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EDITORIAL COMMENT

Dangers and Long-Term Outcomes in Metabolically Healthy Obesity

The Impact of the Missing Fitness Component*

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Obesity is a major public health problem. According to the latest data from the National Health and Nutrition Examination Survey (2015 to 2016), as many as 40% of adults and 19% of youths are obese, and these rates have not changed significantly over the past 20 years (1). It is well established that obesity has many adverse effects on cardiometabolic parameters and cardiovascular disease (CVD) risk factors, such as glucose intolerance, diabetes, atherogenic lipids, blood pressure, and increased levels of inflammation, all of which lead to marked increases in most CVD, including coronary heart disease (CHD), stroke, heart failure (HF), and atrial fibrillation (2,3). Given these consequences of obesity, it has been emphasized that obesity can never be "healthy" (4-7); however, a frequently debated condition has been the "metabolically healthy obesity" (MHO) prototype, basically referring to obese individuals who have relatively normal levels of plasma lipids, glucose, and blood pressure, a group of obese subjects that might not be at an increased risk of CVD, especially CHD (7,8).

On the other hand, several recent papers, including the present study by Mongraw-Chaffin et al. (5-7,9) have focused on the dangers and long-term outcomes of the MHO phenotype. A recent report by Bell et al. (5) suggested that a high number of those with MHO eventually develop "metabolic un-healthiness" or metabolic unhealthy obesity (MUO) over time. Additionally, in a more recent report from The Health Improvement Network study, Caleyachetty et al. (6) reported that those with MHO still had an increased risk of CVD, particularly HF, and even CHD.

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In this issue of the *Journal*, Mongraw-Chaffin et al. (9) from the Multi-Ethic Study of Atherosclerosis followed 6,809 participants and found that, although those with MHO did not have a significantly increased risk of incident CVD, it is not a stable condition and comprises a heterogeneous group of obese subjects. During 12.2 years of follow-up, almost one-half of these participants with MHO developed metabolic syndrome (MetS). Those who had this "unstable" pattern of previous MHO indeed had a subsequent increased risk of CVD during the follow-up, with progressive increase in CVD risk over time after developing the MetS. They suggested, therefore, as did Bell et al. (5) and Caleyachetty et al. (6), that MHO may not be so healthy after all and may often still be associated with future risk of MetS and subsequent elevated risk of CVD.

As stated previously, it has been suggested that many patients with MHO may not be at increased risk of CVD (7,8). In fact, a major published study has suggested that although HF may increase with any category of obesity, including MHO, this was not the case with CHD (7). The development of MetS, however, was associated with subsequent increased risk of CVD, especially CHD (9). As shown in the present study by Mongraw-Chaffin et al. (9), with persistent obesity and increasing weight, many individuals with

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MHO may convert to MUO over time and develop characteristics of MetS. Clearly, therefore, prevention of obesity in the first place is most prudent; prevention of progressive weight gain over time among the overweight and mildly obese is also of high importance to prevent development of MetS and subsequent risk of CVD.

Additionally, besides prevention of obesity and progressive weight gain, the current paper by Mongraw-Chaffin et al. (9) also emphasizes the importance of the prevention of the development of the MetS and adequate treatment of MetS if it develops. The best treatment of MetS may be vigorous nonpharmacologic therapy, including prevention of further weight gain with increasing physical activity (PA)/exercise training along with dietary restrictions in calories, simple sugars, and carbohydrates (10). Pharmacologic therapy for atherogenic dyslipidemia, hypertension, and glucose control in those with diabetes with cardioprotective agents may be beneficial in many patients (11).

The role of PA and cardiorespiratory fitness (CRF) in losing and controlling weight and curbing the ill effects of obesity is well established and is often understated, but should be emphasized in the guidelines. A significant limitation of many of the recent studies in obese subjects, including those by Bell et al. (5), Caleyachetty et al. (6), Mørkedal et al. (7), and the present study by Mongraw-Chaffin et al. (9), is lack of information on the role of PA and CRF (4,12,13). Such information will be useful because many studies have indicated that CRF may be more important than weight for predicting long-term prognosis (2–4,12–15). Additionally, when assessing subsequent risk in MHO, it is imperative to assess CRF because substantial available evidence supports that obese people, especially those with MHO, with relatively preserved CRF have an excellent prognosis (4,8,12–15). We suspect, therefore, that only those with MHO and low levels of CRF may have significantly increased risk of CHD and most CVD, except for possibly HF with preserved ejection fraction, which is probably increased universally in obesity (16). In fact, in a recent systematic review published by Roberson et al. (17), in 7 of 7 studies that included assessments for PA/exercise or CRF, MHO was not associated with increased risk of CVD mortality, and 6 of these 7 studies showed no increased risk of nonfatal CVD. Without good assessment of PA and, preferably, assessment of CRF, the true risks associated with MHO may not be adequately assessed. Although the current study by Mongraw-Chaffin et al. (9) used a fairly crude assessment of PA, there were certainly no precise measurements of PA or formal assessment of CRF to assess the role of PA or CRF on conversion of MHO to MetS and subsequent development of CVD.

In a perfect world, everyone would remain lean and fit across their lifetimes, but this is hardly the case in current Westernized societies, in which typically there is both weight gain and loss of CRF with aging (13–15). Clearly, prevention and treatment of obesity, especially moderate and severe degrees of obesity and progressive obesity, are needed, but at least in the overweight and mildly obese patients, greater emphasis is needed to promote PA and increased levels of CRF for the prevention and treatment of most CVD (1–4,8,13–16). The recent data from nearly half a million Chinese men and women showing significantly lower risk of major CVD events in those with regular leisure time PA as well as occupational PA are important testaments for the benefits of PA and CRF in reducing risk of CVD (18).

CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

Despite considerable progress made during the past several decades in primary and secondary prevention of CVD, obesity remains a formidable challenge and public health problem, minimizing and/or neutralizing much of the gains made in the CVD-related adverse outcomes by these measures. Continued high prevalence of obesity is likely to impede future reductions in CVD. It is important to recognize that cardiometabolic risk is directly related to the cumulative and continued exposure to obesity. Although prevention of obesity is the best approach for primary prevention, it has not been previously feasible at the population level. In an effort to identify a subgroup of obese subjects in whom concerted efforts can be made to intervene early to reduce the risk of developing MetS, diabetes, and subsequent CVD, the cohort with minimal or no changes in cardiometabolic abnormalities has been identified as MHO. Several studies, however, including the present paper by Mongraw-Chaffin et al. (9), emphasize that MHO is an unstable condition over the long term and comprises a heterogeneous group of obese subjects, the majority of whom can convert to MUO and develop MetS over time. Early identification of individuals with MHO provides an excellent opportunity for primary prevention at the population level, by instituting simple lifestyle changes, such as weight loss and regular PA, that can prevent conversion to MUO and

development of MetS and subsequent CVD. Indeed, such population-wide healthy interventions are the only hope of preventing the oncoming tsunami of MetS, diabetes, and CVD. Long-term health in the United States and most of the Westernized world depend on these efforts.

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