

Cardiovascular Disease Mortality and Excessive Exercise in Heart Attack Survivors

To the Editor: In an in-depth study of 2377 patients (mean age, 62.9 years; 32% women) published in the September 2014 issue of *Mayo Clinic Proceedings*, Thompson et al¹ reported that higher levels of physical activity up to 7.2 metabolic equivalent of task-h/d were associated with survival benefits in heart attack survivors. Notably, physical activity beyond this level was found to be associated with poorer prognosis—a 2.6- and 3.2-fold increase in risk for all-cause and ischemic heart disease—related mortality, respectively.

The finding by Thompson et al in these extremely active survivors—representing the most active 5% of their cohort—is thought provoking and deserves attention. However, other studies of heart attack survivors, including our own, have failed to identify this increase in mortality risk from higher levels of physical activity or fitness, despite possible transient increases in risk associated with exercise.^{2,3} In the subset of 7794 heart attack survivors in The FIT (Henry Ford Exercise Testing) Project—a retrospective cohort of patients referred for exercise testing—higher levels of physical fitness were consistently associated with greater survival, with the most fit 8% of heart attack survivors having a 76% lower risk for mortality compared with the least fit patients. Similarly, among 37,855 patients in The FIT Project who were free of coronary artery disease, we did not find any increased risk from higher fitness, even among the most fit patients.⁴

Although we recognize the value of cautioning heart attack survivors to avoid excessive exercise, disproportionate amounts of media attention are commonly given to novel findings at the expense of the larger public health message. We submit that the main message to be taken away by heart attack

survivors should not be “exercising too much is dangerous,” simply because, for the overwhelming majority of these patients, increasing physical activity and fitness has tremendous benefit. Such a benefit is a testament to the efficacy and safety of exercise prescriptions and cardiac rehabilitation programs.^{1,3} Unfortunately, only 1 in 2 adults in the United States today is satisfying the minimum exercise recommendations, and even these individuals typically overestimate the amount of exercise they are performing.⁵ Coupling the tendency for patients to overestimate physical activity with cautions about potential hazards of exercise, we fear that both active and inactive individuals may not be fully capitalizing on the maximum survival benefits that can be obtained from lifestyle change.

More research will be needed to verify the relationship between excessive exercise, cardiotoxicity, and mortality in both heart attack survivors and healthier individuals. For now though, we believe it is still too early to sound the alarm on the potential hazards of exercise for all survivors because most patients would not engage in the level of physical activity reported as being potentially harmful. Patients should be encouraged to be as active as their body can tolerate and to avoid strenuous activity that their body is unaccustomed to. We applaud the sound research performed by Thompson et al¹ and will read with great interest their future findings.

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In reply—Cardiovascular Disease Mortality and Excessive Exercise in Heart Attack Survivors

We thank Hung et al for their letter. We agree that these novel results should be approached with caution, and we wish to emphasize that there was a substantial reduction in mortality with increasing exercise up to 30 miles (48 km) per week in our cohort. We suspect that the contrasting findings between The FIT (Henry Ford Exercise Testing) Project and the National Runners' Health Study and National Walkers' Health Study are due to differences in study design.

The FIT Project measured treadmill exercise performance and found that the most-fit heart attack survivors had the largest reduction in mortality, whereas we found an increase in mortality among our most active runners and walkers who had diagnosed coronary heart disease. Fitness, as measured by treadmill exercise performance, is often equated with habitual physical activity, but these 2 parameters are not identical. Elsewhere we have reported that cardiorespiratory fitness and physical activity have very different relationships to cardiovascular disease.¹ This is especially important in heart attack survivors because cardiorespiratory fitness may be strongly influenced by the severity of the initial heart attack, and the severity of the attack likely affects both exercise capacity and survival. We have not directly

measured cardiorespiratory fitness in our cohort but have used 10-km race performance as a surrogate measure because this factor correlates well with maximum oxygen consumption.² The correlation between 10-km performance and exercise dose in our study was only $r=0.29$ (or 9% of the variance), documenting that exercise performance and habitual physical activity are not tightly related. In our cohort, 15% of the runners exceeded 7.2 metabolic equivalent of task-h/d (MET-h/d) of running and constituted our high-mileage runners, but these individuals were not the fittest runners. Specifically, 70% of the high-mileage runners were in the slowest 85% of the 10-km performance times. Consequently, the differences in results between The FIT Project and our report is likely due in part to our measuring habitual exercise and Hung et al's measuring cardiorespiratory fitness.

In addition, the greater risk we observed may be specific to cardiovascular disease mortality rather than morbidity and may involve mechanisms other than the traditional heart disease risk factors. We have reported no increased risk for nonfatal coronary heart disease³ or coronary heart disease risk factors with greater exercise through running at least 39 miles (63 km) per week.^{4,5} In fact, 2 other epidemiological cohorts reporting greater risk at higher exercise levels used mortality as their end point.^{6,7} Finally, we do not know what percentage of the patients in the studies cited by Hung et al ran more than 30 miles (48 km) per week, but we suspect it was not many. Because time-based estimates tend to overestimate exercise energy expenditure, participants reporting 7.2 MET-h/d or more of exercise in other studies (calculated from exercise duration and intensity) may actually be expending considerably less energy exercising than those who ran or walked 7.2 MET-h/d or more in our study (calculated from distance run or walked).⁸

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Ethanol Should Be Subjected to a Randomized Controlled Trial

To the Editor: The meta-analysis by Huang et al¹ in the September 2014 issue of *Mayo Clinic Proceedings* revealed an association between low to moderate ethanol consumption and reduced risk of cardiovascular disease and all-cause mortality (ACM) in hypertensive patients. This study adds additional observational evidence to support the hypothesis that there is a J-shaped curve for ACM vs ethanol consumption, with minimum ACM observed in persons with a low-level long-term ethanol intake of about 10 g/d (about 1 standard serving or drink). This well-designed

study reinforces previous epidemiological data suggesting similar benefits of low levels of ethanol consumption in other populations. What is needed is a large prospective randomized controlled trial comparing ethanol vs placebo to provide the high-quality evidence needed for physicians to prescribe low-dose ethanol for patients who could benefit.

Ethanol has been consumed by humans for millennia, and at high doses it can cause well-known adverse effects, such as hepatitis and cirrhosis. Ethanol abuse can lead to addiction and devastating consequences for at-risk individuals. However, many individuals have no propensity for abuse of ethanol or experiencing any other serious adverse effects of a single serving per day. By the age of 40 years, when cardiovascular disease begins to become a major cause of death, most people know whether they have a tendency to abuse ethanol. With latent and overt alcoholics excluded from randomization, a study could be conducted using capsules of ethanol vs placebo capsules of water (to preserve blinding). If taken in the evening with food, effects on driving accidents should be minimized or eliminated.

If the benefits found in this meta-analysis were associated with any pharmaceutical, there would be great excitement about its potential widespread use, and a phase 3 clinical trial would have been conducted long ago. It is time to obtain definitive proof of the alleged benefits of low-dose ethanol consumption or to disprove them in a randomized controlled trial.

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