

# UC Irvine

## UC Irvine Previously Published Works

### Title

Obesity Paradox as a Component of Reverse Epidemiology in Heart Failure

### Permalink

<https://escholarship.org/uc/item/2v04v0wn>

### Journal

JAMA Internal Medicine, 165(15)

### ISSN

2168-6106

### Authors

Kalantar-Zadeh, Kamyar  
Anker, Stefan D  
Coats, Andrew JS  
[et al.](#)

### Publication Date

2005-08-08

### DOI

10.1001/archinte.165.15.1797-a

### Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

mainly driven by women or equally present in both sexes, and (2) whether the previously described protective effects of peripheral fat mass has implications for the reported obesity paradox. It would be useful to assess whether BMI is a confounder of the association between cardiovascular risk and hip circumference,<sup>5</sup> if this latter anthropometric measure of peripheral adiposity was available for supplementary analysis.

László B. Tankó, MD, PhD  
Claus Christiansen, MD

**Correspondence:** Dr Tankó, Center for Clinical and Basic Research, Ballerup byvej 222, 2750 Ballerup, Denmark (lbt@cibr.dk).

1. Curtis JP, Selter JG, Wang Y, et al. The obesity paradox: body mass index and outcomes in patients with heart failure. *Arch Intern Med.* 2005;165:55-61.
2. Walsh CR, Cupples LA, Levy D, et al. Abdominal aortic calcific deposits are associated with increased risk for congestive heart failure: the Framingham Heart Study. *Am Heart J.* 2002;144:733-739.
3. Tankó LB, Bruun JM, Alexandersen P, et al. Novel associations between bioavailable estradiol and adipokines in elderly women with different phenotypes of obesity: implications for atherogenesis. *Circulation.* 2004;110:2246-2252.
4. Tankó LB, Bagger YZ, Alexandersen P, Larsen PJ, Christiansen C. Peripheral adiposity exhibits an independent dominant antiatherogenic effect in elderly women. *Circulation.* 2003;107:1626-1631.
5. Lissner L, Björkelund C, Heitmann BL, Seidell JC, Bengtsson C. Larger hip circumference independently predicts health and longevity in a Swedish female cohort. *Obes Res.* 2001;9:644-646.

## Obesity Paradox as a Component of Reverse Epidemiology in Heart Failure

We read with great interest the article by Curtis et al<sup>1</sup> on the inverse relationship between BMI and survival in patients with HF due to systolic dysfunction. We were pleased to see that the findings of this study further support our respective groups initial descriptions of an inverse association between BMI and mortality in this patient population.<sup>2-4</sup> However, it is important to note that BMI is not the only conventional cardiovascular risk factor with a paradoxical association with clinical outcomes in patients with HF.<sup>4</sup> High levels of both low-density lipoprotein and total cholesterol have been associated with a survival advantage in HF<sup>5</sup> along with an inverse relationship between blood pressure and outcome in patients with HF.<sup>4</sup> These consistent findings across an array of cardiovascular risk factors in patients with HF support the more inclusive term *reverse epidemiology*.<sup>4</sup> Reverse epidemiology has also been observed in hemodialysis patients, elderly individuals, and patients with advanced malignancies, AIDS, and other chronic diseases.<sup>6</sup> This means that more than 20 million individuals, including 5 million patients with HF, in the United States alone may be subject to this reverse epidemiology. We believe that this could have very important implications for public advice on health matters because conventional recommendations pertaining to the management of cardiovascular risk factors such as weight reduction or aggressive treatment of hypercholesterolemia may not be appropriate.<sup>6</sup>

While such apparently counterintuitive associations may not necessarily be causal, the possibility of the true protective effect of obesity and hypercholesterolemia in these patients cannot be ruled out. It is possible that higher serum cholesterol levels and adiposity in patients with HF are beneficial because the lipoprotein pool serves as an effective scavenger to bind with and neutralize circulating lipopolysaccharide, including bacterial endotoxin.<sup>5</sup> Consequently, high levels of serum lipoproteins may be associated with lower levels of unbound circulating lipopolysaccharide and an inhibition of inflammatory response and thus more favorable clinical outcomes.<sup>3-5</sup>

Therefore, we believe that the paradoxically inverse associations that have been consistently observed between conventional risk factors, such as hypercholesterolemia and obesity, and improved survival in certain chronic disorders such as HF require a more accurate and sophisticated approach to risk factor management. Further studies are clearly needed to elucidate the mechanisms behind this reverse epidemiology affecting obesity and other cardiovascular risk factors so that we offer the best and most effective advice and treatment for our patients. For example, randomized clinical trials of strategies to improve nutritional and metabolic status in HF and other chronic disorders are long overdue.

Kamyar Kalantar-Zadeh, MD, PhD, MPH  
Stefan D. Anker, MD, PhD  
Andrew J. S. Coats, DM  
Tamara B. Horwich, MD  
Gregg C. Fonarow, MD

**Correspondence:** Dr Kalantar-Zadeh, Departments of Medicine and Pediatrics, UCLA David Geffen School of Medicine, Harbor-UCLA Medical Center, 1124 W Carson St, C-1 Annex, Torrance, CA 90502-2064 (kamkal@ucla.edu).

1. Curtis JP, Selter JG, Wang Y, et al. The obesity paradox: body mass index and outcomes in patients with heart failure. *Arch Intern Med.* 2005;165:55-61.
2. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH. The relationship between obesity and mortality in patients with heart failure. *J Am Coll Cardiol.* 2001;38:789-795.
3. Davos CH, Doehner W, Rauchhaus M, et al. Body mass and survival in patients with chronic heart failure without cachexia: the importance of obesity. *J Card Fail.* 2003;9:29-35.
4. Kalantar-Zadeh K, Block G, Horwich T, Fonarow GC. Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. *J Am Coll Cardiol.* 2004;43:1439-1444.
5. Rauchhaus M, Clark AL, Doehner W, et al. The relationship between cholesterol and survival in patients with chronic heart failure. *J Am Coll Cardiol.* 2003;42:1933-1940.
6. Kalantar-Zadeh K, Kilpatrick RD, Kuwae N, Wu DYJ. Reverse epidemiology: a spurious hypothesis or a hardcore reality? *Blood Purif.* 2005;23:57-63.

### In reply

Tankó and Christiansen propose that the obesity paradox in patients with heart failure may be in part mediated by increased production of adiponectin in obese heart failure patients with excess peripheral fat. The Digitalis Investigation Group Trial did not obtain information regarding hip and waist circumference, and thus we are unable to determine whether a pattern of peripheral obesity contributes to the improved outcomes observed in overweight and obese patients. We found no evidence, however, that the associa-

tion of improved outcomes in heart failure patients with excess weight varies by sex. Although women in each BMI category had a lower risk of mortality compared with men, the absolute difference in mortality between patients in the lowest and highest BMI categories were comparable (men, 19.1% difference; women, 16.7% difference) (Table 4 of the original publication).<sup>1</sup>(p59)

Kalantar-Zadeh and colleagues point out that “paradoxical” associations between accepted risk factors and outcomes have been identified in patients with a variety of chronic medical conditions. We agree that the commonality of these findings warrants caution in applying recommendations developed for the general population to patients with chronic disease. As such, we believe there is a

pressing need to understand the mechanisms underlying these phenomena and identify the best strategies for managing modifiable risk factors in patients with chronic diseases including heart failure.

Jeptha P. Curtis, MD  
Yongfei Wang, MS  
Harlan M. Krumholz, MD, SM

**Correspondence:** Dr Krumholz, Yale University School of Medicine, 333 Cedar St, PO Box 208088, New Haven, CT 06520-8088 (harlan.krumholz@yale.edu).

1. Curtis JP, Selter JG, Wang Y, et al. The obesity paradox: body mass index and outcomes in patients with heart failure. *Arch Intern Med.* 2005;165:55-61.