Addressing the Complex Synergy Between Exercise Capacity and BMI and Its Relationship to All-Cause Mortality

In this issue, Rozanski et al\textsuperscript{1} present “Synergistic Assessment of Mortality Risk According to Body Mass Index and Exercise Ability and Capacity in Patients Referred for Radionuclide Stress Testing.” Starting with 54,500 patients undergoing radionuclide stress testing at Cedars Sinai over a 22-year period, they present 21,638 patients for analysis after excluding patients with coronary artery disease at baseline, evidence of ischemia on radionuclide images, those who are age 65 years or older, and a few with missing data or inadequate follow-up. All-cause mortality (ACM) was assessed over a median follow-up of 12.8 years and compared statistically with multivariate adjustment according to pharmacologic (n=7273) versus exercise (n=14,365) test modality and nine body mass index (BMI) groups ranging from less than 18.5 kg/m\textsuperscript{2} to greater than or equal to 40 kg/m\textsuperscript{2}. Exercising patients were further divided into those with less than 8 metabolic equivalent of task (MET) units versus those with greater than or equal to 8 METs. Because patients in the pharmacologic and exercise subgroups were very different, a secondary analysis comparing outcomes by exercise modality was performed on a propensity-matched subset with 4804 patients in each test modality.

The relationship of ACM to BMI in the overall cohort (seen in Figure 1 from Rozanski et al\textsuperscript{1}) was J-shaped with a lowest risk (referent) BMI of 22.5 to 24.99 kg/m\textsuperscript{2}, but there are significant differences between the pharmacologic and exercise subgroups. All-cause mortality was four-fold higher in pharmacologic versus exercise subgroup both in the full cohort (seen in Figure 2 from Rozanski et al\textsuperscript{1}) and propensity-matched subset (seen in Figure 3 from Rozanski et al\textsuperscript{1}), indicating that inability to exercise is an independent risk factor. Among high-risk pharmacologic patients, the ACM showed a 1/x relationship to BMI with rapidly increasing ACM at lower BMI levels and slowly decreasing ACM all the way up to greater than or equal to 40 kg/m\textsuperscript{2} (seen in Figure 2 from Rozanski et al\textsuperscript{1}). This fits the “obesity paradox” previously reported in high-risk cohorts.\textsuperscript{2} For low-risk exercise patients, the relationship was U-shaped with modest elevations (relative risk, approximately 2.0) in the lowest and highest BMI subgroups (seen in Figure 2 from Rozanski et al\textsuperscript{1}), more consistent with community cohorts.\textsuperscript{3} Stratifying exercise patients above and below 8 METs revealed that mortality was lower across most of the BMI groups in more- versus less-fit patients (seen in Figure 4 from Rozanski et al\textsuperscript{1}). A supplemental analysis shows that survival has a strong positive (nonlinear) relationship to exercise level after further stratification into five exercise categories from less than 5 METs to greater than or equal to 12 METs (seen in Supplemental Figure 1 from Rozanski et al\textsuperscript{1}).

To control for reverse causation, censoring deaths in the first 5 years of follow-up did not affect ACM risk at low BMI, but hazard ratios for above the referent BMI were reduced (seen in Supplemental Table 4 from Rozanski et al\textsuperscript{1}).

Overall, the study is very sound. Strengths include the number of patients — large for a stress imaging database — and especially the number of patients who underwent pharmacologic stress. Follow-up was long with careful ascertainment of ACM using three different sources. Body mass index was stratified into more than the usual three or four categories (normal, overweight, obese, and morbidly obese).

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Referral biases exist for any stress testing cohort, especially nuclear cardiology. It is unlikely that more than one-third of patients younger than 65 years of age (n=7273/21,638; 33.6%) in a community cohort would be unable to perform an exercise test, and healthy individuals are seldom referred for a nuclear stress test.

How does the current study reinforce our understanding of the relationship of exercise capacity to long-term prognosis (particularly ACM)? How does it contribute to our unraveling of the obesity paradox?

This study reinforces an important truth in cardiovascular medicine: being fit is good. Exercise capacity is a very important measure of cardiovascular health—a “vital sign,” as expert panels have proposed. At the bottom of the exercise continuum are patients who cannot perform an exercise test. Several important pathways lead from these truths: 1) Consider exercise as the stress modality, whenever possible, to accurately obtain this important vital sign; 2) When patients complain of symptoms limiting their physical activity, the yield of the stress test will likely be higher; and 3) Always consider the exercise capacity—not just the ST-segment response or myocardial perfusion defects—when considering patient management.

Exercise capacity was first shown to be a strong predictor of ACM by Blair et al from the Aerobics Center, and many other large exercise databases have confirmed this finding. The current study becomes the latest to add its support. The Thrombolysis in Myocardial Infarction II (TIMI II) trial first identified higher risk in patients not able to perform an exercise test, and subsequently publications have reported the correlative finding that patients undergoing pharmacological testing show higher mortality than patients performing an exercise test.

Patients who cannot perform an exercise test likely have low levels of physical activity, depriving them of its many beneficial effects on cardiovascular risk factors. Reduced activity also predisposes patients to deep vein thrombosis and subsequent clinical events such as pulmonary embolism and stroke. Lack of exercise leads to a reduction in lean body mass (LBM) and muscle strength; as the Prospective Urban Rural Epidemiology (PURE) study reports, muscle strength significantly lowers case fatality rates in a variety of chronic diseases.

The relationship of BMI to subsequent ACM and its synergy with exercise capacity are more complex. Body mass index cut-points that we use for normal, overweight, and obese do not behave as we wish they would with respect to subsequent ACM. Briefly, we might speculate that: 1) the original WHO Expert Panel didn’t get it right in 1995 or their reference points did not work well for high income countries such as the United States; 2) BMI as a measure of obesity is just too muddled with height plus muscle mass, bone mass, fat mass—and its distribution—and water components; 3) full elimination of reverse causation is challenging; 4) choice of statistical adjustment factors beyond age and sex is arbitrary—adjusting for obesity-driven factors such as diabetes and hypertension may take the “sting” out of being obese.

To better understand the contributions of the current study, we should consider pharmacologic and exercise subgroups separately. A possible explanation of the ACM ∝ 1/BMI relationship in the pharmacological cohort is that maintenance of LBM is protective in high-risk patients, such as the pharmacologic subgroup. Amount of body fat is less relevant or even protective (by identifying individuals with good caloric intake).

The U-shaped relationship of ACM to BMI in the exercise subgroup requires more complex explanations. Stratifying “normal BMI” into several subcategories shows that the obesity paradox is exaggerated by lumping BMI from 18.5 to 24.99 kg/m² as “normal.” This is a useful contribution. In patients who exercised, LBM is likely better preserved overall, thus flattening the lower end of the ACM-versus-BMI curve. With adequate LBM and better long-term survival, the relationship of high fat mass (with suboptimal control of cardiovascular risk factors) to increased ACM is unmasked, creating the U-shaped curve. Because cardiovascular deaths may represent only a fraction of all...
deaths, especially in low-risk cohorts, the effect on ACM is relatively small.

In conclusion, this nicely done study confirms what we know about the benefits of being fit. It also helps us better understand the relationship of BMI to ACM; however, in the end it leaves many questions unanswered. It may take a similarly large dataset with similarly complete follow-up — plus a more sophisticated measure of body composition and specific causes of mortality — to clarify the synergistic effects of body fat, LBM, and exercise capacity on mortality risk.

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