Comments and Responses

Metabolically Healthy Overweight and Obesity

TO THE EDITOR: Kramer and colleagues (1) report that obese persons are at long-term risk for cardiovascular events and total mortality regardless of their metabolic status. The discrimination of participants according to a metabolic score is an oversimplified dichotomous classification that does not reflect the huge heterogeneity of obesity. Metabolically healthy persons, as classically defined, may still have metabolic disorders.

In Kramer and colleagues' meta-analysis, metabolically healthy obese persons had an intermediate risk for total mortality and cardiovascular events, higher than that for metabolically healthy lean and overweight persons but lower than that for metabolically unhealthy overweight and obese persons. However, the metabolically healthy obese group was only at increased risk in the studies with more than 10 years of follow-up. Variation within some components of the metabolic syndrome over time may have influenced these results. Indeed, metabolically healthy obesity is a transient state for one third of patients who may progress to metabolic risk and type 2 diabetes (2). Kramer and colleagues speculate that metabolically healthy obese persons probably have subclinical levels of risk factors that worsen over time (1).

A proinflammatory state is recognized as an important component of the metabolic syndrome, which is mainly associated with abdominal obesity. We recently showed that metabolically unhealthy obese persons have a less favorable inflammatory profile in their visceral adipose tissue than metabolically healthy obese persons, which results from the infiltration by proinflammatory adipose tissue macrophages with increased nucleotide-binding oligomerization domain–like receptorfamily pyrin domain–containing 3 inflammasome activity and interleukin-1β production. Furthermore, metabolically unhealthy obesity was associated with fewer anti-inflammatory T regulatory lymphocytes in visceral adipose tissue (3).

Of interest, Wildman and associates (4) report that overweight and obese women without clustering of cardiometabolic risk factors still have abnormal levels of inflammatory markers. In our study, metabolically healthy obese persons similarly had an intermediate inflammatory pattern in their visceral adipose tissue concerning interleukin-1β production and gene expression with lower levels of inflammatory markers **<<AU: Correct?>>** than metabolically unhealthy obese persons but higher levels than metabolically healthy lean persons (3). This finding agrees with Kramer and colleagues' data on mortality and cardiovascular events (1).

Chronic silent inflammation may contribute to the elevated risk for cardiovascular events and overall mortality (1, 5) and may be a potential mechanism linking abdominal obesity and cardiovascular risk. Differences in the inflammatory pattern of visceral adipose tissue may explain why metabolically healthy obese persons still have an elevated cardiovascular risk that is intermediate between that of metabolically healthy lean and overweight persons and metabolically unhealthy overweight and obese persons.

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**Potential Conflicts of Interest:** **<<AU: Waiting for Dr. Scheen to resubmit author form.>>**

References

1. Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions?: A systematic review and meta-analysis. Ann Intern Med. 2013;159:758-69. [PMID: 24297192]

2. Appleton SL, Seaborn CJ, Visvanathan R, Hill CL, Gill TK, Taylor AW, et al; North West Adelaide Health Study Team. Diabetes and cardiovascular disease outcomes in the metabolically healthy obese phenotype: a cohort study. Diabetes Care. 2013;36:2388-94. [PMID: 23491523]

3. Esser N, L'homme L, De Roover A, Kohnen L, Scheen AJ, Moutschen M, et al. Obesity phenotype is related to NLRP3 inflammasome activity and immunological profile of visceral adipose tissue. Diabetologia. 2013;56:2487-97. [PMID: 24013717]

4. Wildman RP, Kaplan R, Manson JE, Rajkovic A, Connelly SA, Mackey RH, et al. Body size phenotypes and inflammation in the Women's Health Initiative Observational Study. Obesity (Silver Spring). 2011;19:1482-91. [PMID: 21233809]

5. Hinnouho GM, Czernichow S, Dugravot A, Batty GD, Kivimaki M, Singh-Manoux A. Metabolically healthy obesity and risk of mortality: does the definition of metabolic health matter? Diabetes Care. 2013;36:2294-300. [PMID: 23637352]