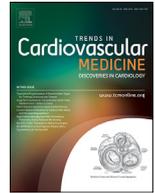




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## Trends in Cardiovascular Medicine

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## Editorial Commentary: The obesity paradox in cardiovascular disease: Deeper phenotyping to get to the heart of the matter



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The review by Xia, Lloyd-Jones, and Khan in this issue of *Trends in Cardiovascular Medicine* provides insight regarding the obesity paradox. The *obesity paradox* refers to the paradoxical yet consistently replicated observation that individuals with cardiovascular disease (CVD) classified as overweight/obese according to body mass index (BMI) tend to live longer than normal-weight individuals [1].

As noted by Xia et al. [1], using BMI to classify individuals as overweight or obese has major limitations. First, BMI fails to distinguish between fat versus lean mass. The distinction is important because the presence of more muscle mass may indicate less unintentional weight loss prior to study enrollment, or (like excess fat stores), provide additional metabolic reserve after CVD diagnosis. Simply determining whether total or regional amounts of lean mass modify the obesity paradox will be an important initial step. However, there is heterogeneity in muscle biochemical and functional properties, termed “muscle quality”. Molecular markers of muscle quality, such as markers of mitochondrial biogenesis and fat transport and oxidation, can be measured using invasive muscle biopsy techniques [2]. But standard physical performance tests provide a non-invasive, real-life index of muscle quality and function that have been associated with CV outcomes [3]. In a study of 1506 men with existing hypertension, muscular strength, an index of muscle quality, was inversely associated with all-cause mortality [4]. Quantification of muscle mass and the inclusion of muscle biopsies or physical performance tests in cohorts of individuals with CVD are needed to determine whether muscle mass and/or quality modify the obesity paradox.

Second, BMI offers no information about regional fat distribution or fat characteristics. Like the differences in muscle tissue, several recent studies have suggested that all adipose tissue is not the same. Dysfunctional adiposity, defined as visceral fat and evidence of insulin resistance, was associated with new-onset prediabetes and diabetes in a study of 732 adults with obesity [5], but total body fat and BMI were not linked to incident diabetes in the same study. Centrally-distributed adipose tissue, measured with a CT scan, was also associated with excess CV mortality and CV risk factor abundance in the Framingham cohort [6,7]. Waist circumference was an independent predictor of mortality across BMI categories in patients with end-stage renal disease, providing further

support for the idea that patterns of fat distribution matter in chronic disease states [8]. Adipose tissue functions as an endocrine organ, and inflammatory and hypoxic proteins and adipokines secreted in varying concentrations from different fat depots have robust and largely negative systemic effects. The differential associations between central/visceral versus subcutaneous fat and mortality may be attributable to pro-inflammatory or otherwise undesirable endocrine properties of visceral versus subcutaneous fat depots [9].

Xia et al. [1] also discuss the poorly understood relationship between obesity, cardiorespiratory fitness, physical activity, and mortality in individuals with CVD. For example, a recent study of 774 black and white men and women detected an obesity paradox in heart failure patients with low exercise capacity ( $\leq 4$  METS) but found that the obesity paradox did not exist in heart failure patients with an exercise capacity  $\geq 4$  METS [10]. The investigations included in the review in this issue also detected the obesity paradox in low-fit or sedentary individuals. Patients with both lower BMI and low fitness might be fundamentally different, sicker patients, who have a more aggressive disease course or have endured a longer duration of disease. Low BMI-low fit patients might have less favourable body composition or poorer muscle and fat quality. Deeper phenotyping of muscle and fat tissue and exercise capacity is needed to better understand the obesity paradox in CVD and inform treatment.

Whether increasing physical activity and/or improving fitness, independent of changes in body weight, improves outcomes in individuals with CVD is not known, though Vanhees, et al., found that every 1% improvement in fitness achieved during a 3-month cardiac rehabilitation program was associated with a 2% lower hazard ratio of cardiovascular mortality in men with coronary disease [11]. Regular exercise participation has measurable effects on body composition, muscle quality, and non-traditional CVD risk factors, such as autonomic and endothelial function [12,13], that are also associated with mortality. Thus, performing physical activity or improving fitness might increase survival in individuals with CVD even without changing BMI [14]. Along these lines, there have been few randomized, controlled studies of intentional weight loss in patients with CVD. A study of patients with atrial fibrillation found that sustained weight loss, induced by diet and exercise, was associated with better survival [15]. When bigger doses of exercise were used to induce significantly greater weight loss in patients participating in a cardiac rehabilitation program, the group

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that performed the biggest exercise dose and experienced the most weight loss achieved parallel, graded improvements in endothelial function, measured in-vivo with flow-mediated dilation [16]. These results suggest that increasing physical activity, improving fitness, or intentional weight loss might improve outcomes in individuals with CVD via multiple potential pathways, but larger trials in diverse populations and women are needed.

Finally, however perplexing the obesity paradox may be, there is no paradox in prevention. While the current review offers explanations for the obesity paradox in individuals with CVD, the authors also emphasize that there is no doubt that obesity increases the risk of CVD in the first place. Public health efforts should focus on life-long achievement and maintenance of a favourable BMI and adoption of favourable lifestyle factors, especially regular exercise.

### Acknowledgments

ALC is funded by the American Heart Association (18CDA34110038).

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