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Contribution of Cardiorespiratory Fitness to the Obesity Paradox

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ABSTRACT

Until recently, cardiorespiratory fitness (CRF) has been overlooked as a potential modifier of the inverse association between obesity and mortality (the so-called obesity paradox), observed in patients with known or suspected cardiovascular (CV) disease. Evidence from five observational cohort studies of 30,104 patients (87% male) with CV disease indicates that CRF significantly alters the obesity paradox. There is general agreement across studies that the obesity paradox persists among patients with low CRF, regardless of whether adiposity is assessed by body mass index, waist circumference, or percentage body fat. However, among patients with high CRF, risk of all-cause mortality is lowest for the overweight category in some, but not all, studies, suggesting that higher levels of fitness may modify the relationship between body fatness and survival in patients manifesting an obesity paradox. Further study is needed to better characterize the joint contribution of CRF and obesity on mortality in diverse populations.

Controversy exists as to whether exercise or weight exerts a greater influence on risk of death. In their 1999 landmark report of over 25,000 men from the Aerobic Center Longitudinal Study (ACLS), Wei and colleagues[1] found that men with a body mass index (BMI) ≥30 kg/m^2 (i.e. obese) who also had high levels of cardiorespiratory fitness (CRF; i.e. fit) were no more likely to die from cardiovascular (CV) disease or all-causes than normal-weight (i.e. BMI 18.5–24.9 kg/m^2) and fit men. A similar ACLS study published that same year found that measures accounting for body fat mass and distribution produced results similar to BMI.[2] Together, these seminal papers formed the basis of the "fat and fit" hypothesis which suggests that higher CRF attenuates the increased mortality risk associated with excess adiposity in the general population. Numerous studies in both men and women from the ACLS[3] and from other large observational datasets[4] have since replicated these findings.

In not all populations, however, is a direct association observed between obesity and mortality. About a decade ago, an unexpected finding that overweight and obese patients undergoing percutaneous coronary interventions had reduced mortality when compared to their lean counterparts was first reported by Gruberg et al.[5] who coined the term "obesity paradox." This inverse association between obesity and mortality has been repeatedly observed in patients with established CV disease.[6] Despite its prevalence, however, fully accounting for this observation remains elusive.

Since most studies reporting an obesity paradox have used BMI to assess adiposity,[7] critics have argued that this phenomenon is simply an artifact of the limitation of BMI to

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Abbreviations and Acronyms

ACLS = Aerobics Center Longitudinal Study

BMI = body mass index

%BF = body fat

CHD = coronary heart disease

CRF = cardiorespiratory fitness

CV = cardiovascular

HF = heart failure

HR = hazard ratio

MET = metabolic equivalent

VETS = Veterans Exercise Testing Study

WC = waist circumference

WHR = waist-to-hip ratio

accurately measure excessive adiposity in both healthy and diseased populations.[8] Others have pointed out that the protective effect of a higher BMI in patients with established chronic diseases is to be expected.[7] For example, many chronic diseases are complicated by muscle wasting and nutritional inadequacy associated with a lower BMI. Recently however, a growing body of evidence suggests that CRF may provide the most complete explanation for the obesity paradox.[9] That is, CRF may, at least in part, account for the inverse association between obesity and mortality observed in patients with established CV disease. In this article, we review five observational cohort studies that investigate the modifying influence of CRF on the obesity paradox in patients with CV diseases, and discuss possible mechanisms underlying these effects.

Low CRF as a CV disease risk factor

Low CRF has long been established as an independent predictor of CV morbidity,[10] and mortality,[11,12] as well as mortality from all-causes.[13,14] However, due to difficulties measuring CRF, along with the lack of operational definition of "fitness," it is often underutilized as a clinical CV disease risk factor.[15] CRF measurements are obtained from specialized exercise tests, which require expensive laboratory equipment and trained personnel. Whereas conventional risk factors, like blood lipid panels, are routinely performed in preventive screenings, typically only patients with known or suspected CV disease are referred for exercise testing. Another obstacle concerns the absence of a standardized classification system as exists, for example, for BMI. This has led to some variations as to what constitutes "low" CRF. In the first ACLS report on CRF and mortality, fitness categories were based on age and sex norms of treadmill time with low CRF defined as the lowest 20%.[13] Other studies of CRF and mortality in patients with CV diseases have used absolute cutoff points to define low CRF based on metabolic equivalents (METs) of 4,[16] 5,[14] and 6.[17] When expressed as percentiles of their respective populations, these MET values range from approximately the lowest 20%[14] to the lowest 40%.[16,17] Regardless of the classification system used, however, it is worth noting that "low" CRF is consistently associated with higher risk of mortality.[14,16,17]

Recent longitudinal data reporting on changes in CRF provide more compelling evidence of the prognostic power of CRF on CV morbidity and mortality. In one ACLS study[18] of 14,345 men, maintaining or improving CRF over a period of 6.3 years was associated with substantially lower CV disease mortality, regardless of BMI change [HR (95% CI): 0.56 (0.37–0.85) and 0.59 (0.37–0.95) for maintaining or improving CRF, respectively]. In another ACLS study[19] of 3148 healthy adults, the development of CV disease risk factors associated with global fat gain over a period of 2.1 years was attenuated when CRF was maintained or improved. The importance of CRF in predicting adverse health outcomes is underscored by the American Heart Association's recent policy statement advocating for the development of a national adult CRF registry to provide a sufficiently representative sample of the US population for accurate interpretation of CRF measures.[20] Whereas most studies about the obesity paradox include adjustments for traditional CV risk factors such as hypertension and smoking history, measurements of CRF are missing in all but a few recent studies.[9] Given that low CRF is such a powerful predictor of CV disease and mortality risk, it is plausible that it represents an unmeasured confounder of the obesity paradox that could have considerable explanatory power.

CRF and the obesity paradox in CV diseases

A comprehensive literature search was conducted using the PUBMED database (National Library of Medicine, Bethesda, MD) inclusively through July 2013 on epidemiological studies using the keywords: obesity; cardiorespiratory fitness; and cardiovascular diseases. References within identified papers as well as articles that had come to the attention of the authors through other means were also examined for suitability. Six studies were identified examining the obesity paradox in patients with CV diseases, that also included objectively measured CRF.[16,17,21–24] One study[21] provided only unadjusted mortality rates, which precluded meaningful comparisons with other studies. Therefore, we evaluated five studies that included adjusted multivariate analyses for combined fitness-adiposity categories and summarized key findings by order of publication below (see Table 1).

In the first study,[22] 12,417 middle-aged men from the Veterans Exercise Testing Study (VETS) with a mean follow-up of 7.7 years for all-cause mortality, both fitness and BMI were independently and inversely associated with mortality. When jointly modeled, a significantly lower mortality risk was found for men classified with high fitness (>10 METs)/overweight [HR (95% CI): 0.43 (0.32–0.59)] and high fitness/obese [HR (95% CI): 0.52 (0.34–0.82)], compared to the reference group (high fitness/normal weight). Conversely, mortality risk was 1.5 to 4.5 times higher for men with low CRF (<5 METs) across BMI categories, with the highest mortality risk seen in the underweight subgroup [HR (95% CI): 4.48 (3.06–6.57)]. Thus, fitness altered the obesity paradox in that overweight and obesity were only protective against premature mortality in