, although additional amounts of activity are associated with additional risk reductions, these additional risk reductions are of smaller magnitudes), which is similar to the curvilinear, inverse dose-response curve for physical activity and all-cause mortality concluded by the 2008 Guidelines expert panel, when 5 levels of physical activity were used (based on data from 11 studies).5

Among >20 000 women in the Women’s Health Study,57 followed for >10 years, physical activity was assessed in a fashion similar to that of the Harvard Alumni Health Study. After adjustment for age, smoking, parental history of myocardial infarction, alcohol, diet, menopausal status, and use of postmenopausal hormones, the hazard ratios for CHD across these categories were 1.00, 0.84, 0.76, and 0.62, respectively, with P for trend=0.001 (Figure 5). The shape of this curve in women appears more linear than the curvilinear shape seen in men; this is likely due to the lower levels of physical activity in women, so that the portion of the dose-response curve seen in these women represents the more linear shape of the dose-response curve at the lower end of the physical activity spectrum.

**Physical Inactivity Versus Overweight/Obesity**

There is current interest in whether higher levels of physical activity (or fitness) can ameliorate the increased risk for
premature mortality or CHD/CVD associated with being overweight or obese. In part, this has arisen because the prevalence of overweight and obesity in the United States has increased dramatically over the past 2 decades. In addition, whereas effective strategies exist for weight loss, the vast majority of people who lose weight do not maintain their weight loss over time.

Although some studies indicate that being physically fit can mitigate the excess risk for premature or CVD mortality associated with being overweight or obese, other studies indicate a more nuanced relation, with each risk factor (inactivity or overweight/obesity) independently being associated with increased risk, of about equal magnitude but not canceling the increased risk of the other. Thus, physical activity was significantly and inversely related to risk, independent of body mass index, in these other studies. In addition, body mass index was significantly and directly related to risk, independent of physical activity. Higher levels of physical activity did not remove the increased risk associated with obesity. The highest risks were observed among subjects who were both inactive and overweight/obese. An example of a study supporting the former viewpoint is the Aerobics Center Longitudinal Study. In multivariate analyses, compared with fit and normal-weight subjects, fit but obese (body mass index 30 to 34.9 kg/m²) subjects did not have an increased risk (relative risk = 1.12 [0.76 to 1.12]) for premature mortality, but unfit subjects of normal weight did (relative risk = 3.63 [2.47 to 5.32]). In contrast, findings supporting the latter viewpoint come from the Nurses’ Health Study. Compared with active and normal-weight women, active but obese women had an elevated risk for CHD (relative risk = 2.48 [1.84 to 3.34]), as did inactive women with normal weight (relative risk = 1.48 [1.24 to 1.77]). Women who were both inactive and obese experienced the highest risk (relative risk = 3.44 [2.81 to 4.21]).

A recent review concluded that more research is needed; however, on the basis of the available limited data, higher levels of physical fitness appear to be able to offset the increased risk of CVD associated with being overweight or obese. However, higher levels of physical activity do not (for more discussion on physical fitness versus physical activity, see below), with studies of physical activity indicating that inactivity and overweight/obesity represent independent risk factors, of about equal magnitude, which do not cancel each other. However, for type 2 diabetes mellitus, a major risk factor for CVD, the data are more consistent in showing that being overweight or obese is associated with far greater increases in risk of developing type 2 diabetes mellitus than being unfit or being inactive and that higher levels of physical fitness or activity do not ameliorate the increase in risk of type 2 diabetes mellitus. With regard to whether there are differences by age, gender, or race/ethnicity, the data are too limited to be able to make any definitive statements.

**Additional Issues**

**Studies of Physical Fitness**

Physical activity and physical fitness represent distinct, though related, characteristics. Physical activity is any bodily movement produced by skeletal muscle that results in energy
Physical fitness is a set of attributes that one possesses (based on genetic profile) or achieves from regular physical activity, including muscular endurance (or cardiopulmonary fitness), muscular strength, body composition, and flexibility. In many individuals and particularly in those who have low levels of physical activity, increases in physical fitness can be achieved by increasing one’s physical activity. However, physical fitness also has a genetic component, and improvement in physical fitness is highly variable across individuals who undergo an exercise program. Additionally, physically fit individuals find it easier to be physically active.

Studies of physical fitness and CHD/CVD risk in men and women observe findings that are congruent with those from studies of physical activity. In part, this may reflect the greater precision with which physical fitness is measured, as contrasted with self-reported physical activity in observational epidemiological studies. Additionally, physical fitness and physical activity measure different, though related, characteristics. A recent study of cardiorespiratory fitness and all-cause mortality, in which most deaths were likely due to CVD, showed similar associations in white and black men.

The intent of this review is to focus on studies of physical activity rather than physical fitness because studies of physical fitness, although a marker of recent physical activity, cannot provide the direct information needed to make public health recommendations with regard to the kinds of activity and their intensity, duration, and frequency that is needed for health. Nonetheless, studies of physical fitness can provide useful data to inform public health recommendations. In the Aerobics Center Longitudinal Study, physical activity was obtained by self-reported questionnaires and then compared with cardiorespiratory fitness as measured by maximal treadmill exercise testing. Men with low and moderate levels of cardiorespiratory fitness reported an average of 112 and 130 min/wk of walking, respectively. In women, the corresponding walking times were 128 and 148 min/wk, respectively. These data indicate that cardiorespiratory fitness of a moderate level can be achieved by following current physical activity guidelines recommending at least 150 min/wk of moderate-intensity physical activity, of which brisk walking is an example. In addition, data from the Aerobics Center Longitudinal Study show that cardiorespiratory fitness of at least a moderate level is associated with lower rates of premature mortality and CVD risk.

Sedentary Behavior
There has been recent interest in “inactivity” physiology as separate and distinct from “activity” physiology. In part, this stems from the realization that if one follows current recommendations and walks briskly for, say, 30 min/d in at least 10-minute bouts, for the remaining 15.5 hours of the day (assuming 8 h/d of sleep), one can sit most of the time or make many brief, spontaneous movements (eg, fidgeting, standing up, and sitting down) that would not “count” toward physical activity recommendations. A person who exercises for 30 min/d but sits most of the rest of the day may actually expend less total energy than someone who does not exercise.
but is constantly “puttering” around. Animal studies show that experimentally decreasing spontaneous standing and ambulatory time in rats had a far greater magnitude of deleterious effect on lipoprotein lipase regulation compared with the magnitude of the beneficial effect of adding exercise to rats’ normal activity.80

Several studies have shown that sedentary behavior, such as the amount of time watching television, using a computer, or playing video games, is associated with obesity,81,82 metabolic syndrome,83 and type 2 diabetes mellitus,84 all of which increase the risk of developing CHD/CVD. Additionally, a recent study that followed >1700 men and women in the Canadian Fitness Study for 12 years reported that increased sitting time was directly related, in a graded time, “1/4 of the time,” “1/2 of the time,” “3/4 of the time,” or “almost all of the time”) was directly related, in a graded fashion, to all-cause and CVD mortality.85 Of special interest was the observation that even among people active enough to meet physical activity recommendations, those spending more time sitting were at increased risk of all-cause and CVD mortality compared with those sitting less. If these findings are confirmed by additional studies, targeting and decreasing sedentary behavior may prove to be an effective and independent mechanism for decreasing cardiovascular risk in addition to increasing physical activity.

Conclusions

There is substantial evidence to indicate that physically active individuals have lower rates of CHD and CVD. This review summarizes the data supporting the assertion and is based primarily on the systematic evidence review behind the 2008 Guidelines and supplemented by 4 recent studies published after the review. Although all of the data discussed in this review have come from observational epidemiological studies that cannot prove cause and effect, many plausible biological mechanisms demonstrated in randomized clinical trials (discussed in other articles in this review) strongly support a causal relation. The most active individuals, compared with the least active, have an ~30% to 40% risk reduction.

Of specific interest in this review is whether the inverse relation is present across age, gender, and racial/ethnic groups. The available data indicate that the relation holds for younger and older individuals, but limited data are available for individuals aged ≥80 years. As for gender, there is substantial evidence to indicate that the same inverse association exists in women as well as men, and there are suggestive data that the magnitude of association may be even more pronounced in women. With respect to racial/ethnic groups, there are few data on nonwhite populations, but the available data indicate that the inverse association is also present across different racial/ethnic groups.

This review also examined dose-response relations between physical activity and risk of CHD/CVD. It is clear that increasing amounts of physical activity are associated with additional risk reductions in both men and women, although the shape of the dose-response curve is not well defined. Because of the heterogeneity of data collected and analyzed in physical activity studies, less clear is what specifically constitutes “moderate” or “high” amounts of physical activity. The available data, however, are consistent with the 2008 federal physical activity guidelines that require at least 150 min/wk of moderate- or 75 min/wk of vigorous-intensity aerobic physical activity and that state that additional benefits occur with 300 min/wk of moderate- or 150 min/wk of vigorous-intensity aerobic physical activity.

This review is limited by interstudy variation in data collected on physical activity, as well as its classification. The expert panel concluded in the 2008 Guidelines that “uniform data collection is needed with respect to the type of physical activity (eg, leisure-time, occupational) and physical activity characteristics (intensity, duration, amount).” Recently, technological advances have increased rapidly, allowing for greater accuracy and precision of the assessment of physical activity in free-living populations, especially through the use of motion sensors and physiological monitoring. These improvements, along with uniform and detailed data collection, will lead to a better understanding of the health benefits and dose response of physical activity.

In conclusion, although there is a large body of evidence clearly supporting reduced risks of CHD/CVD with physical activity, details of the relationship are less clear. Further research on older populations, particularly those older than 80 years, as well as in racial/ethnic minorities is needed. Additionally, future studies that can provide more detail on the dose-response relation are important to inform future physical activity recommendations. The available data on dose response have come primarily from observational studies with self-reported physical activity. Although these data are useful and can be valid, self-reports have limitations with regard to their imprecision, limited ability to identify light-intensity physical activity (for example, it is harder to accurately report household chores, which tend to be light intensity, but easier to accurately report a regular exercise regimen such as running for 1 hour, 3 d/wk), and limited ability to assess sedentary behavior comprehensively. The costs of devices using technological advances that allow for greater accuracy and precision of the assessment of physical activity and sedentary behavior in free-living populations, such as motion sensors (eg, accelerometers) and physiological monitors (eg, heart rate monitors) have decreased over time, making their use increasingly feasible in large-scale cohort studies. Using these devices in free-living populations to study associations with clinical end points, such as CVD end points, will lead to a better understanding of the health benefits of physical activity and dose-response relationships.

Disclosures

Dr Lee serves as a consultant for Virgin HealthMiles and serves on its Scientific Advisory Board. E.J. Shiroma reports no conflicts.

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