Commentary

Is the Metabolically Healthy Obesity Phenotype an Irrelevant Artifact for Public Health?

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Some obese persons do not develop (at least in the short term) the metabolic complications of obesity that are thought to be causally linked to cardiovascular events or premature mortality. This phenomenon has been termed “metabolically healthy obesity” (MHO), and it has received much attention recently, to the extent that some authors argue that “new metrics” must be developed to estimate the risk associated with obesity beyond body mass index. In this commentary, we argue that the MHO phenotype is not benign and as such has very limited relevance as a public health target. More efforts must be allocated to reducing the distal and actual causal agents that lead to weight gain, instead of the current disproportionate scientific interest in the biological processes that explain the heterogeneity of obesity.

metabolic syndrome; obesity; prevention; risk factors

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; MHO, metabolically healthy obesity; MUO, metabolically unhealthy obesity.

Editor’s note: An invited commentary on this article appears on page 742, and the authors’ response appears on page 745.

The obesity epidemic poses one of the greatest global challenges to health-care systems in this century. A recent study of US adults showed that the prevalence of obesity, defined as body mass index (BMI; weight (kg)/height (m)^2) ≥30, rose from 19% in 1980 to 34% in 2013 (1). It is well established that overweight and obese individuals are at higher risk of suffering from cardiovascular diseases, type 2 diabetes, and some cancers (2). In addition, obesity is associated with numerous comorbid conditions, such as an increased risk of osteoarthritis (knee and hip) (3) and sleep-disordered breathing (4). Despite the strong evidence of the many negative health consequences of obesity, some obese persons do not develop (at least in the short term) metabolic complications that are thought to be causally linked to cardiovascular events or premature mortality (5), such as dyslipidemia, abnormal glucose metabolism, and systemic inflammation. This phenomenon has been termed “metabolically healthy obesity” (MHO), and it has received much attention recently, to the extent that some authors argue that “new metrics” must be developed to estimate the risk associated with obesity beyond BMI (6). Despite the growing scientific interest related to the characterization of subgroups of obesity based on their associated metabolic risks (5), in this commentary we argue that the MHO phenotype is not benign and as such has very limited relevance as a public health target. (Our key messages are summarized in the Appendix.)

THE DICHOTOMOUS CLASSIFICATION OF OBESITY: CONVENIENT TRUTHS FOR CLINICIANS?

The MHO phenotype was first described in 1982 by Sims, as noted by Samocha-Bonet et al. (7). Since then, many investigators have described the particular characteristics that may distinguish these individuals from those at higher metabolic risk, the associated mortality and disease risks in each subgroup, and the mechanisms that may lead to this seemingly favorable phenotype (5). However, there is a lack of consensus...
among authors about how to define metabolic health. For example, we recently found at least 30 different definitions of metabolic health in the literature (8), mainly based on various combinations of 4 conventional criteria: blood pressure, high-density lipoprotein (HDL) cholesterol, triglycerides, and plasma glucose. Other components less commonly used to define MHO were homeostasis model assessment of insulin resistance, waist circumference, diagnosis of type 2 diabetes, total cholesterol, C-reactive protein, and the ratio of triglycerides to HDL cholesterol. Recent efforts to develop a standardized definition of MHO have also appeared (9, 10); for example, the very specific definition proposed by van Vliet-Ostapchouk et al. (9) was having a BMI $\geq 30$ and none of the following criteria: systolic blood pressure $\geq 130$ mm Hg, diastolic blood pressure $\geq 85$ mm Hg, or use of antihypertensive medication; fasting blood glucose concentration $\geq 110$ mg/dL, nonfasting blood glucose concentration $\geq 126$ mg/dL, use of blood glucose–lowering medication, or diagnosis of type 2 diabetes; HDL cholesterol level $\leq 40$ mg/dL (in men) or $\leq 50$ mg/dL (in women) or medical treatment for low HDL cholesterol level; triglyceride concentration $\geq 151$ mg/dL or use of medication for elevated triglyceride level; and diagnosis of cardiovascular disease. Plourde and Karelis (10) defined MHO as: waist circumference $\geq 80$ cm (women) or $\geq 94$ cm (men), fasting blood glucose concentration $<101$ mg/dL, HDL cholesterol concentration $\geq 50$ mg/dL (women) or $\geq 40$ mg/dL (men), triglyceride concentration $<1.7$ mg/dL, and blood pressure $<120/80$ mm Hg.

The legacy of the eminent epidemiologist Geoffrey Rose offers important insights when considering the public health utility of the MHO phenotype. Traditionally, a medical diagnosis assumes that disease is a dichotomous state (a person either has or does not have the disease). Rose questioned this assumption and clearly articulated that the distinction between health and disease is commonly a medical artifact: “Disease is nearly always a quantitative rather than a categorical or qualitative phenomenon, and hence it has no natural definitions” (11, p. 8). Operationally dichotomizing a continuous risk factor in order to know the proportion of subjects above or below a certain threshold of interest is perhaps an efficient and convenient way to target persons who are most at risk in the population, but Rose emphasized that it is a mistake to consider this arbitrary decision an accurate description of the biological status of each individual rather than an operational convenience. In this sense, if disease were interpreted in terms of a continuum based on grade of severity, this would widen the task of preventive medicine. Despite the fact that MHO subjects (10%–51% of the total prevalence of obesity (8)) do not display traditional metabolic risk factors (hypertension, dyslipidemia, insulin resistance), recent studies have consistently shown that persons with the MHO phenotype are at higher risk of developing fatty liver (12) (a strong predictor of type 2 diabetes) or subclinical coronary atherosclerosis (13) than their normal-weight and metabolically healthy counterparts. Further support for the view that the MHO phenotype is not harmless comes from 3 recent meta-analyses (14–16) in which MHO individuals were at increased risk of all-cause mortality, cardiovascular events, or type 2 diabetes. In the context of Rose’s definition of human health and disease, these findings bring into question the extreme focus medicine has placed on surrogate outcomes (17) that are invariably used in an artificially dichotomous fashion to identify “disease.”

Other reasons used to justify the stratification (by metabolic profile) of obese persons are efficiency and cost-effectiveness (i.e., saving resources by specifically targeting obese people at higher metabolic risk) (5) and the assumption that persons with MHO and persons with “metabolically unhealthy obesity” (MUO) respond differently to various interventions (lifestyle changes, bariatric surgery) (5). However, both of these assertions are lacking a solid theoretical framework about how to apply preventive strategies, and neither of them is evidence-based. Although the economic argument supporting the stratification of obese populations is appealing, especially during times of global economic recession, this argument may be misleading: It is well established that epidemiologic findings have limited relevance for individuals because of the relatively poor predictive performance of values that denote “abnormal” levels of most established risk factors (17). For example, persons with a high serum cholesterol concentration are nearly 3 times more likely to die from ischemic heart disease than those with a low serum cholesterol concentration; but when a screening test is performed, the performance is poor: For a false positive rate of 5%, only 15% of those who would later die of ischemic heart disease would be identified (18). On the other hand, it has been suggested that MHO patients do not achieve metabolic benefits after lifestyle interventions (19, 20), although this has been contradicted by studies showing substantial metabolic improvements after lifestyle interventions, irrespective of the metabolic status of obese participants (21, 22). Therefore, certain suggested advantages of stratification by metabolic status are not compelling.

**PREVENTION STRATEGIES AND OBESITY**

Despite the lack of consensus, the simultaneous rise in the prevalence of obesity in almost all countries seems to be driven mainly by changes in the global food system (23), with the reduced physical demands of many modern occupations possibly playing a role (24). Worriyngly, no country in the world to date has reversed its obesity epidemic. Some barriers to action were recently discussed by Roberto et al. (25): lobbying from the food and restaurant industry, limited ability or unwillingness of governments to implement policies, absence of pressure from civil society for political action, and the lack of empirical assessment of the effects of many policies. Many debates about the causes and solutions of the obesity epidemic are based on dichotomies (25)—for example, treatment versus prevention priorities. Indeed, we agree with Kleinert and Horton (26) that this debate is at best distracting and hinders progress. It must be clearly stated that both types of strategies (individual- and population-level) are needed.

Efforts based on pharmacological, behavioral, or surgical therapies may ameliorate the medical consequences of obesity. Undoubtedly, clinical practice is extremely useful in many situations. Nevertheless, it should be openly recognized that further investments in this predominantly individual approach will not reverse the obesity epidemic, because 1) medical therapies or dramatic lifestyle changes do not modify the distal causes of obesity (i.e., modern processed
food and the built environment) and 2) individualized lifestyle modifications are commonly unsuccessful and inaccessible. Human behavior is largely automatic, cued by environmental stimuli. Thus, further progress in the prevention of obesity should target environmental variables instead of focus on the disproportionate importance assigned to human conscious reflection. As suggested by Kleinert and Horton’s words (26), the current growing scientific interest in the heterogeneity of obesity may potentially distract us and perhaps hinder further progress on the core issue: how to shift (to the left) the whole population BMI distribution.

Importantly, some detailed solutions have appeared. For example, there is certain consensus on actions that should be taken to promote healthy diets (the NOURISHING framework (27)) (25). Raising taxes on certain foods could produce huge public health benefits, as historically occurred with tobacco smoking or alcohol consumption. Governments could selectively tax unhealthier products and use that revenue to subsidize the production of nutrient-rich foods. In addition, changes in urban design promoting active methods of transport should be massively adopted. However, these types of initiatives will face enormous resistance, because they threaten the principles and values of globalization (i.e., reliance on motorized transport, free trade, privatization, less government intervention). The World Health Organization’s Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2020 (28) has a modest target of no increase in the worldwide prevalence of obesity between 2010 and 2025 (26). A key message in the Lancet Obesity Series, published in 2011, was that “the obesity epidemic will not be reversed without government leadership” (26, p. 2326). Therefore, the main challenge is whether governments will implement regulatory actions to halt the obesity epidemic.

SHIFTING THE FOCUS BEYOND BMI FOR POPULATION HEALTH? APPLYING THE “OCCAM’S RAZOR” PRINCIPLE

The rapid development in genomic medicine has created high expectations about the application of personalized medicine (29). As a result, there is a visible divide between individually targeted interventions and population-based strategies. Undoubtedly, advancements in basic science will positively impact future population health—assuming that a large majority of the population will have access to the relevant pharmaceuticals or other products, which clearly is not always the case in less wealthy countries, or even in wealthy countries with no free health care and large socioeconomic disparities (such as the United States). Nonetheless, genuine discoveries that have a measurable impact on the population’s health are very rare. In full agreement with Kuller (30), we think that the separation of epidemiology from biology may explain why incorrect public health messages are regularly disseminated by laboratory scientists and clinicians. The belief that a better mechanistic knowledge about diseases will delineate future prevention and treatment strategies is widely accepted among many scientists and the public. To illustrate this point, the World Obesity Federation recently gathered a group of researchers to discuss the MHO phenotype (7). They concluded, “A greater understanding of the MHO phenotype has important implications for therapeutic decision-making, characterization of subjects in research protocols, and medical education” (7, p. 705). Under this paradigm, the use of new technologies or biomarkers may become the main driver in research and clinical practice.

Although persons with MHO display a more favorable metabolic profile relative to those with MUO, when compared with normal-weight metabolic health, the MHO phenotype still displays increased values for cardiovascular risk factors, on average (i.e., higher blood pressure and lower HDL cholesterol level) (13). The best epidemiologic evidence indicates a strong direct association between increasing BMI (from 20 to 21) and higher risks of developing cardiovascular diseases (2), type 2 diabetes (2), some types of cancer (2), osteoarthritis (3), and sleep-disordered breathing (4). Assuming that we were able to treat MUO successfully and change it to MHO, it is worthwhile here to remember another axiom in preventive medicine: “A large number of people exposed to a small risk may generate many more cases than a small number exposed to a high risk” (11, p. 24). However, even this possible scenario remains far from reality. Recently examining the natural course of MHO across 20 years in a large population-based study, Bell et al. (31) demonstrated that half of MHO subjects progressed to MUO. In theory, persons with high BMI may share other characteristics (confounders) that could lead causally to metabolic risk. Nonetheless, in a recent Mendelian randomization study, Würtz et al. (32) concluded that increased adiposity has causal adverse effects on numerous risk markers for cardiovascular disease and type 2 diabetes in nonobese young adults. The scope of this commentary has been the public health burden related to weight gain, especially to obesity. It is worth mentioning, however, that a normal body weight is only 1 of many determinants of metabolic health.

In summary, policies that ensure the equitable distribution of and access to nutritious and calorically balanced food, along with an environment that empowers individuals and makes physically active lifestyles the easy and preferred option, should be cornerstones in the prevention of obesity. In addition, the promotion of more physically active lifestyles (i.e., active commuting) will generate other benefits for the planet, by drastically reducing humanity’s environmental footprint to sustainable levels. The principle enunciated by philosopher William of Ockham in the 14th century, “Entia non sunt multiplicanda praeter necessitatem” (“More things should not be used than are necessary”), summarizes the core message of the present essay. We believe that public health will benefit very little, if at all, from complex biological definitions of obesity and systems for characterizing obesity. Simple anthropometric variables (weight, height, waist circumference) give us enough information for public health surveillance and action. Governments must implement and continuously evaluate population-wide interventions that target the actual causes of obesity, not only its surrogate consequences.

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REFERENCES


APPENDIX

• The majority of obese individuals in a population develop metabolic risk factors (metabolically unhealthy obesity (MUO)). Clinical practice may partially ameliorate the medical consequences of obesity.

• In the long term, at least half of obese persons without metabolic risk factors (metabolically healthy obesity (MHO)) progress to MUO.

• MHO is not a benign condition. Persons with MHO are at increased risk of developing fatty liver, subclinical coronary atherosclerosis, diabetes, and cardiovascular events and of experiencing premature all-cause mortality compared with normal-weight subjects and the metabolically healthy.

• Intervention efforts must be allocated to reducing the distal causal agents that lead to weight gain instead of focusing disproportionately on the biological processes that explain the heterogeneity of obesity.

• Otherwise, efforts based predominantly on individualized approaches to treatment will not produce substantial public health benefits.