Fitness, Fatness and Mortality

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FRANKLIN: ***Fitness, Fatness and Mortality.*** *Increased adiposity, physical inactivity, and reduced levels of cardiorespiratory fitness are strong and independent predictors of cardiovascular and all-cause mortality. However, the interrelationships among these variables on health outcomes is complicated and sometimes controversial. Numerous population studies in apparently healthy men and women, those with varied coronary risk factors (e.g., hypercholesterolemia, cigarette smoking, hypertension, overweight/obese, impaired fasting glucose, or type 2 diabetes), and those with suspected or known coronary heart disease have now identified a low level of cardiorespiratory fitness (bottom 20%) as an independent risk factor, identifying a cohort with a poor long-term prognosis. A consistent observation in these studies was that after adjusting for potential confounding variables, aerobic capacity was a stronger prognostic indicator than conventional risk factors or other exercise test variables. Although regular physical activity or exercise training may not make all people lean, it appears that an active way of life may have significant survival benefits, even for those who remain overweight/obese. (J HK Coll Cardiol 2010;18(Suppl 1:37-42)*

Cardiorespiratory fitness, Diabetes, Metabolic syndrome, Mortality

Introduction

In 1998, in response to an emerging body of scientific evidence, the American Heart Association reclassified obesity as a *major* modifiable risk factor for coronary heart disease (CHD).[1] Overweight and obesity often presage metabolic and cardiovascular consequences, placing individuals at higher risk for premature CHD morbidity and mortality. Indeed, obesity is classified as the only central cardiovascular risk factor that adversely impacts all of the other associated risk factors (Figure 1). Numerous studies have now substantiated that obesity confers an independent and additive risk of all-cause and cardiovascular mortality, even in the absence of other risk factors or metabolic derangements.[2,3] Other reports suggest that excess adiposity is strongly associated with the premature occurrence of acute myocardial infarction.[4,5] Although some obese patients with cardiovascular disease have lower adverse events and mortality than their leaner counterparts (i.e., the "obesity paradox"),[6] purposeful weight reduction appears warranted in this escalating patient subset.[7]

Regular physical activity and improved cardiorespiratory fitness, expressed as metabolic equivalents (METs; 1 MET = 3.5 mL O_2/kg/min), are believed to be cardioprotective; however, a widely-cited meta-analysis concluded that these variables had significantly different relationships to cardiovascular disease.[8] The risk decreased linearly when plotted as a function of the cumulative percentages of the samples ranked from least fit or active, to most fit or active (Figure 2). Nevertheless, there was a precipitous drop in risk when comparing the lowest (0) to the next-lowest fitness category (i.e., 25th percentile). Beyond this demarcation, the reductions in risk paralleled those observed with increasing physical activity, but were nearly twice as great for cardiorespiratory fitness. Thus, it appears that extremely low aerobic fitness (i.e., lower than the 25th percentile of the fitness distribution)

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Received October 22, 2010; accepted November 1, 2010

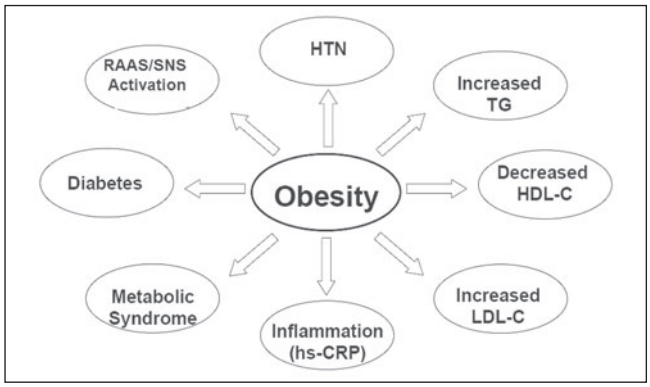

Figure 1. *Obesity is considered as the only central and potentially reversible cardiovascular risk factor that negatively impacts all the other primary and secondary risk factors. HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; RAAS/SNS, renin-angiotensin-aldosterone system/sympathetic nervous system; TG, triglycerides.*

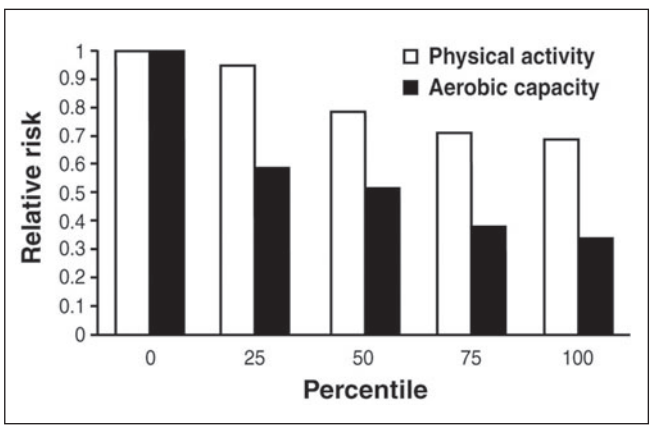

Figure 2. *Relative risks of coronary heart disease and cardiovascular disease in relation to increasing percentiles of physical activity and aerobic capacity. At the highest levels (100) the reductions in risk are essentially twice as great for aerobic capacity (cardiorespiratory fitness). Data adapted from Williams PT. Physical fitness and activity as separate heart disease risk factors: a meta-analysis. Med Sci Sports Exerc 2001;33:754-61.*[8]

warrants consideration as a risk factor, and deserves screening and intervention.

This review summarizes selected studies that have addressed body habitus (i.e., adiposity, body mass index [BMI]) and cardiorespiratory fitness, with specific reference to metabolic syndrome and diabetes, and the modulating influence that these variables have on prognosis, independently and collectively. The multiple mechanisms by which moderate-to-vigorous exercise training may reduce the risk of obesity and it's related metabolic consequences will also be discussed.

Fitness, Fatness and Mortality

Since the mid 1990s, several studies have examined the relationship between cardiorespiratory fitness and/or habitual physical activity and mortality in normal-weight, overweight and obese men and women. A landmark study of >25,000 men who were followed-up for an average of 8.5 years reported that moderate-to-high fit men with a BMI >30 kg/m^2 had approximately one third the age-adjusted death rate of their leaner (<27 kg/m^2) low-fit counterparts.[9] The age-adjusted mortality rates for these cohorts were 18.0 and 52.1 deaths per 10,000 man-years, respectively. Similarly, Wei et al[10] reported that low fitness is an independent predictor of mortality in normal-weight, overweight, and obese men; the relative risk of all-cause mortality for these respective cohorts was approximately 3, 4.5, and 5 when unfit versus fit subjects were compared. The investigators concluded that although regular physical activity or exercise training may not make all people lean, it appears that an active way of life may provide significant survival benefits, even for those who remain overweight.

Myers et al[11] reported on 6,213 consecutive men with and without CHD who were referred for treadmill testing for clinical reasons. The relative risk of death over a 6.2±3.7 year follow-up for obese men (BMI ≥30 kg/m^2) achieving an estimated functional capacity of <5 METs was 2.35 as compared with the most fit cohort (those achieving >8 METs). Sui et al[12] examined the influence of cardiorespiratory fitness and adiposity

on mortality in older adults. A cohort of >2600 adults aged 60 years and older (20% women) enrolled in the Aerobics Center Longitudinal Study were evaluated and followed over a 12 year duration. Fitness, estimated from maximal treadmill exercise test time (minutes), predicted mortality risk after adjusting for BMI, waist circumference, or percent body fat. The investigators emphasized that clinicians should consider the importance of preserving exercise capacity by recommending regular moderate-to-vigorous physical activity for older patients, normal-weight or overweight alike.

Hu et al[13] examined whether higher levels of physical activity (i.e., time spent exercising per week) can counter the elevated risk of death associated with excess adiposity. During a 24-year follow-up of 116,564 women aged 30 to 55 years who were free of known cardiovascular disease and cancer, there were 10,282 deaths. The relative risk of death of lean (BMI <25 kg/m^2)-active, lean-inactive, obese (BMI ≥30 kg/m^2)-active, and obese-inactive was 1.00, 1.55, 1.91, and 2.42, respectively. It was concluded that both increased adiposity and reduced physical activity are strong and independent predictors of death.

Exercise in the Prevention and Treatment of Metabolic Syndrome

There is a pathophysiological cascade by which physical inactivity predisposes to a cluster of metabolic diseases, including the metabolic syndrome. With our increasingly hypokinetic lifestyle, skeletal muscle downregulates its capacity to convert nutritional substrates to energy (adenosine triphosphate). Inactive skeletal muscle's impaired ability to oxidize glucose and fatty acids presumably results in hyperinsulinemia, hypertriglyceridemia, and ultimately increased cardiovascular risk.[14] On the other hand, moderate-to-vigorous leisure-time physical activity diminishes the magnitude of all 5 risk factors that are associated with the metabolic syndrome (Table 1).[15] An increase in physical activity also improves insulin action in obesity, with or without a concomitant reduction in body weight and fat stores.[16] This is an important (and often overlooked) salutary effect, suggesting that physical activity is as efficacious in preventing insulin resistance as losing body weight.

Nearly a decade ago, researchers examined the effects of moderate and vigorous physical activity over

Table 1. Influence of physical activity (and inactivity) on the characteristics of the metabolic syndrome

Characteristics of the metabolic syndrome	Impact of physical inactivity	Impact of physical activity
Large abdominal circumference: Women >35 inches Men >40 inches	Increases	Decreases
Hypertriglyceridemia: >150 mg/dL	Increases	Decreases
Low HDL cholesterol: Women <50 mg/dL Men <40 mg/dL	Decreases	Increases
High blood pressure: >130/85 mmHg	Increases	Decreases
High fasting blood glucose: >100 mg/dL	Increases	Decreases

HDL=high-density lipoprotein

a 4-year period in 612 middle-aged men without evidence of the metabolic syndrome.[17] Subjects who engaged in >3 hours per week of moderate-intensity leisure-time physical activity were *half as likely* as sedentary control subjects to develop metabolic syndrome. Moreover, men in the upper third of cardiorespiratory fitness (those who engaged in >3 hours per week of vigorous activity) were *75% less likely* than their unfit counterparts to develop the disorder. This was the first prospective study to show that low levels of leisure-time physical activity and aerobic fitness predict the development of the metabolic syndrome, even after adjustments for potential confounding variables (age, BMI, smoking habit, alcohol intake, socioeconomic status, and other coronary risk factors).

More recently, several investigators have examined the relationships among habitual physical activity, cardiorespiratory fitness, metabolic syndrome, and all-cause and cardiovascular mortality. Overall, these studies suggest that higher levels of daily physical activity and/or aerobic fitness are associated with a decreased clustering of risk factors that delineate the metabolic syndrome.[18-21] In one widely-cited report,[22] the age-adjusted cumulative odds ratio for abnormal markers of the metabolic syndrome was 3.0 for the least-fit men compared with moderately-fit ones, and 10.1 when compared with the most-fit men (Figure 3).

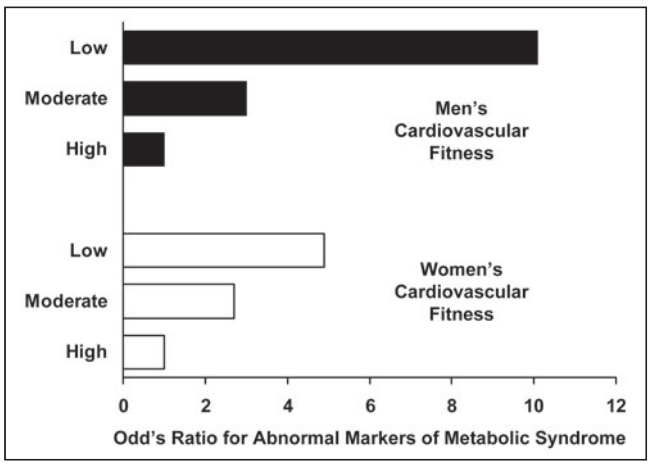

Figure 3. *Prevalence of metabolic syndrome in men and women decreases as cardiovascular fitness increases. Data adapted from Whaley MH, Kampert JB, Kohl HW 3rd, et al. Physical fitness and clustering of risk factors associated with the metabolic syndrome. Med Sci Sports Exerc 1999;31:287-93.*[22]

Among women, the age-adjusted cumulative odds ratio was 2.7 for the least-fit women when compared with moderately-fit ones, and 4.9 when compared with the most-fit women (Figure 3). Others have reported that higher levels of cardiorespiratory fitness are associated with a substantial reduction in health risk for a given level of visceral and subcutaneous fat,[23] and that fitness provides a strong protective effect against all-cause and cardiovascular mortality in men with the metabolic syndrome.[24,25] Accordingly, these data strongly support the role of structured exercise, regular physical activity, or both, as interventions designed to prevent and treat the metabolic syndrome.[26]

Exercise in the Prevention and Treatment of Diabetes

The worldwide prevalence of diabetes mellitus is skyrocketing and is projected to increase to roughly 300 million by the year 2025. Most (≥95%) of the new cases are a result of type 2 diabetes mellitus.[27] Obesity is strongly associated with the development of type 2 diabetes mellitus, and nearly 90% of individuals who have this metabolic condition have a BMI >25 kg/m^2, signifying overweight or obese.[28] The risk of developing type 2 diabetes has also been directly linked with increased sedentary time, specifically the hours of television viewed each week.[29] Other longitudinal epidemiologic studies in men[30] have now shown that those in the low-fitness group at baseline (the least 20% of the cohort) are at increased risk for developing impaired fasting glucose or diabetes as compared with their high-fit counterparts (the most fit 40% of the cohort).

To examine the relationships between cardiorespiratory fitness, BMI, and cardiovascular mortality in 2316 men with diabetes, but no history of stroke or myocardial infarction, Church et al[31] performed medical examinations on each, including a maximal exercise test between 1970 to 1997 with mortality surveillance through 1998. A significantly higher adjusted risk of mortality was observed in men with a low fitness level, regardless of whether they were normal weight, overweight, or obese. The investigators concluded that medical care providers should give

increased attention to counseling for increasing physical activity and improving fitness in their patients with diabetes, irrespective of their BMI. Lyerly et al[32] extended these analyses to a cohort at increased risk of cardiovascular disease, that is, middle-aged women (n=3044) with impaired fasting glucose or previously undiagnosed diabetes who underwent preventive medical examinations, including a maximal treadmill exercise test between 1971-2001. Patients were categorized into age-adjusted low (bottom 20%), moderate (next 40%), or high fitness (most fit 40%) groups. During a mean follow-up of 15.6 years, 171 deaths were recorded. There was an inverse association between cardiorespiratory fitness, expressed as METs, and all-cause mortality, even after adjusting for potential confounding variables. Death rates in overweight/obese unfit women (bottom 20%) were more than double those in fit women (moderate and high cardiorespiratory fitness) with BMIs ≥25 kg/m^2. In contrast, there was no association between overweight or obesity and overall deaths in this cohort of 'at risk' women.

Cardioprotective Effects of Endurance Exercise

Two meta-analyses[33,34] have now shown that regular exercise participation can decrease the overall risk of cardiovascular events by up to 50%, presumably from multiple mechanisms, including antiatherosclerotic, anti-ischemic, anti-arrhythmic, antithrombotic, and psychological effects (Figure 4). Because more than 40% of the risk reduction associated with exercise training cannot be explained by changes in risk factors, Green et al[35] proposed a cardioprotective "vascular conditioning" effect, including improved vascular reactivity, enhanced nitric oxide vasodilator function, altered vascular structure, or combinations thereof. Because sympathetic drive at rest is reduced and vagal tone is increased, decreased vulnerability to threatening ventricular arrhythmias has also been postulated to reflect training-induced adaptations in autonomic control. Recently, Kodama and associates[36] reported that each 1-MET increase in exercise capacity confers a 13% and 15% reduction in all-cause mortality and cardiovascular events, respectively.

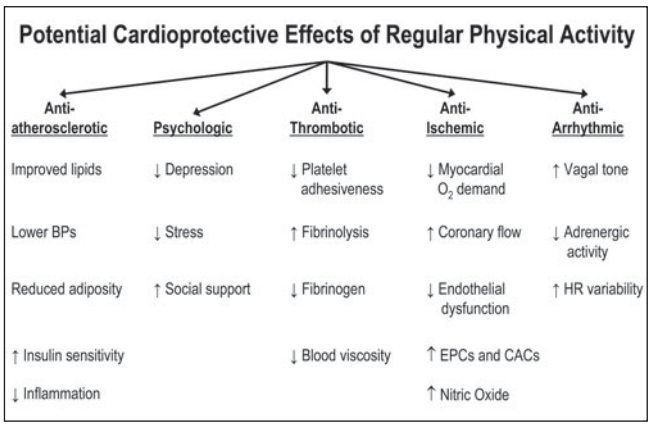

Figure 4. *Potential mechanisms underlying the role of moderate-to-vigorous physical activity in reducing the likelihood of initial or recurrent cardiovascular events. BP= blood pressure; CACs=cultured/circulating angiogenic cells; EPCs=endothelial progenitor cells; HR=heart rate; ↑ = increased; ↓ =decreased; O_2=oxygen.*

Summary and Conclusions

Lee et al[37] emphasized that obesity is an established risk factor for chronic disease, but losing weight and keeping it off is challenging, to say the least. Perhaps physicians and allied health professionals should focus less on weight loss and more on how to enhance and maintain health for people of varied body habitus. Collectively, the present review and other recent reports[38,39] support the hypothesis that cardiorespiratory fitness provides a strong, graded, inverse association with cardiovascular and all-cause mortality in normal weight, overweight, and obese men and women, with and without other co-morbid conditions (e.g., metabolic syndrome, impaired fasting glucose, diabetes mellitus). It appears that the least active, least fit, "high-risk" patient cohort (bottom 20%) may especially benefit from structured exercise, increased lifestyle physical activity, or both, to improve survival.[40]

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