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SPECIAL ARTICLE

Less Sitting, More Physical Activity, or Higher Fitness?

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Abstract

Epidemiological studies have found that time spent in sedentary behaviors, levels of physical activity, and cardiorespiratory fitness are all associated with mortality rates. They are also related to the risks of obesity, type 2 diabetes mellitus, hypertension, cardiovascular disease, aging-associated frailty, and cancer. The evidence is such that the National Institutes of Health recently launched a new Common Fund initiative aimed at identifying the molecular transducers of adaptation to physical activity in various tissues and organs. It has been estimated that 9.4% of all 57 million deaths in the world in 2008 could be attributed to physical inactivity, which translates into more than 5 million deaths worldwide. Physical inactivity has a deleterious effect that is comparable to smoking and obesity. Importantly, this global estimate relates to levels of physical activity and does not take into account sedentary behavior and cardiorespiratory fitness. Currently, there are national and international guidelines for physical activity level that are highly concordant. The weekly recommendations include 150 minutes of moderate-intensity activity, 75 minutes of vigorous-intensity activity, or some combination of moderate and vigorous activity with 2 days of resistance exercise. However, these guidelines offer no recommendations regarding sedentary time or goals for cardiorespiratory fitness levels. It will be increasingly important for disease prevention, successful aging, and reduction of premature mortality to broaden the focus of the public health message to include not only more physical activity but also less sitting and higher cardiorespiratory fitness. We briefly review the evidence and discuss key issues to be addressed to make this approach a reality.

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Epidemiological studies have found that time spent in sedentary behaviors, level of physical activity, and cardiorespiratory fitness are all associated with mortality rates. Other studies have revealed that they are also related to the risks of obesity, type 2 diabetes mellitus, hypertension, cardiovascular disease, aging-associated frailty, and cancer. These observations are complemented by multiple experimental studies and controlled interventions. The evidence is such that the National Institutes of Health (NIH) recently launched a new Common Fund initiative aimed at identifying the molecular transducers of adaptation to physical activity in various tissues and organs.[1]

It has been estimated that 9.4% of all 57 million deaths in the world in 2008 could be attributed to physical inactivity, which translates into more than 5 million deaths worldwide.[2] Physical inactivity has a deleterious effect that is comparable to smoking and obesity.[2] If only deaths from noncommunicable diseases were considered, the proportion of deaths attributable to physical inactivity is appreciably higher. This is an issue of great importance because there were 36 million deaths due to noncommunicable diseases (63% of all deaths) in 2008, and this number will increase to 55 million by 2030.[3]

Importantly, these global estimates relate to levels of physical activity, and they do not take into account sedentary behavior and cardiorespiratory fitness. Currently, there are national and international guidelines for physical activity level that are highly concordant .[4,5] The weekly recommendations include 150 minutes of moderate-intensity activity, 75 minutes of vigorous-intensity activity, or some combination of moderate and vigorous activity with 2 days of resistance exercise. However, they offer no recommendations regarding sedentary time or goals for cardiorespiratory fitness levels. We speculate that it will be increasingly important for disease prevention, successful aging, and reduction of premature mortality to broaden the focus of the public health message to include less sitting, more physical activity, and higher cardiorespiratory fitness. We briefly review the

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evidence and discuss key issues to be addressed to make this approach a reality.

SITTING AND ALL-CAUSE MORTALITY

The independent role of sedentary behavior as a risk factor for poor health and premature mortality has received considerable attention in recent years.[6,7] Sedentary behavior has been defined as any waking behavior characterized by an energy expenditure that is less than or equal to 1.5 times the resting metabolic rate while in a sitting or reclining posture.[8] It has been operationalized in several ways in scientific studies, including the use of television viewing as a marker of sedentary time,[9] time spent at low counts on an accelerometer (ie, <100 counts per minute),[10] or self-reported time spent sitting.[11] Sedentary time has been differentiated from physical inactivity per se in that physical inactivity (or insufficient physical activity) represents the lack of attaining physical activity recommendations (ie, 150 min/wk of moderate-intensity activity or 75 min/wk of vigorous-intensity activity) rather than participating in sedentary behaviors such as sitting or reclining.[12] It is possible that an individual can be considered physically active by meeting the guidelines yet also engage in several hours of sedentary behavior.[13]

The term *sedentary* is derived from the Latin word *sedere*, which literally means "to sit."[14] The first study that comprehensively examined sitting as an independent risk factor for mortality was based on analyses of mortality rates in the Canada Fitness Survey follow-up study.[15] The results revealed a significant positive dose-response association between daily sitting and mortality from all causes as well as from cardiovascular diseases. The dose-response association was observed after stratification by sex, smoking status, body mass index (BMI) category, and physical activity level. A recent meta-analysis of time spent sitting and all-cause mortality in 6 prospective studies reported a 34% higher risk among adults sitting more than 10 h/d compared with 1 h/d, after adjustment for physical activity.[11] Further, the dose-response association was nonlinear, with hazard ratios (HRs) of 1.00 (95% CI, 0.98-1.03), 1.02 (95% CI, 0.99-1.05), and 1.05 (95% CI, 1.02-1.08) for every 1-hour increase in sitting time in intervals between 0 to 3, 4 to 7, and more than 7 h/d total sitting, respectively, after adjustment for physical activity.[11]

Most studies to date have reported independent effects of sitting by statistically adjusting for level of physical activity and/or stratifying the sample into those who are meeting or not meeting physical activity recommendations. Overall, the results indicate that sitting may be an independent risk factor; however, the results also suggest that the relative risks of sitting are more pronounced in people who are not meeting physical activity guidelines (insufficiently active). The results of a recent meta-analysis revealed that the effect of sedentary time on all-cause mortality was greater among those with low levels of physical activity (HR, 1.46; 95% CI, 1.22-1.75) compared with those with high levels of physical activity (HR, 1.16; 95% CI, 0.84-1.59).[6]

Although there is evidence that greater sedentary time is associated with an increased risk of all-cause mortality, research is needed on the dose-response associations between sedentary behavior and health outcomes and the effects of interventions to reduce sedentary behavior. At the present time, we do not know the threshold of sedentary behavior for health outcomes, and we also do not know the effects of replacing sedentary behavior with other activities such as standing, walking, or moderate to vigorous activity. Further information on both of these issues will be important to inform public health recommendations related to sedentary behavior, and more research is required using novel epidemiological analytical approaches such as compositional analysis and isotemporal substitution analysis, as well as carefully conducted intervention studies.

PHYSICAL ACTIVITY AND ALL-CAUSE MORTALITY

The role of physical activity in the prevention of chronic disease and premature mortality is well established.[2] More than 50 years of systematic epidemiological and intervention research contributed to the development of the *2008 Physical Activity Guidelines for Americans*,[4] which call for 150 minutes of moderate activity, 75 minutes of vigorous activity, or some combination of moderate and vigorous activity. Similar guidelines have been promoted by other countries and by the World Health Organization.[5]

The seminal studies of Morris et al[16] on physical activity and coronary heart disease

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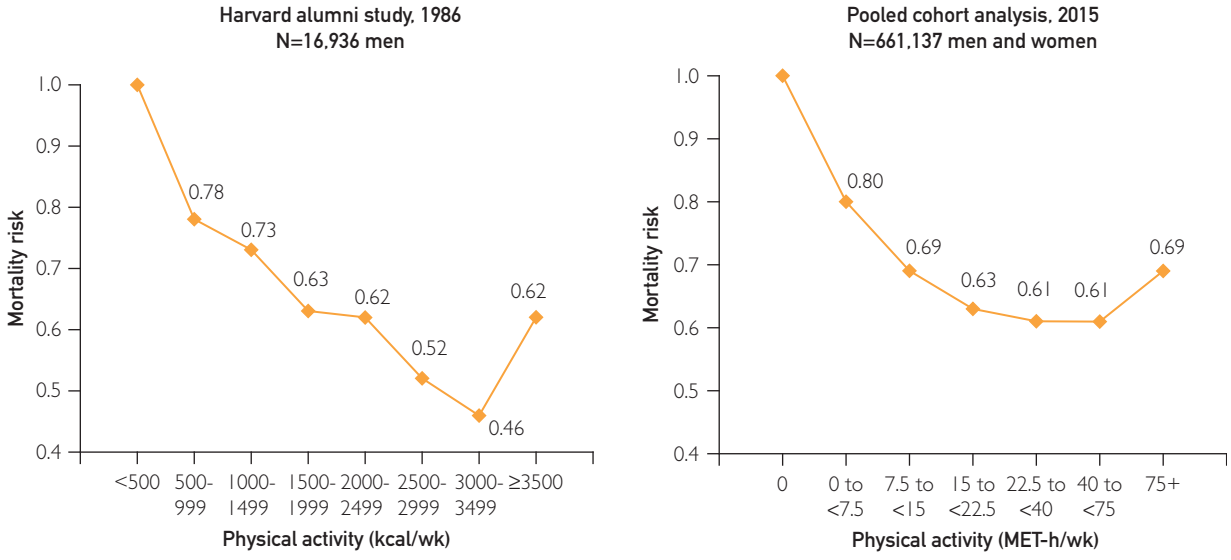

FIGURE 1. Relative risks for all-cause mortality associated with levels of physical activity among 16,936 men from the Harvard Alumni Study followed up for 12 to 16 years[19] and a pooled analysis of 661,137 men and women from 6 cohort studies followed up for a median of 14.2 years.[21] MET-h/wk = metabolic equivalent of task-hours per week.

incidence and mortality in London Transport workers and British civil servants marked the beginning of the modern era of physical activity epidemiology.[17] These studies were followed by a series of investigations conducted by Paffenbarger et al on the effects of occupational (San Francisco longshoremen)[18] and leisure-time physical activity (Harvard alumni).[19] These early studies identified physical inactivity as a powerful independent predictor of mortality from heart disease and from all causes.[20] A recent pooled-cohort analysis of 6 prospective studies including 661,137 participants aged 21 to 90 years revealed a dose-response association between leisure-time physical activity and all-cause mortality.[21] Meeting the 2008 physical activity recommendations for Americans was associated with significant reduction in mortality risk, and the dose-response association between physical activity and mortality mirrored findings in earlier reports, including results from the Harvard Alumni Study (Figure 1).

Of particular interest is the degree to which the effects of physical activity are independent of other risk factors. For example, the inclusion of a marker of obesity as a covariate has a minimal influence on estimates of risk associated with physical inactivity, and stratified analyses reveal significant protective effects of physical activity at all levels of body weight.[22] Further, results from the Harvard Alumni Study indicated significant linear trends for all-cause mortality across levels of physical activity irrespective of smoking status, levels of high blood pressure, and BMI.[19] Thus, the beneficial effects of physical activity for the reduction of all-cause mortality risk appear to be robust and largely independent of the presence of other risk factors.

CARDIORESPIRATORY FITNESS AND ALL-CAUSE MORTALITY

The first studies on cardiorespiratory fitness and mortality were published more than 30 years ago.[23] Cardiorespiratory fitness is defined here as either maximal oxygen uptake or maximal work capacity and is measured typically with a treadmill or cycle ergometer test. Cardiorespiratory fitness can also be estimated by submaximal exercise tests. The first study to use maximal exercise tests with all-cause mortality as the outcome was published in 1989.[24] The results revealed that low cardiorespiratory fitness, defined as the least fit 20% in each age/sex group, had adjusted relative risks and attributable fractions comparable to those for smoking, hypercholesterolemia, hypertension, family history of coronary heart disease, BMI, and elevated serum glucose level.

These early observations were confirmed by a meta-analysis of 33 eligible studies with a total of 102,980 participants.[25]

Furthermore, changes in fitness were associated with mortality during follow-up in a study of 9777 men who had 2 maximal exercise tests.[26] The mean interval between tests was 4.9 years, and there was an average of 5.1 years of follow-up after the last test, during which time there were 223 deaths. Men who were unfit at both examinations had an age-adjusted all-cause death rate of 122.0 per 10,000 man-years of follow-up, and men who improved from unfit at the first examination to fit at the final examination had an age-adjusted death rate of 67.7 per 10,000 person-years, and this pattern was observed in all age groups.

All-cause mortality was determined in a population of more than 40,000 women and men who provided self-reports of their physical activity and completed a maximal exercise test at a baseline examination and were then followed up for more than 12 years.[27] Physical inactivity was not associated with mortality in models including cardiorespiratory fitness, but low fitness was a significant mortality predictor after controlling for physical inactivity. Fit individuals had more than 35% lower odds of mortality after adjusting for inactivity and other major risk factors.

INTRINSIC AND ACQUIRED CARDIORESPIRATORY FITNESS

Low cardiorespiratory fitness is a powerful predictor of health problems and premature death. To better understand the public health implications of this observation, one would need to untangle the intrinsic and acquired components of cardiorespiratory fitness at the individual level. The intrinsic level of cardiorespiratory fitness can be measured by testing for maximal oxygen uptake adjusted for body mass in a person who has a life history of being sedentary with no history of exercise training or sports participation. For instance, among 174 sedentary young adult males (17-35 years of age) in whom maxmal oxygen uptake ($\dot{V}O_{2max}$) was measured twice (on separate days) at baseline in the HERITAGE (Health, Risk Factors, Exercise Training and Genetics) Family Study,[28] the mean value was 41 mL of oxygen per kilogram of body weight per minute with an SD of 8 mL of oxygen. The distribution of $\dot{V}O_{2max}$ scores was almost perfectly Gaussian, which implies that about 7% of the participants had a $\dot{V}O_{2max}$ of 29 mL/kg or less (1.5 SD below the mean) and the same percentage exhibited a level of about 53 mL/kg or higher, an extraordinary degree of heterogeneity among people who were confirmed as sedentary with no substantial amount of exercise training in their past.

Cardiorespiratory fitness can be improved in most people by regular physical activity of moderate to high intensity.[28,29] To illustrate this point, the same 174 young adult males from the HERITAGE Family Study[28] were trained for 20 weeks with perfect adherence to the exercise training protocol. The gain in $\dot{V}O_{2max}$ (expressed as percentage of the baseline measurement) was 16% (SD, 9%), with a distribution of scores clearly skewed to the right, ie, skewed in the direction of the high gainers or the most highly responsive to the same exercise prescription. A substantial fraction increased cardiorespiratory fitness by 40% or more, whereas a large number gained 10% or less. The gains expressed in percentage of pretraining baseline level (percentage $\dot{V}O_{2max}$ gain) are the same on average in men and women and do not vary across age groups.[28,30,31] The intrinsic cardiorespiratory fitness level adjusted for age, sex, BMI, and body composition is characterized by a heritability component of the order of 50%.[32] Similarly, the ability to improve $\dot{V}O_{2max}$, expressed in terms of gains in milliliters of oxygen, has a heritability level of about 45%.[28] Interestingly, there is no correlation between baseline, intrinsic fitness level, and its response to regular exercise, with an r^2 ($\times 100$) of the order of 1%.[28] In other words, intrinsic cardiorespiratory fitness is independent of its responsiveness to regular physical activity.

These observations raise many questions that urgently need to be addressed for proper public health messaging. For instance, can we find a simple and reliable way of distinguishing between individuals with intrinsic cardiorespiratory fitness level unaffected by regular exercise vs those in whom the measured fitness level is a composite of intrinsic capacity plus physical activity exposure? If so, is there a difference in the fitness-mortality curves between the 2 cardiorespiratory fitness groups? What are the

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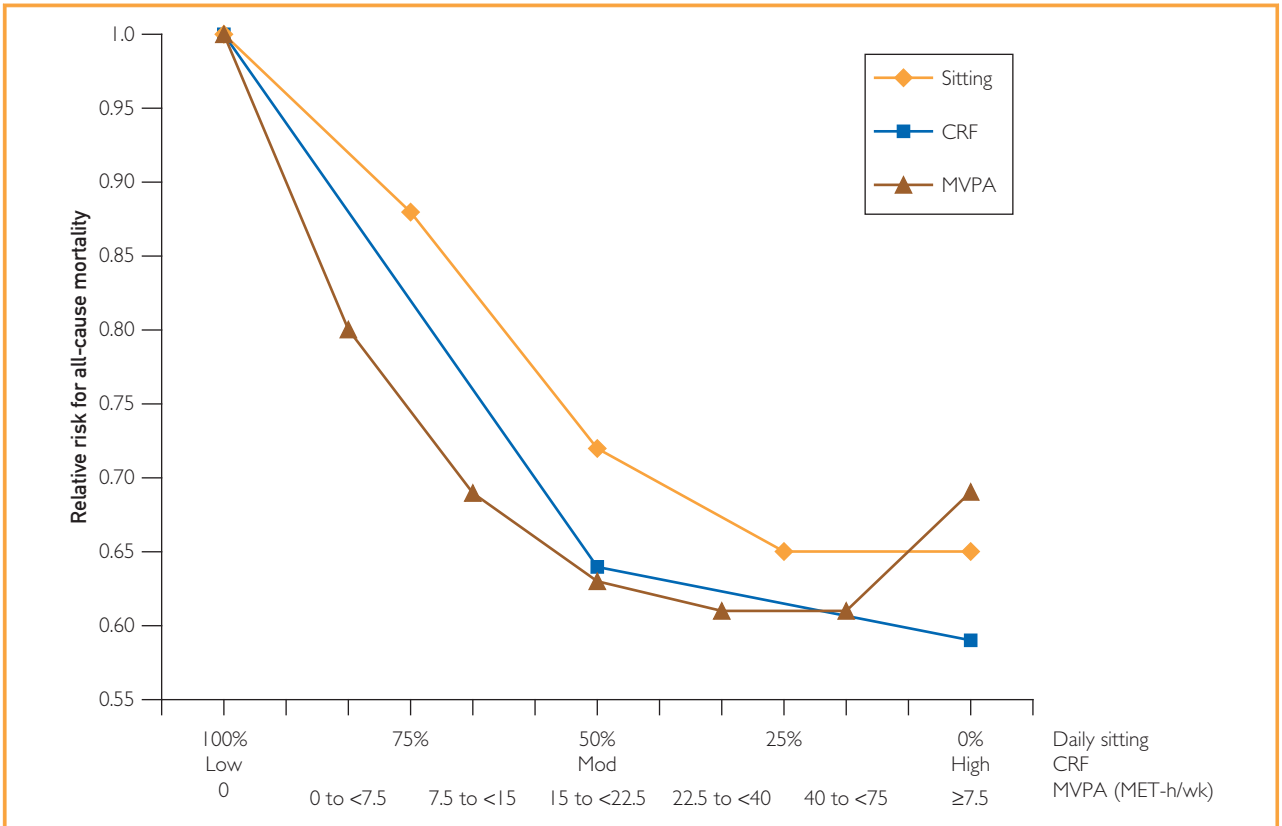

FIGURE 2. Relative risks for all-cause mortality associated with daily sitting among 17,103 men and women followed up for a mean of 12.0 years,[15] cardiorespiratory fitness (CRF) from a meta-analysis of 102,980 participants from 33 published studies,[25] and moderate to vigorous physical activity (MVPA) among 661,137 men and women from 6 cohort studies followed up for a median of 14.2 years.[21] Relative risks are from models that include a variety of covariates as described in the original studies.

biological differences between the two fitness groups at the level of the cardiovascular system, brain, lung, liver, kidneys, skeletal muscle, and adipose tissue? What can we learn from biological differences among low fitness—inactive vs low fitness—active vs high fitness—inactive vs high fitness—active subgroups of middle-aged or older individuals? An overarching question would be whether persons with a high intrinsic cardiorespiratory fitness level have lower mortality rates comparable to those who have a more modest intrinsic fitness level but are exercising regularly? Even though no human study has addressed these critical questions, one study based on the comparison of sedentary rats with low and high intrinsic aerobic capacity reported a 28% to 45% shorter life span in the rats with the low intrinsic aerobic capacity compared with the more intrinsically fit animals, none of which were exposed to regular exercise before.[33]

IMPLICATIONS OF THE EVIDENCE FOR PUBLIC HEALTH RECOMMENDATIONS

In the earlier sections of this article, we provided succinct reviews of the scientific evidence that sedentary behavior, regular physical activity, and cardiorespiratory fitness have strong associations with premature mortality (Figure 2). Low cardiorespiratory fitness may be the strongest of these risk factors because the associations with mortality indicators remain strong even after adjustment for physical activity level. We certainly have ample evidence that cardiorespiratory fitness has a significant genetic component, but we also know that most inactive people who start exercising do improve their fitness level.[28] Another relevant factor is that large epidemiological studies have found that adults who increase their cardiorespiratory fitness have substantial reductions in the risk for mortality during follow-up.[26,34,35] We do need more evidence on

health outcomes for individuals who increase their activity but do not improve their cardiorespiratory fitness. The mechanisms underlying the association between sedentary behavior and mortality are not well understood. It is clear that replacing sitting time with low levels of light activity will not have large effects on either moderate to vigorous physical activity levels or cardiorespiratory fitness. However, there is some evidence that sedentary behavior translates into slightly lower levels of cardiorespiratory fitness in both men and women.[36] Thus, it would seem appropriate at this time to focus on improving all 3 risk factors of sedentary behavior, physical activity, and cardiorespiratory fitness with targeted public health efforts.

Recent research into the effects of sedentary behavior on health has garnered considerable attention by researchers and by the media. However, it is difficult to understand why cardiorespiratory fitness has not received more attention by scientific and public health groups. Although we have accumulated extensive evidence on the health benefits of cardiorespiratory fitness over the past 25 years, there has been no consensus recommendation. We recommend that major organizations such as the Institute of Medicine, NIH, Centers for Disease Control and Prevention, World Health Organization, and other groups consider developing relevant guidelines. We do not suggest that sedentary behavior and physical activity level be ignored but simply believe that it is counterproductive to continue to ignore the value of cardiorespiratory fitness as a prognostic indicator.

More research is also needed on muscular strength as a risk factor for health outcomes. Current US physical activity guidelines recommend 2 d/wk of resistance training exercise. Current evidence suggests that both cardiorespiratory fitness and muscular fitness make independent health contributions,[37] but additional research on muscular fitness, after taking cardiorespiratory fitness into account, is needed to further establish clear recommendations.

One important area of investigation to pursue has to do with the mechanisms associated with the protective effects of low levels of sedentary behavior, moderate to high levels of physical activity, and cardiorespiratory fitness. It would be of great interest to know the mechanisms responsible for the reduction in risk of disease or of premature death beyond the changes in the traditional cardiovascular and diabetes risk factors. From prior research, one can speculate that short sedentary time, being physically active, and higher fitness level result in improved endothelial function; ischemic preconditioning; improved autonomic tone; more extensive tissue and organ cross talk attributable to exercise-induced circulating myokines, adipokines, and other cytokines; progenitor cell recruitment in multiple tissues; balance between the generation and buffering of reactive oxygen species molecules; and regulation of cellular autophagy and apoptosis. Interestingly, it has been suggested that sedentary behavior per se is associated with shorter leukocyte telomere length, a known marker of premature mortality.[38] Research on mechanisms may greatly benefit from the recently launched NIH Common Fund initiative on the molecular transducers of adaptation to physical activity.[1]

CONCLUSION

This review illustrates the importance of sedentary behavior, physical activity level, and cardiorespiratory fitness to health outcomes and premature death. There are associations among these variables, but there also is evidence supporting their independence as health-related variables. Additional research is needed to address several outstanding questions that would help clarify their public health implications. We encourage health authorities and funding agencies to focus more attention on these issues.

Abbreviations and Acronyms: **BMI** = body mass index; **HR** = hazard ratio; **MET** = metabolic equivalent of task; **NIH** = National Institutes of Health; $\dot{V}O_{2max}$ = maximal oxygen uptake

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