Editorials

Survival of the Fittest — More Evidence

In 1859, Charles Darwin published his theory of evolution as an incessant struggle among individuals with different degrees of fitness within a species.[1] At that time, his explanations created remarkable controversy, but they were to revolutionize the course of science. Darwin's writings reflected conclusions drawn from years of study and observation. Now, nearly 150 years later, in the era of evidence-based medicine and rigorous scientific method, when fitness is measured and study subjects are followed for years, the data supporting the concept of survival of the fittest are strong and compelling. 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.

Cardiorespiratory fitness, or physical fitness, is a set of attributes that enables a person to perform physical activity.[2] It is determined, in part, by habitual physical activity and is also influenced by several other factors, including age, sex, heredity, and medical status.[2] Physical fitness is best assessed by a measure of maximal or peak oxygen uptake (volume of oxygen consumed, measured in milliliters of oxygen per kilogram of body weight per minute), which is viewed as an index of energy expenditure. Since the direct measurement of the volume of oxygen consumed requires specialized equipment and expertise, many large-scale studies estimate fitness levels by measurement of the duration of exercise, the peak exercise stage, or estimates of the peak energy expenditure (in metabolic equivalents [MET]) achieved during graded exercise-tolerance tests. One MET is defined as the oxygen uptake when a person is at rest, which is equivalent to 3.5 ml of oxygen per kilogram of body weight per minute.[3] The use of this measure has the advantage of providing a common assessment of fitness for use with various exercise protocols. Treadmill protocols are often used, since they are simple and do not require much skill, with the caveat that the excessive use of handrails for support reduces the work being performed and makes estimates of oxygen uptake unreliable.[4]

In this issue of the *Journal,* Myers et al.[5] provide more evidence regarding the relation between fitness and survival in their analysis of 6213 consecutive male patients (mean [±SD] age, 59±11 years) referred to a clinical exercise-testing laboratory. These data differ from large-cohort data drawn from population-based studies and data from subjects with a common medical condition in that the outcomes in subjects with cardiovascular disease are compared with the outcomes in subjects without cardiovascular disease within this large sample of men who were tested for clinical reasons by a single group of investigators. A total of 3679 men with coronary artery disease, heart failure, peripheral vascular disease, or an abnormal exercise test (angina, ST-segment depression, or both) were categorized as having cardiovascular disease; 2534 men were found not to have cardiovascular disease. The end point of death from any cause occurred in 1256 patients after a mean follow-up period of six years (average annual mortality, 2.6 percent).

After adjustment for age, Cox proportional-hazards analysis demonstrated that the peak estimated exercise capacity achieved during the exercise test was the strongest predictor of the risk of death among patients with cardiovascular disease and among those without cardiovascular disease. A nearly linear reduction in mortality was observed as fitness levels increased, and each increase of 1 MET in exercise capacity conferred a 12 percent improvement in survival. Notably, the risk of death among those with a peak exercise capacity of less than 5 MET was nearly double the risk among those with a peak exercise capacity of more than 8 MET. The relative risk for those in the lowest quintile of fitness was four times that of those in the highest quintile of fitness, both among those with cardiovascular disease and among those without cardiovascular disease.

According to subgroup analyses of patients with such cardiovascular risk factors as hypertension, diabetes, smoking, and obesity, those with an exercise capacity of less than 5 MET had a mortality rate that was about twice that among those with an exercise capacity of more than 8 MET. Since exercise capacity declines by approximately 10 percent per decade after 30 years of age,[6] the authors addressed the question of whether an evaluation of fitness relative to that expected for the patient's age was a better predictor of death than an absolute measure of fitness. They found that the absolute peak exercise capacity outperformed the percentage of age-predicted exercise capacity for both those with cardiovascular disease and those without cardiovascular disease. One might expect to find a difference between the risk of death predicted by the absolute level of fitness and the risk predicted by the age-related level among subjects older than 65 years of age because exercise capacity is generally lower in elderly persons. No difference was found, although the number of subjects over 65 in this cohort may have been too small to allow the investigators to detect a difference.

Since 24 percent of the subjects were taking beta-blocking drugs, this study provided an opportunity

to assess whether the use of these drugs affects the predictive power of measured exercise capacity. Several types of analyses were performed, and no interaction was found. Although this study was limited to men, there is no reason to believe that its conclusions cannot be applied to women, particularly since a previously published large cohort study demonstrated a similar relation between fitness and survival in both men and women.[7]

Thus, Myers et al. place valuable and readily applicable conclusions on the desk of the clinician. Absolute fitness levels as determined by an exercise test represent a continuum of risk — i.e., greater fitness results in longer survival. Fitness levels are important predictors of survival in persons with and without cardiovascular disease, as well as in those with specific cardiovascular risk factors, whether or not they are taking beta-blocking drugs.

The link between survival and fitness or physical activity, found in both large cohort studies and smaller studies of subjects with specific medical conditions, is convincingly presented in the 1996 Surgeon General's report on physical activity and health[2]; as a result of this report, the promotion of physical activity and improved physical fitness has become a part of our national public health agenda.[8] Although it seems obvious to conclude that healthier persons, who by their nature have higher levels of fitness, will live longer, a wealth of emerging data provides new and exciting insights into this relation. Encouraging data from patients with[9,10] and without[11,12] cardiovascular disease demonstrate that less fit or less active persons can improve their survival if they increase their level of fitness or physical activity. A program of regular exercise can improve fitness by 15 to 30 percent within three to six months.[13]

It is now becoming clear that exercise modulates many biologic mechanisms to confer cardioprotection. Exercise improves the lipid profile and glucose tolerance, reduces obesity, and lowers blood pressure.[3] However, modification of atherosclerotic risk factors does not fully explain the benefits that have been observed. Positive effects of exercise on vascular function, autonomic tone, blood coagulation,[3] and inflammation[14] are likely to contribute to improved cardiovascular health and survival. Accordingly, the Centers for Disease Control and Prevention,[15] the American Heart Association,[16] and the American College of Sports Medicine[15] recommend that all people adopt a physically active lifestyle and, specifically, that all adults engage in moderately intense physical activity for at least 30 minutes on most — and preferably all — days of the week.

Inherent in this recommendation are the dose (i.e., total energy expended per week) and the intensity (i.e., the energy requirements per unit of time for a given activity). Randomized, controlled prospective trials are needed to evaluate the effects of a variety of combinations of dose and intensity of activity on specific health outcomes, including cardiac events, both in a large cohort that is representative of the population and in specific groups (e.g., young persons, elderly persons, or patients with known cardiovascular disease). Indeed, the lowest threshold for a dose and an intensity that would confer specific survival and cardiovascular benefits is not known, nor is the ideal prescription for a dose and an intensity that would result in specific biologic outcomes or total cardiovascular health. But in the meantime, the data from the study by Myers et al. compel the clinician to go beyond the identification of risk to the initiation of interventions, such as the prescription of increased physical activity and exercise, in order to modify risk, particularly in patients with low levels of fitness.

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Childhood Obesity and a Diabetes Epidemic

CHILDHOOD obesity has reached epidemic proportions; worldwide, approximately 22 million children under five years of age are overweight.[1] During the past three decades, the number of overweight children in the Unites States has more than doubled. In 1983, 18.6 percent of preschool children in the United States were defined as overweight, and 8.5 percent were defined as obese; by 2000, 22.0 percent of preschool children were overweight and 10.0 percent were obese.[1] Data from the National Longitudinal Survey of Youth indicate that the prevalence of overweight has increased by 21.5 percent among non-Hispanic black children, 21.8 percent among Hispanic children, and 12.3 percent among non-Hispanic white children.[2] Similar increases in the prevalence of obesity have been observed worldwide.[3] Childhood obesity is the most serious and prevalent nutritional disorder in the United States.

Obesity has a substantial effect on cardiovascular risk. Childhood obesity is directly linked to abnormalities in blood-pressure, lipid, lipoprotein, and insulin levels in adults, as well as to the risk of both coronary artery disease and diabetes.[4] Becque and coworkers[5] evaluated the incidence of risk factors for coronary heart disease in a group of obese adolescents and documented that 80 percent had elevated systolic blood pressure, diastolic blood pressure, or both. Furthermore, they found that 97 percent had four or more of the following cardiovascular risk factors: elevated serum triglyceride levels (more than 100 mg per deciliter), low levels of high-density lipoprotein cholesterol (below the 10th percentile for age and sex), increased total cholesterol levels (more than 200 mg per deciliter), elevated systolic blood pressure, diastolic blood pressure, or both (above the 90th percentile for age and sex), diminished maximal oxygen consumption (less than 24 ml per kilogram of body weight per minute), and a strong history in the immediate family of coronary heart disease, myocardial infarction, angina pectoris, or high blood pressure.[5]

Obese children also have a higher prevalence of insulin resistance and type 2 diabetes. As the prevalence of childhood obesity increased between 1982 and 1994, the incidence of type 2 diabetes increased by nearly a factor of 10, according to one report from Cincinnati.[6] The authors of that report also observed that in 1996, one third of all new cases of diabetes in children 10 to 19 years of age could be classified as type 2, resulting in an age-specific incidence of 7.2 per 100,000 children per year.[6] Among Japanese schoolchildren, the incidence of type 2 diabetes increased from 0.2 to 7.3 per 100,000 children per year between 1976 and 1995[7] — an increase that was attributed to changing dietary patterns and increasing rates of obesity among these children. In some areas of Japan, type 2 diabetes has now become the dominant form of diabetes in children and adolescents.[8]

The study by Sinha et al.[9] in this issue of the *Journal* has for the first time determined the prevalence of impaired glucose tolerance in obese children, documenting impaired glucose tolerance in 25 percent of 55 obese children (4 to 10 years of age) and in 21 percent of 112 obese adolescents (11 to 18 years of age). In addition, clinically asymptomatic, or silent, type 2 diabetes was uncovered in 4 of the 112 obese adolescents (4 percent).

Besides documenting the high incidence of impaired glucose tolerance in severely obese children, Sinha and coworkers also demonstrated that insulin resistance and fasting hyperproinsulinemia were the most important predictors of impaired glucose tolerance. Neither the degree of obesity nor a family history of diabetes was a significant risk factor for glucose intolerance. However, Sinha and coworkers studied only children who were markedly obese. All the children they studied had a body-mass index (the weight in kilograms divided by the square of the height in meters) above the 95th percentile for age and sex (a body-mass index of more than 29 for children and more than 35 for adolescents). In contrast, Sinaiko et al.[10] have shown that, in adolescents, there is a significant correlation between the body-mass index and the degree of insulin resistance as measured by the hyperinsulinemic–euglycemic clamp technique. In the Sinaiko study, body-mass index ranged from 14 to 42. Since Sinha and coworkers studied a group of severely obese children and adolescents, it is possible that if their study group had included subjects with a broader range of adiposity, other factors might have predicted the presence of impaired glucose tolerance.

Finally, Sinha and coworkers performed a second glucose-tolerance test in several subjects to confirm the diagnosis of impaired glucose tolerance. They also demonstrated, in two of three subjects who were followed for two to five years, that impaired glucose tolerance progressed to frank diabetes.

Epidemiologic evidence from the past 20 years has demonstrated that the increasing incidence of type 2