Behavioral Cardiovascular Risk Factors
– Effect of Physical Activity and Cardiorespiratory Fitness on Cardiovascular Outcomes –

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Primary and primordial prevention of cardiovascular disease (CVD) requires not only identification of risk factors, but also appropriate and timely therapy. In order to prevent the expected increase in prevalence of CVD, it is essential that clinicians are aware of behavioral cardiovascular risk factors. A basic review is critical to clarify the difference between physical activity and fitness, as well as to discuss the role each plays in cardiovascular outcomes. We discuss observational epidemiological studies and randomized control trials that have examined the effect of physical activity and cardiorespiratory fitness on CVD. (Circ J 2016; 80: 34–43)

Key Words: Cardiovascular disease; Epidemiology; Fitness; Physical activity

Despite major improvements in its treatment, cardiovascular disease (CVD) remains the leading cause of death worldwide. In 2012, 17.5 million people died of CVD and this figure is expected to grow to 23.6 million by 2030. Thus, understanding risk factors is integral to the prevention of CVD-related morbidity and mortality. Preserving cardiovascular health and treating modifiable risk factors instead of advanced disease benefits the long-term health of patients. Models for risk prediction have evolved since cardiovascular epidemiology began in the 1930s. Various 5- and 10-year risk prediction models have been widely adopted, and include common variables such as age, sex, cholesterol, smoking status, diabetes, and systolic and diastolic blood pressures (SBP, DBP). However, despite abundant research focused on understanding the effect of physical activity and fitness on cardiovascular outcomes, these risk models do not include physical activity or fitness. In 2013, the American College of Cardiology/American Heart Association (ACC/AHA) Work Group examined the contribution of potential risk markers, including cardiorespiratory fitness, to risk assessment or reclassification when added to traditional variables. At that time, they concluded that the evidence for contribution of cardiorespiratory fitness to risk assessment for a first atherosclerotic CVD event was inconclusive.

While raising awareness on prevention, the AHA encourages the improvement of cardiovascular health. The impact goals of the AHA include, “by 2020, to improve cardiovascular health of all Americans by 20% while reducing deaths from CVD and stroke by 20%.” The committee was tasked with defining cardiovascular health, a concept that encompasses the presence of 7 ideal health behaviors and factors, including physical activity level. Thus, the AHA claims that cardiorespiratory fitness is an uncertain risk factor, but physical activity at goal levels is an ideal health behavior. This review aims to distinguish physical activity from physical fitness, more specifically cardiorespiratory fitness, as well as to address the question whether physical inactivity and cardiorespiratory fitness are independent risk factors for CVD.

Definition of Terms

Although physical activity, exercise, and physical fitness are closely related, they are distinct and require unique assessment methods. Physical activity is defined as “any bodily movement produced by skeletal muscles that results in energy expenditure.” Physical activity is measured via criterion methods, objective methods, and subjective methods. Criterion methods include doubly labeled water, indirect calorimetry, and the gold standard, direct calorimetry. Doubly labeled water measures metabolic rate and requires ingesting 2 isotopes of water and assessing the difference in elimination rates of the isotopes over a certain time period. Indirect calorimetry uses oxygen consumption or carbon dioxide elimination to indirectly estimate energy expenditure, while direct calorimetry measures energy expenditure through heat production. Objective methods of physical activity include pedometers, accelerometers,
and heart rate monitoring. Lastly, subjective methods include questionnaires or surveys. Although each method has advantages and disadvantages, subjective methods are commonly implemented because of applicability to large populations and lower cost. Results from questionnaires are frequently converted into metabolic equivalents (METs). Analysis stems from grouping individuals, for example into moderate or vigorous activity, based on the number of METs achieved. Lastly, regardless of commonalities, physical activity and exercise are not interchangeable. Exercise is a subcategory of physical activity that is "planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective." Physical fitness is defined as "the ability to carry out daily tasks with vigor and alertness, without undue fatigue and with ample energy to enjoy leisure-time pursuits and meet unforeseen emergencies." Physical fitness can be further divided into health-related fitness and skill-related fitness. Cardiorespiratory fitness is a component of health-related fitness, defined as "the ability to perform large muscle, dynamic, moderate-to-high exercise for a prolonged period." Cardiorespiratory fitness is measured by exercise tolerance testing and is reported as a predicted VO2max. VO2max is used to measure cardiorespiratory fitness because it indicates the maximum oxygen uptake a person can attain while performing an exhaustive exercise test. Although predicted VO2max measurements are used frequently, the gold standard involves an expensive and technically difficult direct measurement of VO2 through expired gases. In addition to VO2max, cardiorespiratory fitness can also be expressed in METs.

Despite genetic contributions to fitness, for most individuals, increases in physical activity intensity, duration, and frequency result in increased physical fitness. Conversely, after 3 weeks of bed rest, VO2max decreased 25% in healthy men. As a result, measures of aerobic capacity have been used to "validate" self-reported physical activity. The need for validation stems from the fact that physical activity is most commonly assessed using questionnaires, which are prone to recall bias and misclassification. Several studies of defined cohorts used VO2max as an indirect validation criterion to physical activity questionnaires. The findings from those studies confirm the notion that leisure-time vigorous activity level ascertained from questionnaires can be a reasonably strong predictor of physical fitness indicators, such as VO2max. However, a study done in an elderly population by Tager et al in which treadmill exercise testing results were compared with self-reported leisure-time physical activity in 1,006 individuals, showed a poor correlation between VO2max and self-reported leisure-time physical activity. Thus, although it is helpful to validate physical activity questionnaires with fitness measures, they are not interchangeable, and it is important to distinguish physical activity from physical fitness.

**Physical Activity and Cardiovascular Risk**

Since Morris and colleagues' pioneering study in 1953, the relationship between physical inactivity and increased cardiovascular risk has been extensively studied, reviewed, and incorporated into meta-analysis. By comparing occupational activity levels, Morris et al found that inactive bus drivers in London, England had double the incidence of fatal coronary artery disease (CAD) than their more active counterparts. They paved the way for many reaffirming prospective epidemiological studies comparing cardiovascular outcomes in physically inactive and physically active groups. In 1987, Powell and colleagues performed a landmark systematic review of 43 prospective studies, which supported the association between physical inactivity and incidence of CAD. The median relative risk associated with physical inactivity was 1.9. Of the 43 studies, 10 were controlled for covariates including age, BP, smoking status, and cholesterol.

In 1992, the AHA recognized physical inactivity as a risk factor for CVD. In 1996, the Surgeon General presented a report addressing physical activity and health, emphasizing that "a regular, preferably daily regimen of at least 30–45 min of brisk walking, bicycling, or even working around the house or yard" reduces the risks of developing CAD. In 2008, the United States federal government presented a report outlining Physical Activity Guidelines for Americans, which summarized 30 prospective studies published between 1995 and 2007. Analysis of these studies showed that compared with the least active subjects, the most active men and women had median risk reductions by 30–35% for developing CAD. As a result, they recommended 150 min of moderate intensity physical activity per week or 75 min of vigorous physical activity in sessions of at least 10 min. Since 2008, these recommendations have been used to examine a dose-response between physical activity and the risk of CVD. For instance, in 2011, Sattelmair and colleagues performed a meta-analysis of 33 studies and showed that individuals who engaged in 150 min/week of moderate intensity leisure-time physical activity had a 14% lower CAD risk compared with those reporting no activity. Those who reported 300 min/week of moderate intensity leisure-time physical activity had a 20% lower risk. Li and Siegrist further supported this dose-response relationship in a meta-analysis of 21 prospective studies. Not only was there a dose-response relationship between leisure-time physical activity and CAD in both men and women, but they also found a dose-response relationship between leisure-time physical activity and stroke. It is evident that a consistent, strong, and graded relationship exists between the level of physical activity and CVD.

**Cardiorespiratory Fitness and Cardiovascular Risk**

In addition to physical activity, the relationship between cardiorespiratory fitness and CVD has been well characterized. Furthermore, the effect of fitness on all-cause mortality has been studied. For instance, in 1995, Blair and colleagues examined the effects of changes in physical fitness and mortality. They found that men who went from unfit to fit over a 5-year period had a reduction of 44% in the relative risk of death compared with men who remained unfit. Furthermore, there was a 7.9% decrease in risk of mortality for each minute increase in maximal treadmill time between examinations. Although this study looked at mortality in general, it is clear that cardiorespiratory fitness is critical for maintaining health. Individuals who are unfit at baseline can make vast improvements in their health by becoming more fit.
with a lower risk for all-cause mortality and CVD. Additionally, they found that a 1-MET increase was associated with a 13% risk reduction of all-cause mortality and a 15% risk reduction of CVD.

Although Blair and colleagues examined the implications of changes in physical fitness over time, Vigen and colleagues studied a large population of men and women from the Cooper Center Longitudinal Study and determined that a single measure of low fitness at baseline was associated with both CVD and non-CVD mortality across 3 decades of follow-up, with the association strongest in the short term. Furthermore, a study done by Gupta and colleagues also included a single, baseline measure of fitness with 25 years of follow-up. Findings were consistent with prior studies, suggesting that cardiorespiratory fitness is associated with CVD mortality; furthermore, by dividing fitness into quintiles, they found a dose-response relationship. A potential explanation for the more apparent dose-response relationship in men compared with women may relate to the smaller number of female participants diminishing statistical power among women. The study cohort included 49,307 men, but only 17,064 women. Furthermore, these investigators performed a reclassification of the 10- and 25-year risk of CVD mortality in men, as well as 25-year risk of CVD mortality in women. When fitness was added to a traditional risk factor model, all measures of discrimination and reclassification improved, especially in women. In particular, Harrell’s C statistic increased from 0.84 to 0.86 when fitness was added to the 10-year model for men. In 2012, Barlow et al compared baseline measures of cardiorespiratory fitness in a large cohort of men and women deemed low risk by the Framingham Risk Score. By following these individuals for 30 years, they found that low-risk individuals in the highest quintile of cardiorespiratory fitness had the greatest protection from CVD death over the 30-year span (hazard ratio [HR] 0.29, 95% confidence interval [CI]: 0.16–0.51). Furthermore, their results were very similar to the analysis by Kodama et al, in that a 1-MET increase in cardiorespiratory fitness corresponded to an 18% reduction in cardiovascular mortality.

Although current recommendations from the Task Force in the 2013 ACC/AHA Guidelines leave it uncertain as to whether or not cardiorespiratory fitness is a risk factor for CVD, the aforementioned studies provide evidence in favor of designating cardiorespiratory fitness as a risk factor. However, when evaluating for novel risk markers it is important to not only consider discrimination, calibration, and reclassification, but also cost-effectiveness, a component not addressed in the study by Gupta et al. Additionally, there are notable limitations to the aforementioned studies by Blair et al., Vigen et al., and Barlow et al. All 4 studies came from the Cooper Center Longitudinal Study, a homogeneous study population that is predominantly white with similar socioeconomic status. Furthermore, fitness was measured using the Balke protocol, a symptom-limited treadmill test that allows for estimation of fitness levels in METs. Although fitness is commonly measured using this approach, the current gold standard is a graded maximal exercise test with VO2 measurements via expired gases. Additionally, the baseline model in the reclassification study by Gupta et al lacked measurement of high-density lipoprotein cholesterol (HDL-C), a known risk factor that could have influenced the results. Despite limitations, these studies support the importance of high cardiorespiratory fitness in protecting against all-cause and CVD-related mortality. The AHA made recommendations to address some of these limitations in a 2013 policy statement regarding the need for a national registry. The statement emphasized the importance of creating a formal multicenter cardiorespiratory fitness database to provide a sufficiently representative sample of the population. Furthermore, they also stressed the necessity of clearly defining levels of cardiorespiratory fitness in order to standardize studies across different subgroups and locations. Overall, epidemiological studies of cardiorespiratory fitness provide reasonably convincing evidence of an independent association with the risk of CVD. However, additional studies are needed in order to determine whether or not cardiorespiratory fitness is an independent, novel risk marker for CVD that adds clinical value.

### Reduction of Traditional Risk Factors

Although epidemiological studies identified an association between physical inactivity, cardiorespiratory fitness and CVD, identifying biologically plausible mechanisms of this relationship is crucial to being able to evaluate for causality and to better understand the effects of CVD risk reduction with exercise training. Recommendations to increase physical activity and fitness have been underused as interventions because providers fail to see the independent role they play in prevention. Instead, they are thought to moderate the influence of traditional risk factors. Traditional non-modifiable risk factors for CVD include age, sex, race, and family history of CVD. Physiological, potentially modifiable risk factors include dyslipidemia, hypertension, diabetes, obesity, and smoking status. This section will focus on the role exercise and fitness play in attenuating the harmful effects of the aforementioned physiological risk factors.

Studies of the effect of physical activity and increased fitness on preventing and improving traditional risk factors are abundant. Frequent physical activity and increased physical fitness are associated with lower BP, reduced risk for the development of hypertension, and improved lipid profile. The 2013 ACC/AHA Guidelines advise adults to engage in 3–4 40-min sessions a week of aerobic physical activity to reduce low-density lipoprotein cholesterol (LDL-C) and non-HDL-C as well as to lower blood pressure. Furthermore, a meta-analysis by Durstine and colleagues showed lower triglyceride and higher HDL-C levels in physically active individuals through both observational cross-sectional studies and exercise-training intervention studies.

In addition to reduced risk for dyslipidemia, exercise also lowers BP. In the Harvard Alumni Study, men who regularly participated in sports activity had a 19–24% reduced risk of developing hypertension. In 2002, a meta-analysis of 54 randomized controlled trials reported by Whelton et al showed that previously sedentary adults could decrease SBP by 4 mmHg (95% CI, 3–5 mmHg) and DBP by 3 mmHg (95% CI, 2–3 mmHg) with regular aerobic exercise. Furthermore, all frequencies, intensities and types of aerobic exercise lowered BP in people who were normotensive or hypertensive, overweight or normal weight, black, white or Asian. Additionally, BP was significantly reduced in individuals who increased aerobic exercise independent of a change in body weight. Researchers have also explored the relationship between fitness and BP. For example, Barlow et al examined a large group of normotensive women and found a 61% and 81% lower risk of developing hypertension for women in the middle and high fitness categories, respectively, in comparison with low-fit participants. In 2014, Liu et al examined a large cohort of aging, healthy men and found that fitness was an effect modifier of the SBP aging trajectory. Lastly, Jurasscheck
that when adjusted for differences in baseline body mass index (BMI) and fasting glucose, the diet only group had a 31% reduction in the risk of developing diabetes, the exercise group had a 46% reduction, and the dietary changes plus exercise intervention had a 42% reduction.

Thus, changes in lifestyle, in particular adding exercise, can reduce the risk of developing diabetes significantly. Instead of trying to assess the effect of diet and exercise separately, Tuomilehto et al. randomized 522 middle-aged overweight men and women with impaired glucose tolerance to either a lifestyle intervention group with individualized counseling regarding diet and physical activity or a control group. After 4 years, the overall incidence of

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**Figure 1.** (A, B) Percent of risk associated with physical activity and cardiovascular disease attributed to traditional risk factors. (Adapted with permission from Mora S, et al.47)
diabetes in the intervention group was reduced by 58%. The study provides further evidence that type 2 diabetes can be prevented in high-risk men and women with lifestyle changes. Additionally, a landmark study by the Diabetes Prevention Program assessed the effect of either lifestyle changes or metformin in reducing the incidence of diabetes in high-risk individuals. Although both interventions were effective, the lifestyle intervention reduced the incidence of diabetes by 58% while the metformin group reduced the incidence by 31%. More recently, in 2014, Yates et al examined adults from 40 countries at high risk of type 2 diabetes and CVD and found that among men and women in various regions and age groups, increased ambulatory activity at baseline and changes in ambulatory activity were associated with a lower cardiovascular event rate.

Exercise is not only associated with a reduced risk of developing dyslipidemia, hypertension, and diabetes, but also with greater weight loss and reduced morbidity and mortality in individuals who are overweight or obese. A review of 43 studies by Shaw et al in 2006 found that exercise had a positive effect on body weight in people who were overweight and obese. They also concluded that weight loss secondary to exercise was only marginal compared with no treatment; however, when compared with dietary interventions, the amount of weight loss increased substantially. Regardless of weight loss, individuals with abdominal obesity/metabolic syndrome who reported being very active have a 50% reduction in CVD risk compared with sedentary individuals. In regards to exercise and smoking cessation, a recent review by Ussher et al in 2014 looked at 20 studies and found that only 2 provided evidence that exercise helped smoking cessation in the long term. The remaining studies had limited power or used exercise interventions that were not intense enough to achieve the desired level of exercise. Overall, the preventive effects of increased physical activity and cardiorespiratory fitness on cardiovascular outcomes are in part secondary to the important moderating influences on traditional CVD risk factors.

**Prevention of Arterial Dysfunction and Anti-Inflammatory Effects**

Although exercise plays a role in favorably modulating traditional cardiovascular risk factors, as described, the association between physical activity, cardiorespiratory fitness and CVD is also partly independent from traditional CVD risk factors. In 2007, Mora and colleagues performed a large, prospective study in order to assess the relative contribution of various risk factors to CVD. The risk factors investigated explained 59% of the activity-related reduction in CVD. They showed that the association is not fully explicable by known covariates (Figure 1). Additionally, findings from the Canadian-led INTERHEART study, a case-control study of individuals from 52 countries, showed that in men and women of all ages worldwide, mild to moderate physical activity is associated with reduced risk of heart attack, independent of other traditional risk factors. Possible biological mechanisms to explain the reduced, independent risk associated with physical activity include improvement in arterial function and anti-inflammatory effects. The beneficial effects of physical activity may also be attributed at least in part to reductions in sympathetic nervous system activity evidenced, for example, by resting bradycardia and increased heart rate variability.

As noted previously, advancing age is a risk factor for CVD, with >90% of CVD occurring in middle-aged and older adults. Aging contributes to CVD risk through arterial dysfunction, exemplified by stiffening of the large elastic arteries and the development and progression of systemic vascular endothelial dysfunction. Clinicians are able to evaluate the stiffness of large arteries through the aortic pulse wave velocity and arterial pulse augmentation index. Exercise has been shown to affect carotid artery stiffness. For example, aerobic exercises, such as running, swimming or rowing, are associated with higher carotid artery compliance (ie, reduced stiffness) with age when compared with age-matched inactive adults. Conversely, solely resistance-trained adults have reduced carotid artery compliance, or increased stiffness when compared with age-matched inactive adults. In 2009, Sugawara and colleagues explored the mechanism underlying how endurance training improves arterial compliance in 7 healthy sedentary adults. First, they found that endurance training via walking and jogging led to a 34% increase in arterial compliance. Furthermore, by testing arterial compliance before and after a 12-week exercise training with a-adrenergic blockade, they found that in middle-aged and older adults endurance training enhanced carotid artery compliance through reduction in a-adrenergic receptor-mediated vascular tone. Exercise not only lowers large elastic artery stiffness in middle-aged and older adults, but in youth as well. For example, Palve et al showed that higher levels of physical activity in boys and young adults had favorable effects on carotid artery elasticity even when measured 21 years later.

Arterial dysfunction also results from endothelial dysfunction. Endothelial dysfunction plays a central role in the pathogenesis of atherosclerosis and in the associated acute cardiovascular events. According to Davignon and Ganz, reduced nitric oxide (NO) bioavailability is one of the characteristic features of vascular endothelial dysfunction. NO is an endothelium-derived vascular protective and vasodilatory molecule generated by the action of endothelial NO synthase (eNOS) on L-arginine. Endothelium-dependent dilation (EDD) is used in humans to assess vascular endothelial function. Several techniques for measuring EDD are available, including brachial artery flow-mediated dilation (FMD) assessed non-invasively by ultrasound and forearm blood flow in response to acetylcholine infusion. By using these techniques to measure EDD before and after exercise interventions, researchers are able to assess the effects of exercise on vascular endothelium. For example, using both a cross-sectional and interventional study, DeSouza et al showed that regular aerobic exercise improved endothelial vasodilatory function in healthy middle-aged and older sedentary men. The 3-month regular aerobic exercise interventional study resulted in a significant increase in endothelium-dependent vasodilation. Interestingly, these improvements occurred without an increase in VO2max. The improved endothelial function with exercise in peripheral arteries has also been observed in coronary arteries in a prospective study of 19 men with CAD randomized to either a 4-week exercise training intervention or a sedentary control group. By examining coronary vascular response to increasing doses of acetylcholine before and after the exercise period, Hambrecht et al found that exercise decreased acetylcholine-induced vasoconstriction and improved coronary blood flow, both signs of improved coronary endothelial function. In their commentary on the study by Hambrecht et al, Vita and Keaney proposed that increased shear stress secondary to exercise might increase the expression of the enzyme responsible for NO synthesis, eNOS, and as a result, improve endothelial function. Indeed, a subsequent study by Hambrecht et al found that the improvement in endothelium-dependent vasodilatory capacity after exercise...
physical activity may suppress low-grade systemic inflammation. Exercise increases expression of the PGC1α gene, which is responsible for encoding the transcriptional coactivator PGC1α (peroxisome-proliferator-activated receptor-γ (PPAR-γ) coactivator 1α). PGC1α suppresses chronic inflammation in muscle partly by reducing ROS production. PGC1α is thus viewed as one of the key upstream regulators by which exercise reduces inflammation. Furthermore, exercise reduces visceral fat mass, increases the production of anti-inflammatory cytokines, and metabolic health effects.

Inflammation is a key factor in the development of atherosclerosis, insulin resistance, and ultimately in the pathogenesis of CVD. Chronic low-grade inflammation accompanies traditional risk factors, but also occurs independently of them. This chronic state of inflammation is exemplified by an increase in the concentrations of inflammatory mediators such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1, IL-6, interleukin-1 receptor antagonist (IL-1ra), soluble tumor necrosis factor receptor (sTNF-R), and C-reactive protein. Upregulation of proinflammatory cytokines and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase stimulate the release of superoxide, which reacts with and inactivates NO. NADPH oxidase enzymes are one of the key sources of reactive oxygen species (ROS), oxygen-derived small molecules, including superoxide, that reduce NO bioavailability and induce vascular dysfunction. Notably, physical activity benefits the vasculature through increased expression of eNOS and the phosphorylation of eNOS on Ser1177 in addition to increased circulating EPCs. On the other hand, physical inactivity leads to deleterious vascular and metabolic health effects.

Training in patients with stable CAD was related to increased expression of eNOS as well as increased abundance of its active Ser1177 phosphorylated form. A later study by Steiner et al also examined the effects of supervised endurance training on endothelial regenerative capacity in a group of 20 patients with cardiovascular risk and CAD. After 12 weeks, they found a significant increase in circulating bone marrow-derived endothelial progenitor cells (EPCs), which play an important role in the maintenance of endothelial function and organ perfusion. Increased EPCs were also associated with an increase in NO synthesis and improvement in FMD. Thus, exercise not only improves EDD in healthy adults, but also in individuals with CAD. In addition to looking at potential positive effects of exercise on endothelial function, studies exploring the negative effects of physical inactivity have also been done. For example, Hamburg and colleagues measured vascular function as well as insulin sensitivity in 20 healthy subjects at baseline and during 5 days of strict bed rest. During the course of the study, subjects were allowed to get out of bed only for 30 mins each day. After the 5 days, these inactive subjects developed insulin resistance, microvascular dysfunction, dyslipidemia, and increased BP. It is thus clear that physical activity benefits the vasculature through increased expression of eNOS and the phosphorylation of eNOS on Ser1177 in addition to increased circulating EPCs. On the other hand, physical inactivity leads to deleterious vascular and metabolic health effects.
reduces the expression of Toll-like receptors on macrophages and monocytes.63 In general, levels of proinflammatory cytokines, TNF-α and interleukin-1β, do not change with exercise; rather exercise provokes an initial increase primarily in IL-6, followed by an increase in IL-1ra, an anti-inflammatory cytokine, and IL-10.63 The release of IL-6 from skeletal muscle during exercise not only promotes the release of anti-inflammatory cytokines, but also downregulates the production of TNF by monocytes and stimulates the release of cortisol and adrenaline from the adrenal glands.63 The anti-inflammatory effects of exercise have been examined in both cross-sectional and longitudinal studies in humans. For example, a cross-sectional study looking at sedentary and physically active groups of elderly found a 2-fold higher percentage of inflammatory monocytes in the sedentary group.58 In addition to exhibiting anti-inflammatory effects, aerobic exercise also helps reduce oxidative stress through the stimulation of antioxidant and suppression of pro-oxidant pathways.56 In sum, reversing oxidative stress, endothelial dysfunction and reducing inflammation are among the key mechanisms responsible for the cardiovascular health benefits of exercise56 (Figure 2).

Randomized Controlled Trials

A key step in establishing causality, beyond just association, is trial evidence, if it demonstrates that modifying a risk factor alters the prognosis. However, studies examining the effects of exercise on clinical outcome events in individuals without known CVD are lacking. Instead, the effect of exercise on primary CVD prevention is assessed through changes in calculated risk scores. For example, in 1997, Dunn and colleagues64 assessed the effect of a lifestyle physical activity intervention compared with a structured exercise intervention on CVD risk factors among healthy, sedentary men and women. After the 6-month intervention, both groups had a significant increase in cardiorespiratory fitness and reductions in total cholesterol, total cholesterol/HDL-C ratio, DBP, and percentage of body fat. Furthermore, among the 6-month participants as a whole, there was a 15% reduction in CAD risk, calculated by the Framingham Coronary Risk Score.64 Tully et al65 examined the effects of a 12-week, unsupervised program of “30-min brisk walking, 5 days a week.” Subjects aged 50–65 years were enrolled in either the intervention group or control group, and baseline as well as post-intervention measures of BP, BMI, cholesterol, fitness and Framingham Risk Score were compared.65 Tully and colleagues concluded that the 12-week unsupervised program resulted in improved fitness and decreased cardiovascular risk, reflected by improved Framingham risk scores.65 Kirk and colleagues showed that physical activity counseling improved glycemic control and the status of cardiovascular risk factors in people with type 2 diabetes.66 Although the aforementioned studies showed that increasing physical activity and physical fitness decrease the risk for CVD, they do not provide evidence that clinical outcomes change (Figure 3).

Association of physical activity with cardiovascular outcomes has been examined only in populations at high risk for CVD events, a requirement for a study to be of practical size. For example, a recent clinical outcome trial conducted in 16 centers in the USA by the Look AHEAD Research Group examined whether an intensive lifestyle intervention consisting of caloric restriction and increased physical activity would decrease cardiovascular morbidity and mortality among 5,145 overweight and obese patients with type 2 diabetes.67 The primary endpoint of this trial was defined as the first occurrence of nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina or death. As postulated, compared with the control group, the lifestyle intervention produced greater reductions in weight, SBP and DBP, glycated hemoglobin, and greater increase in HDL-C and greater improvement in physical fitness. Unexpectedly, the trial was stopped early after a median of 9.6 years because of apparent futility. Despite the beneficial changes in the aforementioned cardiometabolic risk factors and in diabetic control in the intervention group compared with the control group, there was a lack of a significant difference in cardiovascular outcomes between groups.67 A number of potential explanations have been proposed for the null result of intensive lifestyle modification on the primary outcome, including (1) greater use of cardioprotective drugs (statins and antihypertensive medications) in the control group, which may have diminished the difference in outcomes between the 2 groups.68 That the medical treatment was more intensive in the control group may not be surprising because during the trial patients and their healthcare providers received annual reports on the patients’ updated cardiovascular risk factors and the goals recommended by the American Diabetes Association. Expectedly, any lack of optimal lifestyle in the control group was compensated with more intensive pharmacological management67 to reach the recommended targets. Additional factors that may have contributed to the null result were (2) inclusion of hospitalization for angina as an endpoint;68 (3) insufficient duration of the study, with speculation by experts that a benefit on cardiovascular outcomes might need >10 years;68 (4) insufficient difference in weight loss between the 2 trial groups, which averaged 4% during the entire study but only 2.5% at the end;67 and (5) it is also possible that physical exercise and fitness are of greater benefit in the prevention of primordial CVD whereas diabetics typically have established CVD that is occult. Although intensive lifestyle intervention did not reduce cardiovascular morbidity and mortality, it did significantly improve a number of other important clinical outcomes, including a 31% reduction in the...
risk of advanced kidney disease and a 14% reduction in the risk of diabetic retinopathy.67

Another large clinical trial that investigated the benefits of exercise was the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION).68 This trial randomized 2,331 stable patients with heart failure to usual care with or without an aerobic exercise training program that included 36 supervised sessions followed by participation in a home-based regimen using exercise equipment provided to them. There was no statistically discernable difference between the usual-care-only and the prescribed exercise in the primary endpoint of death or hospitalization from any cause over median follow-up of 30 min (HR 0.93; 95% CI 0.84–1.02, P=0.13). However, after adjustment for prespecified baseline characteristics, the HR for the primary endpoint was 0.89 (95% CI 0.81–0.99, P=0.03). Thus, regular exercise was associated with a significant although modest reduction in all-cause mortality and hospitalization. This modest reduction can be attributed partly to lower exercise adherence in the exercise group, suggesting the need in future studies to find creative ways to improve and maintain adherence to exercise. As with the Look AHEAD trial, one can reasonably question whether the exercise intervention may have been more effective in the prevention of primordial CVD than in the treatment of advanced CVD. Although the improvements with exercise and other lifestyle modifications appear at best modest in the large randomized studies, additional randomized trials with clinical outcomes are needed to further assess the effects of exercise and improved fitness on the risk for CVD, particularly among lower risk populations. Furthermore, when designing new randomized controlled trials, clinicians should be aware of the challenges of exercise adherence and work with patients to better understand and break down these barriers.

**Future Directions**

It is evident that physical inactivity and low cardiorespiratory fitness are associated with a greater risk for incident CVD. However, the 2013 ACC/AHA Work Group deemed cardiorespiratory fitness as an uncertain risk factor because the studies included did not adequately discuss discrimination, calibration, reclassification, or cost-effectiveness.70 Thus, future studies are needed in order to determine the benefit of including cardiorespiratory fitness in risk prediction. Additionally, despite abundant research, physical inactivity remains staggeringly high. According to 2012 data from the National Health Interview Survey, 29.9% of adults do not engage in leisure-time physical activity.71 Physical inactivity was higher among women than men and higher in non-Hispanic black and Hispanic adults than non-Hispanic white adults.71 Thus, fresh approaches to promoting physical activity and fitness are much needed.

Randomized controlled trials have looked at the success of interventions on improving and maintaining physical activity levels.64 In 2012, Murray et al performed a systematic review of factors associated with uptake and completion of cardiovascular lifestyle behavior change and found 5 significant predictors: emotional status, access to transport and cost of programs, knowledge, understanding and beliefs about the condition and healthy lifestyles, and lastly, quality of personal support.72 Clinicians should be aware of these barriers when informing patients about the importance of behavioral lifestyle changes. Furthermore, exercise programs should be culturally appropriate, with implementation of population approaches at both the federal and state level for increasing physical activity. Additionally, it is important to identify and engage individuals most likely to benefit. With technologies being investigated to improve cardiovascular risk stratification, the idea of personal risk reduction through physical fitness is also on the horizon.

**Conclusions**

Physical inactivity is an independent risk factor for CVD. In regards to cardiorespiratory fitness, numerous studies have provided evidence for the association between cardiorespiratory fitness and CVD; however, future studies are needed before it can be formally recognized as a novel risk marker. As the prevalence of CVD continues to rise, it is essential to focus on primordial prevention of CVD, including finding creative ways to increase physical activity as well as determining whether or not cardiorespiratory fitness is a clinically useful risk marker. Controlled clinical trials of increased physical activity and improved fitness among apparently healthy subjects are much needed to establish a benefit on cardiovascular outcomes.

**References**

Physical Activity, Fitness and CV Outcomes


