Metabolically healthy obesity: what's in a name?

Faidon Magkos

Department of Nutrition, Exercise, and Sports, University of Copenhagen, Copenhagen, Denmark

ABSTRACT

Metabolically healthy obesity refers to an obesity phenotype with no or little evidence of metabolic dysfunction. Lower liver fat content and visceral adipose tissue, greater insulin sensitivity and secretion, greater cardiorespiratory fitness, and a predominantly lower body (i.e., leg) fat deposition are key physiological traits of a metabolically healthy phenotype. About 35% of all subjects with obesity are metabolically healthy. These individuals have approximately half the risk of developing type 2 diabetes and cardiovascular disease compared with metabolically unhealthy subjects with obesity, but they still have a significantly greater risk (by 50–300%) compared with metabolically healthy lean subjects. Therefore, absence of metabolic risk factors in people with obesity should not be a contraindication for weight-loss treatment. Metabolically healthy obesity needs to be treated, and this need is reinforced by the fact that this phenotype is not stable over time, as ∼50% of these subjects will cease being metabolically healthy within ∼10 y. Intervening early is therefore important. Weight loss dose-dependently decreases visceral adipose tissue and liver fat content, and it improves multiorgan insulin sensitivity and β-cell function (i.e., it beneficially affects many of the physiological traits of a metabolically healthy phenotype); however, weight loss is very difficult to maintain. This typically results in disappointment among patients and hinders adherence, which is likely critical for the limited success of most weight-loss treatments in the long term. On the other hand, using ≥1 metabolic health targets in a non-weight-loss-centered treatment paradigm that includes prudent dietary changes and increased physical activity can serve as an appropriate first goal that can help motivate patients toward the long-term goals of obesity treatment. *Am J Clin Nutr* 2019;110:533–539.

Keywords: cardiovascular disease, diabetes, metabolically normal obesity, risk, excess weight

Introduction

The past 4 decades have witnessed a worldwide increase in the average BMI and the prevalence of overweight and obesity. The global age-standardized mean BMI (in kg/m^2) increased from <22 in 1975 to >24 in 2014, and the prevalence of obesity increased from 3–6% to 11–15%, respectively, so that in 2014, worldwide ∼266 million men and 375 million women were obese (1). Both an increase in energy intake (2) and a decrease in physical activity (3)—or an increase in sedentary behaviors (4)—have been proposed to be primarily responsible for this alarming trend by promoting a shift toward positive energy balance. Obesity is a multifactorial disease, but it typically develops as a result of small but chronic changes in energy balance—that is, when energy intake exceeds energy expenditure; the excess calories are stored in the body as fat (5). BMI correlates fairly well with body fat in both men and women, and it is therefore used to diagnose obesity, even though there is considerable variability in the percentage body fat (by more than 10 units) for any given BMI value (6, 7). From the evolutionary perspective, accumulation of body fat serves to provide fuel in periods of limited access to calories. Lean individuals with ∼12 kg of fat in their body (∼18% of body weight) can survive for ∼2 mo without food (8), whereas obese individuals can have >100 kg of body fat (∼50% of body weight) and can survive with no calorie intake for >1 y (9). Unfortunately, in modern times, when energy-rich food is readily available and accessible, there is excess accumulation of fat in the body (i.e., obesity), and this negatively affects most physiological functions and nearly all organ systems (10). As a result, obesity reduces survival by several years and increases total mortality, most notably mortality from cardiometabolic diseases such as type 2 diabetes, liver diseases, and cardiovascular diseases (11).

Nevertheless, it has become apparent that not all subjects with obesity present with an abnormal cardiometabolic profile, just as not all lean subjects (i.e., those without overweight or obesity) are necessarily free of metabolic risk factors (12). These individuals are referred to as "metabolically healthy" subjects with obesity. This novel concept may prove valuable for the targeted treatment of obesity, on the basis of stratification of subjects with obesity by metabolic health status (13). Identifying individuals with obesity who are metabolically healthy can potentially help avoid wasting time, effort, and resources on subjects who may not benefit—or benefit less—from weight loss treatment (14–17). This premise remains quite controversial (15, 18), particularly inasmuch as the healthier metabolic profile of subjects with metabolically healthy obesity may not necessarily translate into a lower mortality risk (19). This perspective briefly discusses recent findings on

Address correspondence to FM (e-mail: fma@nexs.ku.dk).

Received May 1, 2019. Accepted for publication June 6, 2019.

First published online June 26, 2019; doi: https://doi.org/10.1093/ajcn/nqz133.

metabolically healthy obesity to promote the idea that no obesity is truly benign and that obesity treatment should shift focus away from body weight and move toward improving metabolic health outcomes.

Definition and Prevalence

Although metabolically healthy obesity, in principle, implies an obesity phenotype without any metabolic abnormalities whatsoever, most investigators have defined metabolically healthy obesity as obesity in the absence of a clearly defined cardiometabolic disorder, such as the metabolic syndrome, insulin resistance, hypertension, diabetes, or dyslipidemia, but seldom in the absence of all of them (20). Therefore, the vast majority of studies have allowed their metabolically healthy obese subjects to have at least some degree of metabolic dysfunction (most commonly, having fewer than 2 metabolic syndrome criteria), and even then there has been considerable variability in the chosen criteria and cutoff values (21). In fact, a meta-analysis of published studies identified 30 different definitions of metabolic health (22). Despite recent attempts to standardize the concept of metabolically healthy obesity by proposing a harmonized definition (23), the absence of consensus and uniform criteria to define metabolically healthy obesity makes estimates of its prevalence somewhat elusive. Using different definitions can result in a 3-fold range in the prevalence of metabolically healthy obesity in the same population (24), with lower estimates being obtained when stricter criteria are being used, both within and between studies (22, 24). These uncertainties notwithstanding, a recent meta-analysis of 40 population-based studies concluded that ∼35% (95% CI: 32%, 39%) of all people with obesity in the world are metabolically healthy (25). Effectively, this raises the possibility that treatment efforts could focus on only 2 out of every 3 people with obesity. Nevertheless, the term "metabolically healthy" is often misinterpreted as meaning without any kind of complications whatsoever and, therefore, without the need to treat. It is important to remember that in addition to cardiometabolic diseases, obesity may be associated with orthopedic problems, reproductive disorders, depression, asthma, sleep apnea, renal disease, back pain, skin infections, cognitive decline, social stigma, and overall reduced quality of life (26). Therefore, absence of metabolic risk factors in people with obesity should not be an indication for labeling individuals with obesity as "healthy" and certainly should not be a contraindication for initiating treatment.

Physiological Traits of Metabolic Health

Many investigators have attempted to identify physiological correlates of metabolically healthy obesity. Stefan et al. (27) assessed ∼1000 individuals stratified by BMI. The prevalence of metabolically healthy phenotype decreased dose-dependently across the BMI strata, from 82% in subjects with normal weight to 62% in subjects with overweight and 42% in subjects with obesity. Principal component analysis was used to identify factors associated with metabolic health and disease. Greater liver fat content and visceral adipose tissue [but also abdominal (i.e., upper body) subcutaneous adipose tissue] were linked to metabolic disease, whereas greater insulin sensitivity, insulin secretion, cardiorespiratory fitness, and leg (i.e., lower body) subcutaneous fat mass were linked to metabolic health (27). Although it remains unclear which, if any, of these factors are causes and which are consequences of metabolic disease, the identified cluster of factors was similar across all BMI strata, suggesting that the underlying determinants of metabolic disease are more or less the same in people with normal weight, overweight, and obesity. In other words, these traits are not merely secondary to excess body fat. For example, a recent study identified several genetic loci related to insulin resistance in the absence of increased BMI and total body fat; these loci were very strongly associated with lower leg fat mass and a less "gynoid" distribution of obesity (28). Collectively, these observations suggest that inadequate expansion of lower body peripheral adipose tissue is a central component of metabolic disease, possibly by promoting storage of excess calories in upper body adipose tissue and organs, such as the liver, that are not traditionally associated with fat storage (29). In turn, accumulation of fat in these organs can disrupt normal physiological function and eventually lead to cardiometabolic disease. This is in line with the adipose tissue expandability hypothesis (30), which postulates that each individual has a maximum capacity for adipose tissue expansion, determined by both genetic and environmental factors. Once this limit is reached, excess calories begin to accumulate as fat in cells other than adipocytes (independent of obesity per se), causing lipotoxic insults including insulin resistance and inflammation (30).

Risk of Cardiometabolic Disease

Meta-analyses of prospective studies have unequivocally demonstrated that metabolically healthy subjects with obesity have approximately half the risk of developing type 2 diabetes (31) and cardiovascular diseases (20) compared with metabolically unhealthy subjects with obesity (**Figure 1**A and B, respectively). This reduction in risk is quite remarkable, but cardiometabolic disease risk is still significantly elevated by 50–300% compared with metabolically healthy lean subjects (i.e., the reference group in Figure 1). Hence, there is a clear need to treat both obesity phenotypes, whether unhealthy or healthy. These data also imply that the presence of obesity confers a smaller increase in risk compared with the presence of metabolic abnormalities per se. The importance of metabolic dysfunction, independent of excess body weight, is exemplified when evaluating risk of cardiometabolic disease among metabolically unhealthy individuals stratified by BMI status. A metabolically unhealthy phenotype, regardless of BMI, is associated with severalfold greater risk of type 2 diabetes (32) and cardiovascular disease (33) compared with a metabolically healthy lean phenotype. Interestingly, the increase in risk associated with the presence of metabolic dysfunction seems to be somewhat greater for lean than for obese subjects (Figure 1C and D, respectively). Likewise, data from The Health Improvement Network cohort in 3.5 million participants demonstrate that independent of BMI status, the presence of progressively more metabolic abnormalities (0, 1, 2, or 3) is associated with a dose-dependent increase in the risk of cardiovascular disease (34). These observations, representing the summation of data from many independent studies, demonstrate that metabolically healthy obesity is a significantly less risky

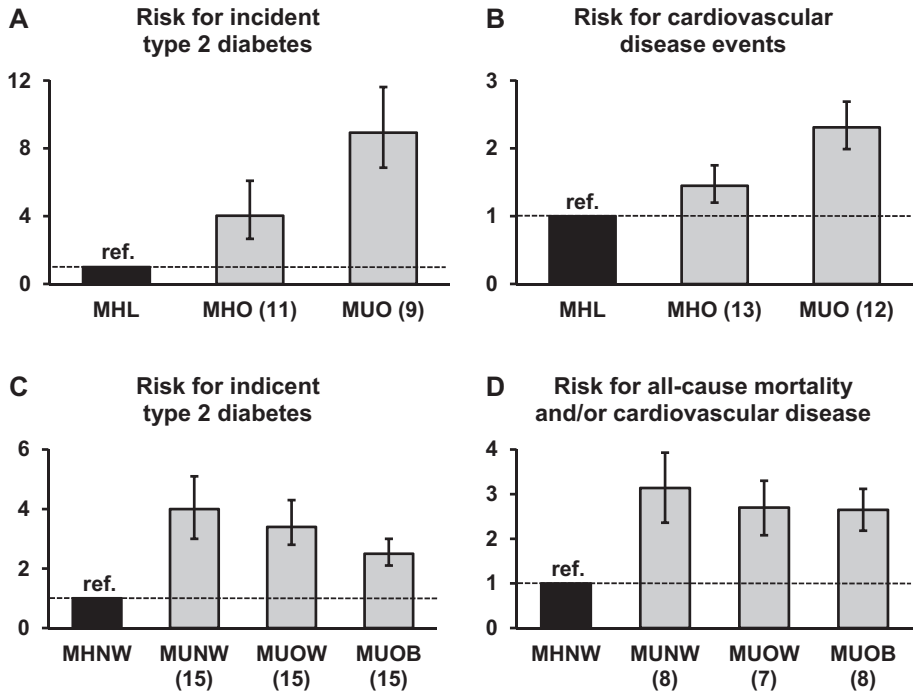

FIGURE 1 (Top) Risk of type 2 diabetes (A) and cardiovascular diseases (B) in MHO and MUO subjects compared to MHL subjects. (Bottom) Risk of type 2 diabetes (C) and cardiovascular diseases and all-cause mortality (D) in MUNW, MUOW, and MUOB subjects compared with MHNW subjects. Numbers in parentheses refer to the number of individual studies evaluating each phenotype. Bars indicate mean values, and error bars indicate the low and high 95% CIs. The risk of all experimental groups in all panels is statistically significantly greater than that of the corresponding reference group ($P < 0.05$). MHL, metabolically healthy lean subjects; MHNW, metabolically healthy subjects with normal weight; MHO, metabolically healthy obese subjects; MUNW, metabolically unhealthy subjects with normal weight; MUO, metabolically unhealthy obese subjects; MUOB, metabolically unhealthy subjects with obesity; MUOW, metabolically unhealthy overweight subjects. Figure based on data provided in the meta-analyses in references 20 and 31–33.

phenotype compared with obesity with metabolic dysfunction, but it is by no means a benign phenotype shielded against the development of cardiometabolic disease (35). This is true even when strict definition criteria are being used—that is, for individuals with obesity who have no metabolic abnormalities—although the increase in risk varies for different cardiovascular outcomes (~100% greater risk of heart failure, ~50% greater risk of coronary heart disease, ~10% greater risk of cerebrovascular disease, and no increase in risk of peripheral vascular disease compared with normal weight individuals with no metabolic abnormalities) (34).

Stability of the Phenotype over Time

A previous study classified subjects with obesity as healthy or unhealthy on the basis of liver fat content alone and found that metabolically healthy subjects were protected against the deleterious metabolic effects of modest weight gain induced by overfeeding (~6% of baseline body weight after 8 wk) (36). Although these results are impressive, what is not known is whether this protection is permanent or just temporary. A recent meta-analysis of 12 cohort studies including a total of 5914 metabolically healthy subjects with obesity found that approximately half (49%; 95% CI: 38%, 60%) developed 1 or more metabolic abnormalities during a natural follow-up period of 3–10 y and therefore ceased being "metabolically healthy" (25). In addition, as shown in a recent report from the Multi-Ethnic Study of Atherosclerosis, conversion from a metabolically healthy obesity phenotype to a metabolically unhealthy obesity phenotype was associated with a significant increase in the risk of cardiovascular disease (by ~60% during a median follow-up of 12.2 y) (37). This was not the case for individuals with obesity who maintained their metabolically healthy phenotype over time, in whom risk was indistinguishable from that in metabolically healthy lean subjects (37). These data suggest that a stable metabolically healthy obesity phenotype may, in fact, not confer significantly increased risk of cardiometabolic disease. Conversion to an unhealthy phenotype can also be observed among subjects without obesity (25, 38), and 30-y follow-up data from the Nurses' Health Study demonstrated that conversion to a metabolically unhealthy phenotype increases cardiovascular disease risk independent of BMI status (39). Overall, these data suggest that metabolic health is a temporary trait, and its loss—which is not necessarily the result of weight gain and obesity—increases the risk of developing cardiometabolic disease. Nevertheless, Appleton et al. (38) observed that although ~30% of subjects with metabolically healthy obesity at baseline converted to an unhealthy phenotype after a natural follow-up of 5.5–10.3 y, the opposite also occurred, with ~16% of subjects with metabolically unhealthy obesity at baseline converting to a healthy phenotype at follow-up. Appropriate interventions to facilitate conversion from a metabolically unhealthy to a metabolically healthy phenotype in individuals with obesity may

therefore be valuable in reducing obesity-related comorbidities. Early treatment is essential because the proportion of subjects who remain metabolically healthy declines almost linearly with age independent of BMI status (39).

Role of Weight Loss in Obesity Treatment

Moderate weight loss has long been considered the cornerstone of obesity treatment, with most scientific organizations and expert panel committees recommending 5–8% weight loss in order to reduce risk of cardiometabolic disease and obesity-related comorbidities (40–43). It is not entirely clear if weight loss has similar beneficial effects in people with metabolically healthy and unhealthy obesity. In response to various lifestyle interventions inducing weight losses of 3–7% in magnitude during a period of 3–9 mo, improvements in several (but not all) metabolic outcomes have been reported to be smaller among people with metabolically healthy obesity compared with those with metabolically unhealthy obesity (14–17), whereas improvements of similar magnitude have been observed after somewhat greater weight loss (8–9%) (18). Whether the amount of weight loss, the duration of the intervention, the type of diet and exercise prescription, the definition of metabolic health, or other factors are responsible for these inconsistent results is not known. A recent study in subjects with metabolically healthy obesity who lost <10% or >10% of their baseline body weight after a 12-mo lifestyle intervention found changes in the plasma metabolome that are consistent with a dose-dependent weight-loss-induced improvement in the cardiometabolic risk profile (44), suggesting that greater weight loss can improve metabolic function in people with obesity irrespective of baseline metabolic status. Clearly, this is an area of investigation in which more research is required.

A variety of approaches can be used to induce clinically significant weight loss (5–8%), including diet, exercise, and pharmacotherapy (45). Among the various dietary treatments, low-calorie diets, high- and low-fat diets, high-protein diets, meal replacements, dietary regimens with and without behavioral and physical activity components, and so on have all been shown to be effective in the short term (46). However, a common characteristic of all approaches is the regain of lost weight over time so that maintenance of a weight loss ≥5% in the long term is unlikely (45, 46). Furthermore, even when an intervention is successful in maintaining modest weight loss for a prolonged period of time, such as ∼6% weight loss after ∼10 y of follow-up in the Action for Health in Diabetes (Look AHEAD) study, there is still no clear beneficial effect on cardiovascular disease morbidity and mortality (47). It is not known if this can be attributed to the presence of diabetes, the older age, the generally low baseline cardiovascular disease risk of the Look AHEAD participants, the gradual decline in body weight in the control group that minimized differences in weight loss from the intervention group at study end (3.5% and 6%, respectively), or possible differences between groups in the composition of lost weight (i.e., fat and lean mass) (47–49). A recent post hoc analysis of the Look AHEAD trial examined weight loss in the entire cohort and found that individuals who lost ≥10% of their baseline body weight in the first year had ∼21% lower risk of the primary outcome and ∼24% lower risk of the secondary outcome during ∼10 y of follow-up compared with individuals with stable weight or weight gain (50). These observations raise the possibility that greater amounts of weight loss may be required to decrease cardiovascular disease morbidity and mortality. However, lifestyle intervention approaches, no matter how intense, are unlikely to treat obesity in the long term (i.e., reduce BMI to <30 kg/m^2) (21). In fact, this may be true even for bariatric surgery, despite the massive amounts of weight loss, because these patients typically start from a much greater baseline BMI (21).

Non-Weight-Loss-Centered Treatment Paradigms

The treatment of obesity need not necessarily focus on the quantitative reduction in energy intake to induce weight loss. Qualitative changes in the diet but also increased physical activity can favorably affect cardiometabolic function and decrease disease risk, even with little accompanying weight loss. Adoption of a more plant-based dietary pattern is increasingly being recommended for lowering cardiometabolic disease risk and improving overall health and well-being (51); however, not all plant-based diets are created equal. In a reanalysis of data from 3 prospective cohort studies in the United States (Nurses' Health Study I and II in women and the Health Professionals Follow-Up Study in men), Satija et al. (52, 53) observed that plant-based diets containing higher amounts of healthy foods such as whole grains, fruits, vegetables, nuts, legumes, oils, tea, and coffee were associated with lower risk of coronary heart disease and type 2 diabetes, but plant-based diets including higher amounts of less healthy plant foods, such as refined grains, potatoes/fries, and foods and beverages high in added sugar, were linked to increased disease risk. Accordingly, a large European randomized controlled trial [the PREDIMED (PREvención con DIeta MEDiterránea) study; reanalyzed] demonstrated that a Mediterranean-style diet without energy restriction can decrease cardiovascular disease and diabetes risk by ∼30% and 20–40%, respectively, during a period of ∼5 y compared with a control low-fat diet, in the absence of significant changes in body weight (54–56). The Mediterranean diet is a relatively high-fat dietary pattern (total fat intake ranges from 30% to >40% of energy; mainly unsaturated vegetable fats) and is characterized by high intake of plant foods (fruits, vegetables, breads, other forms of cereals, potatoes, beans, nuts, and seeds) and olive oil as the principal source of fat; moderate intake of dairy products (principally cheese and yogurt), fish, and poultry; and low intake of red meat, processed foods, and sweets (57). In contrast to the beneficial effects of a high-fat Mediterranean dietary pattern, decreasing total fat intake to <20% of energy while still increasing consumption of fruits, vegetables, and grains, as in the Women's Health Initiative Dietary Modification Trial, did not significantly reduce cardiovascular disease or diabetes risk, despite inducing small amounts of weight loss (0.5–2 kg over 7–9 y) (58–60). These observations emphasize the importance of both diet composition and food sources when evaluating the health effects of diets. A variety of eating patterns can have beneficial effects on metabolic parameters independent of changes in body weight (61, 62), but whether they can help in the conversion of metabolically unhealthy obesity to the metabolically healthy phenotype is not known.

Physical activity has received little attention in studies evaluating morbidity and mortality in metabolically healthy and unhealthy obese and lean individuals. A recent meta-analysis of cross-sectional studies concluded that subjects with metabolically healthy obesity are more physically active, spend less time in sedentary activities, and have ~30% greater cardiorespiratory fitness (an objective measure of aerobic/endurance capacity)—but not different muscle strength—compared with subjects with metabolically unhealthy obesity (63). Cardiorespiratory fitness is an important physiological trait of metabolic health independent of BMI status (27), and adjusting for physical activity or fitness attenuates or abolishes the increase in cardiovascular disease morbidity and mortality associated with metabolically healthy obesity compared with the metabolically healthy normal-weight status (23, 63, 64). Despite the fact that aerobic exercise is less effective than hypocaloric diet in reducing body weight in practice, it is more effective in decreasing visceral fat, which is an adipose tissue depot that is strongly linked with metabolic dysfunction (65). Accordingly, regular exercise training, even with minimal or no weight loss, can bring about a variety of beneficial changes in cardiometabolic risk factors, such as improved insulin sensitivity and glucose homeostasis, enhanced endothelial function, favorable alterations in the blood lipid and lipoprotein profile, lower blood pressure, improved hemostatic function, increased anti-inflammatory markers, and decreased pro-inflammatory markers (66, 67). Putting more focus on increasing time devoted to physical activity and decreasing sedentary time may thus be a critical component of a non-weight-loss-centered approach to treat metabolically unhealthy obesity, help transition into the metabolically healthy obesity phenotype, and ultimately lower cardiometabolic morbidity and mortality in these subjects.

Conclusions

On the basis of the aforementioned findings, it is reasonable to question whether obesity treatment should keep focusing on weight loss per se or shift focus on parameters of metabolic health. Focusing on weight loss as the main treatment outcome can have negative effects on long-term adherence because the gradual slowing of the rate of weight loss with time and the subsequent weight regain can make patients feel disappointed and helpless, and thereby more likely to relapse to pretreatment patterns of eating and physical activity (68). It has been shown repeatedly that adherence to the diet—whichever diet that may be—is a key factor for long-term weight-loss treatment success (69, 70). Achieving 1 or more "easier" metabolic health targets (e.g., reducing fasting or postprandial blood glucose concentrations), despite not losing a significant amount of weight, can act as positive reinforcement and facilitate adherence. Although it remains uncertain if metabolically healthy subjects with obesity will benefit from moderate weight loss (5–10%) to the same extent as their metabolically unhealthy peers (14, 15, 18), there is no doubt that this amount of weight loss has multiple beneficial effects for metabolically unhealthy subjects with obesity (15, 18, 71). Weight loss dose-dependently decreases visceral adipose tissue and liver fat content, and it improves multiorgan insulin sensitivity and β-cell function (71), all of which have been identified as key correlates of metabolic health (27). As a result, ~25–30% of metabolically unhealthy subjects with obesity convert to a metabolically healthy phenotype after a modest ~10% weight loss, even if obesity is not resolved (18, 21). Note, however, that smaller weight losses (2–4%) may not be sufficient to induce a shift from the unhealthy to the healthy obesity phenotype, despite significant improvements in several cardiometabolic risk factors (16, 17).

In addition, there is ample evidence of multiple health benefits of a non-weight-loss-centered paradigm for obesity treatment (66), thereby providing a wide array of possible initial therapeutic targets. In this respect, the concept of metabolically healthy obesity might be an appropriate first goal of treatment, which can motivate patients toward the long-term goal of lower body weight and protection from cardiometabolic disease (21). Implementation of such a treatment paradigm in clinical practice will require a consensus on the definition of metabolically healthy obesity, or at the very least a clear description of initial metabolic health goals. Although this is not going to be an easy process, the historical failure of traditional obesity treatment paradigms suggests we at least start assessing the problem of obesity from a different perspective.

The sole author was responsible for all aspects of this manuscript. The author declares no conflicts of interest.

References

1. NCD Risk Factor Collaboration. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet 2016;387:1377–96.
2. Brown RE, Sharma AM, Ardern CI, Mirdamadi P, Mirdamadi P, Kuk JL. Secular differences in the association between caloric intake, macronutrient intake, and physical activity with obesity. Obes Res Clin Pract 2016;10:243–55.
3. Ladabaum U, Mannalithara A, Myer PA, Singh G. Obesity, abdominal obesity, physical activity, and caloric intake in US adults: 1988 to 2010. Am J Med 2014;127:717–27 e12.
4. Ng SW, Popkin BM. Time use and physical activity: a shift away from movement across the globe. Obes Rev 2012;13:659–80.
5. Rosenbaum M, Leibel RL, Hirsch J. Obesity. N Engl J Med 1997;337:396–407.
6. Gallagher D, Heymsfield SB, Heo M, Jebb SA, Murgatroyd PR, Sakamoto Y. Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. Am J Clin Nutr 2000;72:694–701.
7. Gallagher D, Visser M, Sepulveda D, Pierson RN, Harris T, Heymsfield SB. How useful is body mass index for comparison of body fatness across age, sex, and ethnic groups? Am J Epidemiol 1996;143:228–39.
8. Leiter LA, Marliss EB. Survival during fasting may depend on fat as well as protein stores. JAMA 1982;248:2306–7.
9. Stewart WK, Fleming LW. Features of a successful therapeutic fast of 382 days' duration. Postgrad Med J 1973;49:203–9.
10. Bhoyrul S, Lashock J. The physical and fiscal impact of the obesity epidemic: the impact of comorbid conditions on patients and payers. J Managed Care Med 2018;11(4):10–17.
11. Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet 2009;373:1083–96.
12. Wildman RP, Muntner P, Reynolds K, McGinn AP, Rajpathak S, Wylie-Rosett J, Sowers MR. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999–2004). Arch Intern Med 2008;168:1617–24.
13. Stefan N, Haring HU, Hu FB, Schulze MB. Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. Lancet Diabetes Endocrinol 2013;1:152–62.

14. Karelis AD, Messier V, Brochu M, Rabasa-Lhoret R. Metabolically healthy but obese women: effect of an energy-restricted diet. Diabetologia 2008;51:1752–4.
15. Janiszewski PM, Ross R. Effects of weight loss among metabolically healthy obese men and women. Diabetes Care 2010;33:1957–9.
16. Kantartzis K, Machann J, Schick F, Rittig K, Machicao F, Fritsche A, Häring HU, Stefan N. Effects of a lifestyle intervention in metabolically benign and malign obesity. Diabetologia 2011;54:864–8.
17. Shin MJ, Hyun YJ, Kim OY, Kim JY, Jang Y, Lee JH. Weight loss effect on inflammation and LDL oxidation in metabolically healthy but obese (MHO) individuals: low inflammation and LDL oxidation in MHO women. Int J Obes (Lond) 2006;30:1529–34.
18. Ruiz JR, Ortega FB, Labayen I. A weight loss diet intervention has a similar beneficial effect on both metabolically abnormal obese and metabolically healthy but obese premenopausal women. Ann Nutr Metab 2013;62:223–30.
19. Primeau V, Coderre L, Karelis AD, Brochu M, Lavoie ME, Messier V, Sladek R, Rabasa-Lhoret R. Characterizing the profile of obese patients who are metabolically healthy. Int J Obes (Lond) 2011;35: 971–81.
20. Eckel N, Meidtner K, Kalle-Uhlmann T, Stefan N, Schulze MB. Metabolically healthy obesity and cardiovascular events: a systematic review and meta-analysis. Eur J Prev Cardiol 2016;23:956–66.
21. Stefan N, Haring HU, Schulze MB. Metabolically healthy obesity: the low-hanging fruit in obesity treatment? Lancet Diabetes Endocrinol 2018;6:249–58.
22. Rey-Lopez JP, de Rezende LF, Pastor-Valero M, Tess BH. The prevalence of metabolically healthy obesity: a systematic review and critical evaluation of the definitions used. Obes Rev 2014;15:781–90.
23. Lavie CJ, Laddu D, Arena R, Ortega FB, Alpert MA, Kushner RF. Healthy weight and obesity prevention: JACC health promotion series. J Am Coll Cardiol 2018;72:1506–31.
24. Liu C, Wang C, Guan S, Liu H, Wu X, Zhang Z, Gu X, Zhang Y, Zhao Y, Tse LA, et al. The prevalence of metabolically healthy and unhealthy obesity according to different criteria. Obes Facts 2019;12:78–90.
25. Lin H, Zhang L, Zheng R, Zheng Y. The prevalence, metabolic risk and effects of lifestyle intervention for metabolically healthy obesity: a systematic review and meta-analysis: a PRISMA-compliant article. Medicine (Baltimore) 2017;96:e8838.
26. Hill JO, Wyatt HR. The myth of healthy obesity. Ann Intern Med 2013;159:789–90.
27. Stefan N, Schick F, Haring HU. Causes, characteristics, and consequences of metabolically unhealthy normal weight in humans. Cell Metab 2017;26:292–300.
28. Lotta LA, Gulati P, Day FR, Payne F, Ongen H, van de Bunt M, Gaulton KJ, Eicher JD, Sharp SJ, Luan J, et al. Integrative genomic analysis implicates limited peripheral adipose storage capacity in the pathogenesis of human insulin resistance. Nat Genet 2017;49: 17–26.
29. Cuthbertson DJ, Steele T, Wilding JP, Halford JC, Harrold JA, Hamer M, Karpe F. What have human experimental overfeeding studies taught us about adipose tissue expansion and susceptibility to obesity and metabolic complications? Int J Obes (Lond) 2017;41:853–65.
30. Virtue S, Vidal-Puig A. Adipose tissue expandability, lipotoxicity and the metabolic syndrome—an allostatic perspective. Biochim Biophys Acta 2010;1801:338–49.
31. Bell JA, Kivimaki M, Hamer M. Metabolically healthy obesity and risk of incident type 2 diabetes: a meta-analysis of prospective cohort studies. Obes Rev 2014;15:504–15.
32. Lotta LA, Abbasi A, Sharp SJ, Sahlqvist AS, Waterworth D, Brosnan JM, Scott RA, Langenberg C, Wareham NJ. Definitions of metabolic health and risk of future type 2 diabetes in BMI categories: a systematic review and network meta-analysis. Diabetes Care 2015;38:2177–87.
33. 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.
34. Caleyachetty R, Thomas GN, Toulis KA, Mohammed N, Gokhale KM, Balachandran K, Nirantharakumar K. Metabolically healthy obese and incident cardiovascular disease events among 3.5 million men and women. J Am Coll Cardiol 2017;70:1429–37.
35. Lavie CJ, Deedwania P, Ortega FB. Obesity is rarely healthy. Lancet Diabetes Endocrinol 2018;6:678–9.
36. Fabbrini E, Yoshino J, Yoshino M, Magkos F, Tiemann Luecking C, Samovski D, Fraterrigo G, Okunade AL, Patterson BW, Klein S. Metabolically normal obese people are protected from adverse effects following weight gain. J Clin Invest 2015;125:787–95.
37. Mongraw-Chaffin M, Foster MC, Anderson CAM, Burke GL, Haq N, Kalyani RR, Ouyang P, Sibley CT, Tracy R, Woodward M, et al. Metabolically healthy obesity, transition to metabolic syndrome, and cardiovascular risk. J Am Coll Cardiol 2018;71:1857–65.
38. Appleton SL, Seaborn CJ, Visvanathan R, Hill CL, Gill TK, Taylor AW, Adams RJ; 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.
39. Eckel N, Li Y, Kuxhaus O, Stefan N, Hu FB, Schulze MB. Transition from metabolic healthy to unhealthy phenotypes and association with cardiovascular disease risk across BMI categories in 90 257 women (the Nurses' Health Study): 30 year follow-up from a prospective cohort study. Lancet Diabetes Endocrinol 2018;6:714–24.
40. American College of Cardiology/American Heart Association Task Force on Practice Guidelines Obesity Expert Panel. Executive summary: guidelines (2013) for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Obesity Society published by the Obesity Society and American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Based on a systematic review from the The Obesity Expert Panel, 2013. Obesity (Silver Spring) 2014;22(Suppl 2):S5–39.
41. American Diabetes Association. Standards of medical care in diabetes—2016. Diabetes Care 2016;39:S1–112.
42. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, Lee IM, Lichtenstein AH, Loria CM, Millen BE, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:S76–99.
43. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, Hu FB, Hubbard VS, Jakicic JM, Kushner RF, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. J Am Coll Cardiol 2014;63:2985–3023.
44. Palau-Rodriguez M, Garcia-Aloy M, Minarro A, Bernal-Lopez MR, Brunius C, Gómez-Huelgas R, Landberg R, Tinahones FJ, Andres-Lacueva C. Effects of a long-term lifestyle intervention on metabolically healthy women with obesity: metabolite profiles according to weight loss response. Clin Nutr 2019. In press.
45. Franz MJ, VanWormer JJ, Crain AL, Boucher JL, Histon T, Caplan W, Bowman JD, Pronk NP. Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. J Am Diet Assoc 2007;107:1755–67.
46. Franz MJ, Boucher JL, Rutten-Ramos S, VanWormer JJ. Lifestyle weight-loss intervention outcomes in overweight and obese adults with type 2 diabetes: a systematic review and meta-analysis of randomized clinical trials. J Acad Nutr Diet 2015;115:1447–63.
47. Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013;369: 145–54.
48. Belalcazar LM, Ballantyne CM. Looking back at Look AHEAD through the lens of recent diabetes outcome trials. Circulation 2017;135:720–3.
49. Pownall HJ, Bray GA, Wagenknecht LE, Walkup MP, Heshka S, Hubbard VS, Hill J, Kahn SE, Nathan DM, Schwartz AV, et al. Changes in body composition over 8 years in a randomized trial of a lifestyle intervention: the Look AHEAD study. Obesity (Silver Spring) 2015;23:565–72.
50. Look AHEAD Research Group. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. Lancet Diabetes Endocrinol 2016;4:913–21.
51. Willett W, Rockstrom J, Loken B, Springmann M, Lang T, Vermeulen S, Garnett T, Tilman D, DeClerck F, Wood A, et al. Food in the Anthropocene: the EAT-Lancet Commission on healthy diets from sustainable food systems. Lancet 2019;393:447–92.

52. Satija A, Bhupathiraju SN, Rimm EB, Spiegelman D, Chiuve SE, Borgi L, Willett WC, Manson JE, Sun Q, Hu FB. Plant-based dietary patterns and incidence of type 2 diabetes in US men and women: results from three prospective cohort studies. PLoS Med 2016;13:e1002039.
53. Satija A, Bhupathiraju SN, Spiegelman D, Chiuve SE, Manson JE, Willett W, Rexrode KM, Rimm EB, Hu FB. Healthful and unhealthful plant-based diets and the risk of coronary heart disease in U.S. adults. J Am Coll Cardiol 2017;70:411–22.
54. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. N Engl J Med 2018;378:e34.
55. Estruch R, Martinez-Gonzalez MA, Corella D, Salas-Salvadó J, Fitó M, Chiva-Blanch G, Fiol M, Gómez-Gracia E, Arós F, Lapetra J, et al. Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: a prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial. Lancet Diabetes Endocrinol 2019;7:e6–e17.
56. Salas-Salvado J, Bullo M, Estruch R, Ros E, Covas MI, Ibarrola-Jurado N, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, et al. Prevention of diabetes with Mediterranean diets: a subgroup analysis of a randomized trial. Ann Intern Med 2014;160:1–10.
57. Willett WC, Sacks F, Trichopoulou A, Drescher G, Ferro-Luzzi A, Helsing E, Trichopoulos D. Mediterranean diet pyramid: a cultural model for healthy eating. Am J Clin Nutr 1995;61:1402S–6S.
58. Howard BV, Manson JE, Stefanick ML, Beresford SA, Frank G, Jones B, Rodabough RJ, Snetselaar L, Thomson C, Tinker L, et al. Low-fat dietary pattern and weight change over 7 years: the Women's Health Initiative Dietary Modification Trial. JAMA 2006;295:39–49.
59. Howard BV, Van Horn L, Hsia J, Manson JE, Stefanick ML, Wassertheil-Smoller S, Kuller LH, LaCroix AZ, Langer RD, Lasser NL, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA 2006;295:655–66.
60. Tinker LF, Bonds DE, Margolis KL, Manson JE, Howard BV, Larson J, Perri MG, Beresford SA, Robinson JG, Rodríguez B, et al. Low-fat dietary pattern and risk of treated diabetes mellitus in postmenopausal women: the Women's Health Initiative randomized controlled dietary modification trial. Arch Intern Med 2008;168:1500–11.
61. Evert AB, Dennison M, Gardner CD, Garvey WT, Lau KHK, MacLeod J, Mitri J, Pereira RF, Rawlings K, Robinson S, et al. Nutrition therapy for adults with diabetes or prediabetes: a consensus report. Diabetes Care 2019;42:731–54.
62. Katz DL, Meller S. Can we say what diet is best for health? Annu Rev Public Health 2014;35:83–103.
63. Ortega FB, Cadenas-Sanchez C, Migueles JH, Labayen I, Ruiz JR, Sui X, Blair SN, Martínez-Vizcaino V, Lavie CJ. Role of physical activity and fitness in the characterization and prognosis of the metabolically healthy obesity phenotype: a systematic review and meta-analysis. Prog Cardiovasc Dis 2018;61:190–205.
64. Lavie CJ, Ortega FB, Kokkinos P. Impact of physical activity and fitness in metabolically healthy obesity. J Am Coll Cardiol 2018;71: 812–13.
65. Verheggen RJ, Maessen MF, Green DJ, Hermus AR, Hopman MT, Thijssen DH. A systematic review and meta-analysis on the effects of exercise training versus hypocaloric diet: distinct effects on body weight and visceral adipose tissue. Obes Rev 2016;17: 664–90.
66. Gaesser GA, Angadi SS, Sawyer BJ. Exercise and diet, independent of weight loss, improve cardiometabolic risk profile in overweight and obese individuals. Phys Sportsmed 2011;39:87–97.
67. Lin X, Zhang X, Guo J, Roberts CK, McKenzie S, Wu WC, Liu S, Song Y. Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc 2015;4:e002014.
68. Middleton KR, Anton SD, Perri MG. Long-term adherence to health behavior change. Am J Lifestyle Med 2013;7: 395–404.
69. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. JAMA 2005;293:43–53.
70. Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, McManus K, Champagne CM, Bishop LM, Laranjo N, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med 2009;360: 859–73.
71. Magkos F, Fraterrigo G, Yoshino J, Luecking C, Kirbach K, Kelly SC, de Las Fuentes L, He S, Okunade AL, Patterson BW, et al. Effects of moderate and subsequent progressive weight loss on metabolic function and adipose tissue biology in humans with obesity. Cell Metab 2016;23:591–601.