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EDITORIAL COMMENT

More Appropriate Cardiovascular Risk Screening Through Understanding Complex Phenotypes

Mind the Gap*

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Excess adiposity has long been associated with metabolic dysfunction. However, epidemiological investigations have demonstrated that not all overweight and obese individuals exhibit poor metabolic function (1). Approximately a decade ago, the concept of metabolically benign obesity, a state in which an individual has a high body mass index (BMI) that is not associated with metabolic disturbance was proposed and characterized. Stefan et al. (2) found that obese adults could have insulin sensitivity and intima-media thickness comparable to normal weight individuals. However, it was not known at that time whether the state of metabolic health could persist under circumstances of excess adiposity or whether rates of clinical outcomes such as cardiovascular disease events (CVD) or deaths were similar in metabolically healthy overweight (MHOW) (BMI ≥25 kg/m^2) or metabolically healthy obese (MHO) (BMI ≥30 kg/m^2) individuals compared with others.

Recently, studies have consistently placed MHO individuals between metabolically healthy lean (MHL) and metabolically unhealthy obesity (MUHO) individuals in terms of CVD risk (3), occult cardiac dysfunction (4), and type 2 diabetes (5). Those who have evaluated metabolically unhealthy lean (MUHL) individuals have demonstrated increased CVD risk compared with MHL individuals that is approximately equivalent to MHO (3). Thus, either metabolic dysfunction or elevated BMI appears to increases CVD risk factors.

Both persistence of the MHO state and clinical outcome differences in MHO compared with MUHO, MHL, and MUHL have been tested recently. Obesity without metabolic dysfunction does not necessarily persist over time. One study found increased insulin resistance and inflammation during 20 years of follow-up. However, in the same study, there were no differences in CVD deaths among MHOW/MHO individuals compared with their normal weight counterparts (n = 1,099 men) (6). Meanwhile, other contemporary systematic reviews and meta-analyses found that CVD risk in MHO individuals is between the risk for MHL and MUHO individuals, including mortality risk (7,8). MHO is clearly a misnomer. Obesity is not a benign state, because it increases risk of CVD and death, regardless of metabolic status, although clearly MUHO has the worst prognosis. Pooled analyses also support the belief that normal weight or lean individuals are at increased risk of CVD events or death if they are metabolically unhealthy (7–9).

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In this issue of the *Journal*, Caleyachetty et al. (10) used the power of an enormous population database (3.5 million) to address risks associated with the intersection of weight and metabolic status on CVD. The largest previous individual study was 43,000 individuals. With the size of the Caleyachetty et al.

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(10) study, the investigators were able to more completely classify individuals according to weight (underweight, overweight, obese), and by the number of metabolic abnormalities (0 to ≥3) using electronic health records (EHRs) (1995 to 2015) in The Health Improvement Network (THIN) database. With an impending obesity epidemic, examination of specific CVD outcomes in this way is timely and highly significant.

Caleyachetty et al. (10) confirmed that obesity without metabolic abnormality is not benign. Even with no evident metabolic dysfunction, obese individuals were not healthy; CVD risk was increased, as were all component risks—coronary heart disease, cerebrovascular disease, heart failure, and peripheral vascular disease. As in previous analyses, metabolic dysfunction increased risk of obesity further and also increased CVD risk among normal weight individuals. This is a key finding because approximately 1 in 10 normal weight individuals had ≥1 metabolic issue. The study not only definitively countered the concept of metabolically benign obesity, but also demonstrated great risk to normal weight individuals if metabolic dysfunction is present. Thus, we would suggest an increased need for screening in the normal weight population. Hazard ratios in metabolically unhealthy individuals with normal weight ranged from approximately 1.5 to 2.5 for various CVD outcomes, which is not inconsequential. Often, 1 to 2 metabolic risk factors in normal weight individuals are dismissed as unimportant because they are of healthy weight; however, these data suggest that the normal weight group is at similar risk compared with overweight, and at times, obese individuals, when metabolic abnormalities are present. Certainly, once the number of metabolic abnormalities reached 3, the weight category was irrelevant for most outcomes. Because of the higher prevalence of at least 1 CVD risk factor in the normal weight Asian population, despite a lower cutpoint (≤23 kg/m^2), limiting to weight-based screening might be even more detrimental in Asian populations (11).

In the Caleyachetty et al. (10) study, the metabolic abnormalities studied included diabetes, hyperlipidemia, and hypertension. The American Diabetes Association recommends screening for diabetes beginning at age 45 years for everyone and earlier in overweight and obese individuals with ≥1 risk factor for diabetes (12). Similarly, the U.S. Prevention Task Force (USPTF) recommends screening for dyslipidemia based on age and sex. Men are to be screened for CVD if they are age 35 years or older (grade A evidence) and age 35 years or younger (grade B) if CVD risks factors are present (i.e., diabetes, personal or family history of CVD, smoking, hypertension, and BMI ≥30 kg/m^2). For women, screening is recommended starting at age 45 years if CVD risk is present (grade A). Although the screening interval is not prescribed, the USPTF notes that every 5 years is reasonable (13). Because the population in the Caleyachetty et al. (10) study was primarily in their 40s and 50s, the screening guidelines would be adequate for men, but perhaps not for women. Hypertension and weight screening are routinely performed in adults in the United States, and health providers are urged to treat abnormalities. The results of this large analysis suggested that screening for abnormalities in lipids and glucose handling should be more systematically monitored as well, regardless of body weight, but particularly in the obese.

The Caleyachetty et al. (10) study was not without limitations. The data were extracted from EHRs in 1 network in the United Kingdom only. Most studies to date have been in European countries or among individuals of European descent; thus, replication across various populations is needed. In addition, time variance in BMI and metabolic function were not examined. Nevertheless, THIN is representative of the general U.K. population (14), and the authors correctly note that potential misclassification based on weight change would likely have underestimated, rather than overestimated, the risks for each outcome since people generally have difficulty losing weight. The influence of diet and physical activity could not be evaluated in this EHR-dependent analysis; however, this is important to study to provide further insight into effective strategies to mitigate the elevated risk associated with metabolic derangement.

Because deleterious metabolic effects are attributed to excess adiposity, body composition itself should be evaluated in future studies for its relation to metabolic parameters, CVD events, and deaths. BMI is an imperfect proxy for fat, particularly visceral fat, which may vary with race/ethnicity, sex, and age (15,16), However, despite its limitations, the study by Caleyachetty et al. (10) is pivotal. It is the largest and most conclusive examination of the association between metabolic and body habitus phenotypes and CVD outcomes to date. The reporting of separate categories of CVD outcomes is important and adds clinical relevance. Strengths of the study also include the numerous sensitivity analyses to examine the effects of sex, age, hormone replacement, use of prescription records versus biomarker measurement, type

1 diabetes, and smoking on the analyses. All of these demonstrated the robustness of the primary findings.

In conclusion, obesity increases cardiovascular risk regardless of metabolic status. However, metabolic dysfunction itself also carries risk independent of weight because of the similar results across BMI categories of CVD risk in the Caleyachetty et al. study, and others, when metabolic dysfunction is present. This study supports following the U.S. guidelines for screening of CVD in persons age older than 18 years, even perhaps extending screening, and acting upon findings that suggest metabolic risk to reduce cardiovascular morbidity and mortality.

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