Fat or Fit: What Is More Important?

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The prevalence of obesity is increasing worldwide, and obesity represents one of the major health hazards (1). Obesity was shown to be linked to an increased mortality and morbidity. However, obesity is often associated with modifications of physical activity level. Physical activity level itself affects the health status of the individual and thus may be a confounding variable in the obesity-mortality/morbidity relationship. Understanding the role of physical activity in the development of obesity-associated health hazards appears crucial for effective treatment of obesity and prevention of its complications.

ADIPOSITY AND MORTALITY/MORBIDITY

A large number of prospective studies have paid attention to the relationship between adiposity (i.e., degree of overweight/obesity) and mortality or morbidity. In the classic Framingham Heart Study (2), the degree of obesity predicted the incidence of cardiovascular disease. In the Harvard Alumni Health Study (3), men with the highest BMI (>26.0 kg/m^2) had the highest risk of mortality. The Nurses Health Study (4) shows the lowest all-cause mortality and morbidity rates in subjects with the lowest BMI. The British Regional Heart Study (5) found an elevated all-cause mortality in men with BMI <20 and >30 kg/m^2. A German study in obese subjects did show an elevated risk of all-cause mortality in obese subjects when compared with individuals with the lowest BMI, but, interestingly, did not find a difference in mortality rates between grossly obese ($32 < \text{BMI} < 40$ kg/m^2) and overweight/moderately obese ($25 < \text{BMI} < 32$ kg/m^2) patients (6). Abdominal fat distribution characterized by a higher waist-to-hip and waist-to-thigh ratio increases the risk of mortality not only among obese (BMI ≥30.0 kg/m^2), but also among normal-weight (BMI 18.5–24.9 kg/m^2) young and middle-aged adults (7). Measures of abdominal adiposity strongly and positively predict mortality, independent of BMI, among both white and black adults (8). The EPIC (European Prospective Investigation into Cancer and Nutrition) study recently showed that both general and abdominal adiposity are associated with the risk of death in the European population (9). Measures of abdominal obesity (waist circumference and waist-to-hip ratio) remained strongly associated with mortality after adjustment for BMI (9).

PHYSICAL ACTIVITY AND MORTALITY

Some of the studies cited in the preceding paragraph, as well as many other studies dealing with the relationship between adiposity and mortality/morbidity, did not take into account a possible confounding role of physical activity in this relationship. A number of studies demonstrated that physical activity is independently related to mortality rates (10–13).

The beneficial effect of physical activity on mortality has been recently confirmed in the National Institutes of Health, American Association of Retired Persons Diet and Health Study, which included 252,925 men and women (10). Individuals adhering to the national physical activity guidelines exhibited a lower risk of death than those who were inactive. Subjects meeting the recommendations for moderate activity (at least 30 min on most days of the week) decreased mortality risk by 27%, whereas in those who met recommendations for vigorous activity (at least 20 min, three times per week), a reduction of mortality by 32% was demonstrated.

The study of Manini et al. (11) revealed that free-living physical activity calculated from objective measurements (total energy expenditure assessed by doubly labeled water and resting metabolic rate measured by indirect calorimetry) was strongly associated with lower risk of all-cause mortality in older adults followed up for 6 years. It was shown that free-living activity that expends ~287 kcal/day reduced the risk of mortality by 30% (8).

Leisure-time physical activity was associated with a decrease of all-cause and cardiovascular disease mortality in a study of Finnish men with 10 years of follow-up (12).

A cause-effect relationship between physical activity level and mortality was demonstrated by a prospective study in Harvard College Alumni (13). Physical activity levels were assessed twice during a time interval of 11–15 years, and the observed change was related to mortality. Men who increased their physical activity (by 1,250 kcal/week) had a lower risk of dying when compared with those who remained stable and those who decreased their physical activity (by 24 and 43%, respectively).

CARDIORESPIRATORY FITNESS VERSUS PHYSICAL ACTIVITY

Assessment of physical activity by self-reported questionnaires is subject to recall bias. Obese patients often overestimate their total amount of exercise (14). In addition, physical activity questionnaires do not take into account free-living physical activity due to standing, moving around, and fidgeting. Methods for quantitative assessment of energy expenditure associated with physical activity are available: *1*) the technique of double-labeled water; *2*) indirect calorimetry measurements; and *3*) semi-quantitative assessment with accelerometers. However, their use in large-scale studies is limited because of their cost and methodology. In contrast to problems with physical activity estimation, the assessment of cardiorespiratory fitness (CRF) is an objective and reproducible laboratory measurement.

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Table 1—*Changes in physical fitness and all-cause and cardiovascular mortality in men*

	All-cause mortality	Cardiovascular mortality*
Never fit	122	65
Improved from unfit to fit	68	31
Always fit	40	14

n = 9,777. From Blair et al. (16). *Mortality is expressed per 10,000 person-years.

Although CRF is influenced by age, sex, health status, and genetics, the principal modifiable determinant is habitual physical activity level. Thus, CRF reflects recent physical activity patterns, and it may better reflect the adverse consequences of a sedentary lifestyle than do the self-reporting methods evaluating physical activity.

CRF AND MORTALITY— Blair et al. (15) analyzed cardiovascular and all-cause mortality relative risk (RR) for low- (least fit 20%), moderate- (next 40%), and high-level (most fit 40%) fitness categories by strata according to smoking habit, cholesterol level, blood pressure, and health status. A total of 25,341 men and 7,080 women underwent a complete preventive medical examination that included a maximal exercise test. Independent predictors of mortality among men were low fitness (RR 1.52), smoking (RR 1.65), abnormal electrocardiogram (RR 1.64), chronic illness (RR 1.63), increased cholesterol level (RR 1.34), and elevated systolic blood pressure (RR 1.34). In women, only low fitness (RR 2.10) and smoking (RR 1.99) remained significant independent predictors of mortality. The reason why only these two factors predicted death rate in the cohort of women remain to be elucidated.

PROSPECTIVE STUDIES ON THE EFFECT OF CHANGES IN PHYSICAL FITNESS WITH RESPECT TO ALL-CAUSE AND CARDIOVASCULAR MORTALITY— While in Blair's original study, mortality was related to the CRF assessed at the beginning of the follow-up period, the cause-effect relationship between these two variables was demonstrated more strongly by a prospective study with two fitness assessments of 9,777 men (16). The mean interval between the examinations was 4.9 years and the effect of change (or lack of change) in physical fitness during the follow-up period on mortality was evaluated. As presented in Table 1, the highest age-adjusted all-cause and cardiovascular death rate was observed in men who were unfit at both examinations, whereas men who were fit on both occasions exhibited the lowest mortality rate. In men who improved from unfit to fit, all-cause mortality risk was reduced by 44% and cardiovascular mortality by 52% relative to those who remained unfit at both examinations.

CRF AND MORBIDITY— Low levels of physical activity and CRF are associated with the development of the metabolic syndrome. In a recent study, Hassinen et al. (17) demonstrated that older men and women who were in the lowest sex-specific third of $V_{O_{2max}}$ had a 10-fold higher risk for developing the metabolic syndrome than those who were in the highest third. This study revealed a strong inverse graded association of the CRF with the metabolic syndrome as well as a significant relationship between $V_{O_{2max}}$ and all the components of the metabolic syndrome, as defined by the National Cholesterol Education Program criteria. Therefore, the authors even suggested to include low CRF into the components of the metabolic syndrome.

A low CRF level was found to be an important risk factor for incidence of type 2 diabetes in a study of Japanese men with 14 years of follow-up: the men in the highest quartile of fitness had a relative risk of diabetes that was four times higher when compared with those in the lowest quartile (18).

Other protective effects of CRF

An inverse association between CRF and the development of incident prostate cancer has been demonstrated (19). Being fit was associated with a lower mortality risk from lung cancer and cancers of the gastrointestinal tract in men with diabetes and pre-diabetes (20). Engagement in physical exercise, independent of intensity, was associated with a diminished risk of colorectal cancer, mainly in men (21). CRF reduces the risk of gout in physically active men (22). Two forms of physical activity, namely stair-climbing and brisk walking, were associated with increased bone mineral density at the hip and whole body in postmenopausal women (23). Both are forms of activity that can feasibly be promoted among middle-aged women. Improvements in CRF have positive effects on anxiety, depression, mood status, and self-esteem and are related to higher academic performance (24).

CRF AND/OR PHYSICAL ACTIVITY IN PREDICTION OF MORBIDITY/ MORTALITY— A recent mini-review underscores that both physical activity and CRF are separately and independently associated with metabolic risk profile in children and adolescents (25). Ekelund et al. (26) demonstrated that energy expenditure associated with physical activity predicts a progression toward metabolic syndrome independently from aerobic fitness, obesity, and other confounding factors. In the study of Wei et al. (27), both low CRF and physical inactivity were shown as independent predictors of all-cause mortality in men with type 2 diabetes during an average follow-up of 12 years.

However, in a number of other studies, the positive health effects of physical activity varied as a function of the subjects' CRF, i.e., an interaction between these two variables may be discerned (28). Thus, the inverse association between physical activity and components of the metabolic syndrome that was demonstrated in the European Youth Heart Study was stronger in subjects with low CRF than in fit individuals (29). Similarly, a recent report from the same study confirmed the interaction between CRF and physical activity: the time spent performing vigorous physical activity in low-level fitness children was inversely related to waist circumference, while, surprisingly, in the group with the high level of fitness, the association was positive (30).

Genetic determinants of physical activity and CRF

Heredity plays a marked role in an individual's CRF as well as in the amount of actually performed physical activity. Sedentary individuals with favorable genetic predispositions may demonstrate good performance in treadmill tests (31). According to the HERITAGE Family Study, trainability of $V_{O_{2max}}$ is highly familial and is controlled by a significant genetic component (32). The HERITAGE study also revealed that submaximal working capacity and its response to endurance training are greatly influenced by familial/genetic factors with a predominant contribution from maternal inheritance (33).

RELATIVE IMPACT OF PHYSICAL ACTIVITY/CRF AND ADIPOSITY ON MORTALITY

RELATIVE IMPACT OF PHYSICAL ACTIVITY/CRF AND ADIPOSITY ON MORTALITY— Data demonstrating that fitness can diminish the impact of obesity on morbidity and mortality is of great importance, not only for the development of preventive programs to aid public health, but also for weight maintenance strategies in obesity management. If higher levels of fitness can reduce morbidity and mortality in obese patients, increasing fitness would be an efficient approach with which to address particularly obese subjects who are unable to maintain weight loss in response to weight management.

A large quantity of data on the impact of CRF on the adiposity-mortality relation has been derived from a prospective Aerobic Center Longitudinal Study. The study was carried out with >80,000 individuals over a period of 35 years. The baseline examination included (besides anthropometric and laboratory examinations) treadmill maximal exercise testing. Several studies based on this cohort addressed both the independent and combined effects of fatness and fitness on death rate. These studies demonstrated that low fitness resulted in a greater risk of mortality than fatness, whereas fitness diminished the impact of fatness on mortality.

In the initial study published by Blair et al. (34), the mortality rate over a 5-year period was inversely related to the fitness level. In this study, subjects were stratified into five levels of fitness according to the maximal exercise test results. The greatest decline in the mortality rate was observed when individuals with very low fitness (level 1) were compared with those who exhibited modest levels of physical fitness (level 2). With such a modest increase in fitness, the risk ratio for death declined from 3.44 to 1.37 in men, and from 4.65 to 2.42 in women.

In a later analysis of the Aerobic Center Longitudinal Study (35), which involved 21,925 men aged 30–83 years old followed for 8 years, mortality was assessed in fit versus unfit men in each of the three body fatness BMI categories (19.0 to <25.0, 25.0 to <27.8, ≥27.8). Unfit men had a significantly higher relative risk for all-cause mortality than their fit counterparts in each BMI category (Table 2). Importantly, relative risk for all-cause mortality is lower in fat but fit men when compared with lean but unfit men. This is the crucial finding of the study cited often as "being fat and fit is better than unfat and unfit." The finding suggests that the hazardous health effects of adiposity may be counterbalanced by an improvement of CRF.

Table 2—*Relative risk of all-cause mortality by cardiorespiratory fitness levels in men*

Fitness	BMI (kg/m^2)	Multivariate RR of death*
Fit	19.0 to <25.0	1.00
Unfit	19.0 to <25.0	2.25
Fit	25.0 to <27.8	0.96
Unfit	25.0 to <27.8	1.68
Fit	≥27.8	1.08
Unfit	≥27.8	2.24

n = 21,586. From Lee et al. (35). *Adjusted for age, examination year, smoking habit, and alcohol intake.

The results were partially different in the Lipid Research Clinics Study that was performed during 1972–1998 and involved 2,506 women and 2,860 men in the data analysis (36). Fitness and fatness were both associated with mortality from all causes and from cardiovascular disease. Fatness was defined as the highest quintile of BMI, i.e., BMI >27.7 kg/m^2. For all-cause mortality, the adjusted RRs were 1.32 among the fit and fat, 1.30 among the unfit and nonfat, and 1.57 among the unfit and fat women compared with fit and nonfat women (RR 1.00). Among men, the RRs were 1.44 for the fit and fat, 1.25 for the unfit and nonfat, and 1.49 for unfit and fat. The authors conclude that both fitness and fatness are risk factors for mortality and that being fit does not completely reverse the increased risk associated with increased adiposity. Reported differences in relative impact of fitness and fatness on mortality in these two studies may be due to different characteristics of both cohorts and to differences in statistical analysis. The Aerobic Center Longitudinal Study included 95% Caucasians and 80% were college graduates, whereas the Lipid Research Clinics Study was drawn from more diverse groups.

In the huge Nurses' Health Study, both increased adiposity and decreased physical activity were strong and independent predictors of death (37). Relative risks of death from any cause were 1.55 for lean and inactive women, 1.91 for obese and active, and 2.42 for inactive and obese women, compared with lean and active females. Relative risks of death from cardiovascular disease were 1.89 for lean and inactive women, 2.87 for those who were obese and active, and 4.73 for obese and inactive females. The study also demonstrated that even modest weight gain during adulthood, independent of physical activity level, was associated with increased mortality. The strength of the study is based on both the large cohort (116,564 women) and long-term follow-up (24 years). However, the limitations of the study concerned ethnicity (primarily Caucasians), sex (only women), socioeconomic status (registered nurses), and, also, self-reported body weight that was used for BMI calculation and an evaluation of physical activity with a questionnaire (no CRF measurement).

To evaluate the potential impact of the intensity of physical activity, the Harvard Alumni Health Study investigated association between the intensity of physical activity (evaluated by questionnaires) and mortality rates in men who were subjects of the study for over 15 years (38). The study revealed that light activities were not associated with reduced mortality rates and that only vigorous activities clearly predicted lower mortality rates. The interaction between physical activity and adiposity in prediction of mortality was evaluated in a multivariate analysis. As expected, inactive and overweight men exhibited the highest mortality rate, and active and normal-weight individuals enjoyed the lowest mortality rate. No significant difference in mortality rate was observed between men who were inactive and of normal weight and men who were active and overweight.

PHYSICAL ACTIVITY/FITNESS VERSUS ADIPOSITY AND CARDIOMETABOLIC RISK— The DR's EXTRA Study demonstrated that waist circumference—a core component of metabolic syndrome—markedly weakened the association between CRF and metabolic syndrome (17). Association of adiposity with metabolic risks independent of aerobic fitness was confirmed in a cross-sectional study of Christou et al. (39). BMI, percent body fat, and waist circumference were consistently associated with all metabolic risk factors after partialling out the effects of aerobic fitness and age.

In a population-based sample of 176 men and 217 women selected from the Medical Research Council Ely Study, an increase in physical activity energy expenditure over a period of 5.6 years was associated with reduced metabolic risk independent of change in fatness and fitness (26). However, this study confirmed a strong association between the changes in fat mass or waist circumference with respect to changes of multiple metabolic risk factors even after adjustment for changes in physical activity energy expenditure and aerobic fitness. Lee et al. (40) demonstrated that high levels of CRF in healthy men are associated with a substantial reduction in cardiometabolic health risk for a given level of both visceral and subcutaneous fat.

Many up-to-now published studies evaluating the effect of fitness versus fatness on mortality/morbidity characterized adiposity by simple anthropometric measures as BMI and/or waist circumference. However, the recent meta-analysis of studies on the relationship between physical activity and abdominal fat using imaging techniques revealed that reductions in visceral and total abdominal fat may occur in the absence of changes in BMI and waist circumference (41). Thus, insensitivity of anthropometric indexes to reflect actual amounts of visceral fat may contribute to overestimating the role of fitness in relation to fatness in their effect on cardiometabolic risks.

Both low physical activity and high BMI are independently associated with lipid and inflammatory biomarkers in women (42). High BMI exhibited associations with these biomarkers, which were stronger than low physical activity. However, even a modest level of physical activity (2.5 h of modest physical activity per week, which represents energy expenditure of 1,000 kcal/week) was associated with a more favorable biomarker profile in both normal and overweight/obese women. However, the recent study of Kullo et al. (43) demonstrated that CRF (measured as VO_{2max}) as well is inversely related to inflammatory markers, even after adjustment for age, physical activity level, BMI, and other potential confounding factors. The European Youth Heart Study revealed that in prepubertal children, low-grade inflammatory markers were negatively associated with cardiovascular fitness and positively associated with fatness (44). In agreement with previous findings in adults (42), the influence of fatness on inflammatory markers was slightly higher than that of cardiovascular fitness.

ADIPOSITY VERSUS PHYSICAL ACTIVITY/ FITNESS AND CANCER RISKS— CRF reduced cancer mortality risk in men, independently of adiposity measurements, such as BMI, waist circumference, and percent body fat (45). The Lipid Research Clinics Prevalence Study compared the effect of CRF and obesity in all-cause cancer mortality in men and women. A high level of fitness was a stronger predictor of cancer mortality in men, whereas high BMI was a stronger predictor of cancer mortality in women (46). The essential role of BMI in cancer prediction in women may be associated with increased estrogen production in enlarged fat stores that is not modified by physical activity level.

HOW SHOULD PHYSICAL ACTIVITY BE PRESCRIBED?— Results of the studies mentioned above suggest that regular physical activity has independent efficacy (at least partially) in counteracting obesity-related health risks. Physical activity when used in primary prevention of metabolic and cardiovascular risks should be recommended in terms of character, intensity, duration, maintenance, and frequency. Recent recommendations (47–49) suggest that energy expenditure >1,000 kcal/week may already produce beneficial health effects. This is reflected by the recommendations of at least 30 min of physical activity of moderate intensity on most days of the week. An alternative may be 20 min of vigorous physical activity three times per week. Moderate-intensity exercise seems to be associated with a significantly better adherence than high-intensity exercise (50), and this form of exercise should therefore be recommended, particularly to physically inactive individuals. Exercise advice should be individually tailored to the patient's abilities and health. Prescribing exercise for diabetic patients should take into consideration the presence of complications to optimize the choice of exercise and minimize potential risks to the patient (51). Recently, Healy et al. (52) suggested that the public health recommendations on physical activity should include a longer break period during sedentary time (primarily sitting), since this could be associated with reduced metabolic health risks.

SUMMARY— Since the classic Framingham study was published, many other studies have confirmed its conclusion, i.e., that increased adiposity is associated with increased mortality and morbidity. During recent decades, large studies have also provided evidence that subjects with an increased level of physical activity and/or CRF have lower all-cause mortality and a lower risk of cardiovascular and metabolic diseases and certain cancers. Although regular physical activity contributes to the reduction of adiposity, many beneficial health effects from physical activity are independent from its effect on adiposity. Moreover, a number of studies suggest that physical activity may counterbalance the hazardous health effects of increased adiposity. This suggests that that improvement of CRF in an obese patient might improve his or her health perspective even if the patient remains obese. This conclusion provides a framework for large promotion programs for physical activities designed and targeted for obese patients. It should be noted, however, that the ability to perform physical activity is limited in patients with higher degrees of obesity. Finally, the question whether fat or fit is more important might tend toward fitness but one should take into account that an interaction of both determinants is always present and therefore the individual impact is hard to predict.

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