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Review Article

Controversies in Obesity Treatment

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ABSTRACT

The markedly high prevalence of obesity contributes to the increased incidence of chronic diseases, such as diabetes, hypertension, sleep apnea, and heart disease. Because of high prevalence of obesity in almost all countries, it has been the focus of many researches throughout the world during the recent decades. Along with increasing researches, new concepts and controversies have been emerged. The existing controversies on the topic are so deep that some researches argue on absolutely philosophical questions such as "Is obesity a disease?" or "Is it correct to treat obesity?" These questions are based on a few theories and real data that explain obesity as *a biological adaptation* and also the final results of weight loss programs.

Many people attempt to lose weight by diet therapy, physical activity and lifestyle modifications. Importantly, weight loss strategies in the long term are ineffective and may have unintended consequences including decreasing energy expenditure, complicated appetite control, eating disorders, reducing self-esteem, increasing the plasma and tissue levels of persistent organic pollutants that promote metabolic complications, and consequently, higher risk of repeated cycles of weight loss and weight regain.

In this review, major paradoxes and controversies on obesity including classic obesity paradox, pre-obesity; fat-but-fit theory, and healthy obesity are explained. In addition, the relevant strategies like "Health at Every Size" that emphasize on promotion of global health behaviors rather than weight loss programs are explained.

Keywords: Obesity, Overweight, Obesity paradox, Fat-but-fit

Introduction

Obesity is characterized by excessive fat accumulation in adipose tissues and is prevalent in both the developed and developing countries; for instance, more than 35% of American adults are obese (1). In general, obesity is a complex condition with many causal contributors and is associated with a greater risk of many chronic diseases such as cardiovascular diseases (CVDs), stroke, hypertension, type 2 diabetes mellitus, and certain forms of cancers (2-3). In particular, obesity is related to the development of significant disability and increased risk of mortality during the adulthood (or premature death) (4-5). It also leads to the development of low self-esteem and other psychosocial problems (6). The global epidemic of obesity causes a large burden on the healthcare system, as well as noticeable healthcare-associated costs (7). The main strategies to approach the obesity problem include diet therapy, physical activity, pharmaco-therapy, surgery, behavior therapy, and lifestyle modification (8). Dietary programs and other weight loss strategies are widespread in the general population, and are widely encouraged in public health policy. In other words, 30–50 % of women and 10–30 % of men attempt to lose weight by dieting (9-10). Obviously, these weight loss strategies induce short term weight loss;

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however, they are ineffective in the long term, and also may make unintended consequences. Based on scientific evidence, one-third to two-thirds of the weight lost is regained within 1 year, and approximately within 5 years, all of the lost weight is regained (11). Undoubtedly, the majority of dieters are unable to maintain the reduced weight over the long term; additionally, more than 30% of dieters regain more weight than they lost (12). It is obvious that attempts to lose weight can end with decreased energy expenditure, complicated appetite control, eating disorders, reduced self-esteem, increased weight stigmatization and discrimination, and increased plasma and tissue levels of persistent organic pollutants. Repeated cycles of weight loss and weight regain cause weight cycling or yo–yo dieting with the potential for increased cardiovascular risks (12,14).

Body mass index (BMI, the weight in kilograms divided by height in meters squared) is a generally used parameter for classifying various degrees of adiposity and to evaluate the mortality risk associated with obesity (15). Although many epidemiological studies have shown that obesity is positively associated with higher mortality rates in the general population (4, 16), but consistent inverse associations (the so-called obesity paradox) have been also reported among obese patients with life-threatening diseases like coronary heart disease (17), peripheral artery disease (18), heart failure (19), acute myocardial infarction (20), hypertension (21), and chronic kidney disease (22). The term obesity paradox has been mentioned by Gruberg and colleagues to describe the unexpected finding that overweight and obese patients undergoing percutaneous coronary intervention compared to their normal-weight counterparts had lower mortality rates (23). Based on multiple documents and large meta-analyses, obesity paradox was not difficult to be accepted by scientists and clinicians. Although the existence of obesity paradox is well established, the possible mechanisms are poorly understood.

The current review article deals with evaluating the available information on four different obesity-related paradoxes as follows:

1. ***Classic obesity paradox***: Obesity is protective in some chronic diseases.
2. ***Pre-obesity***: Overweight is protective in normal populations.
3. ***Fat-but-fit***: Obesity is not a risk factor for mortality in fit individuals.
4. ***Healthy obesity***: A sizeable population of obese adults has normal cardio-metabolic risk profiles (24).

Paradox 1: Classic obesity paradox

Whereas obesity is positively associated with higher mortality rates in the general population, numerous studies have indicated that it might be associated with a better survival among obese patients with life-threatening diseases (17-22, 25-26). Based on scientific reports, the most consistent evidence of obesity paradox is observed in patients with known or suspected coronary heart disease (CHD) (Table I). Obviously, overweight and obesity have adverse effects, and increase the prevalence of cardiovascular risk factors and CDVs; however, many studies have reported that overweight and obese patients with various CDVs have better short- and long-term improvement and survival compared with their lean counterparts (27-34). A large systematic review of 40 cohort studies by Romero-Corral and colleagues on 250,152 patients with CHD exhibited significantly lower risks of cardiovascular mortality and total mortality in overweight patients (BMI 25-29.9 kg/m^2) compared with the normal-weight subjects. Obese patients (BMI 30-35 kg/m^2) had no increased risk for cardiovascular mortality or total mortality. However, severely obese patients (≥35.0 kg/m^2) had the highest risk (RR 1.88 [1.05-3.34]) for cardiovascular mortality (17). A cohort study including of 4164 patients with suspected stable angina undergoing elective coronary angiography showed that overweight women had a decreased risk of acute myocardial infarction (hazard ratio [HR] 0.56 [0.33, 0.98]) compared to the normal weight women (35).

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Table 1. Summary of studies reporting an obesity paradox in patients with cardiovascular patients

Author, year (Ref.)	Patient group	Population (% male)	Mean age (years)	Mean follow-up (years)	Adjusted variables	BMI groups (kg/m^2)	Hazard ratio (95% CI) or % deaths
Borgeraas, et al. 2014 (35)	BMI groups and risk of acute myocardial infarction and cardiovascular death in men	4164 (72%)	62	4	Age, current smoking, left ventricular ejection fraction (%), pulmonary disease, angiotensin converting enzyme-inhibitors and loop diuretics	18.5–24.9 25.0–29.9 ≥30.0	1 (referent) 1.11 (0.84, 1.48) 1.80 (1.28, 2.52)
Borgeraas, et al. 2014 (35)	BMI groups and risk of acute myocardial infarction and cardiovascular death in women	4164 (72%)	62	4	Age, current smoking, left ventricular ejection fraction (%), pulmonary disease, angiotensin converting enzyme-inhibitors and loop diuretics	18.5–24.9 25.0–29.9 ≥30.0	1 (referent) 0.56 (0.33, 0.98) 0.56 (0.33, 0.98)
Uretsky, et al. 2010 (36)	CAD (at risk)	3673 (36%)	60	7.5	Age, sex, race, clinical variables, medication use	18.5–24.9 25.0–29.9 ≥30.0	1 (referent) 0.54 (0.43–0.70) 0.49 (0.38–0.63)
Badheka, et al. 2010 (25)	Atrial fibrillation	2492 (61%)	70	3	Age, sex, clinical variables	18.5–24.9 25.0–29.9 ≥30.0	1 (referent) 0.64 (0.48–0.84) 0.80 (0.68–0.93)
McAuley, et al. 2010 (26)	CAD (known or at risk)	12,417 (100%)	57	7.7	Age, race, exam year, clinical variables, medication use, CRF	≤18.5 18.5–24.9 25.0–29.9 30.0–34.9 ≥35.0	1.86 (1.48–2.33) 1 (referent) 0.74 (0.68–0.81) 0.65 (0.59–0.72) 0.96 (0.82–1.12)
Hastie, et al. 2010 (29)	CAD/PCI	4880 (70%)	61	5	Age, sex, clinical variables	<20 20.0–24.9 25.0–27.49 27.5–29.9 ≥30.0	1.70 (0.67–4.27) 1 (referent) 0.68 (0.46–1.00) 0.58 (0.38–0.90) 0.86 (0.59–1.25)
Galal, et al. 2008 (18)	PAD	2392 (75%)	66	4.4	Age, sex, clinical variables, COPD severity, medication use	<18.5 18.5–24.9 25.0–29.9 ≥30.0	1.29 (0.91–1.93) 1 (referent) 0.74 (0.65–0.84) 0.68 (0.54–0.86)
Johnson, et al. 2008 (27)	CAD (known or at risk)	2119 (55%)	56	8.4	Age, sex, clinical variables, CRF	<25.0 25.0–29.9 30.0–34.9 35.0–39.9 ≥40.0	10.7% 8.5% 7.4% 8.1% 3.9%
Uretsky, et al. 2007 (21)	Hypertension and CAD	22576 (49%)	66	2.7	Age, sex, race, clinical variables	<18.5 18.5–24.9 25.0–29.9 30.0–34.9 ≥35.0	1.52 (1.24–1.86) 1 (referent) 0.77 (0.70–0.86) 0.68 (0.59–0.77) 0.76 (0.65–0.88)
Galal, et al. 2007(28)	CAD (known or at risk)	5950 (67%)	61	6	Age, sex, clinical variables	<18.5 18.5–24.9 25.0–29.9 ≥30.0	2.4 (1.7–3.6) 1 (referent) 0.7 (0.6–0.8) 0.6 (0.5–0.8)
McAuley, et al. 2007 (30)	CAD (known or at risk)	6876 (97%)	58	7.5	Age, sex, race, clinical variables, CRF	18.5–24.9 25.0–29.9 ≥30.0	1 (referent) 0.70 (0.63–0.79) 0.65 (0.57–0.76)
Kenchaiah, et al. 2007 (31)	Heart failure	7599 (65%)	65	3.1	Age, sex, clinical variables, medication use	<22.5 22.5–24.9 25.0–29.9 30.0–34.9 ≥35.0	1.69 (1.43–2.01) 1.46 (1.24–1.71) 1.22 (1.06–1.41) 1 (referent) 1.17 (0.95–1.43
Bozkurt & Deswal 2005 (32)	Heart failure	7622 (76%)	64	2	Age, sex, clinical variables, medication use	18.5–24.9 25.0–29.9 ≥30.0	1 (referent) 0.87 (0.79–0.95) 0.82 (0.73–0.92)
Curtis, et al. 2005 (31)	Heart failure	7767 (75%)	64	3.1	Age, sex, clinical variables, medication use	<18.5 18.5–24.9 25.0–29.9 ≥30.0	1.21 (0.95–1.53) 1 (referent) 0.88 (0.80–0.96) 0.81 (0.72–0.92)
Gustafsson, et al. 2005 (34)	Heart failure	4700 (61%)	72	5–8	Age, sex	<18.5 18.5–24.9 25.0–29.9 ≥30.0	1.56 (1.33–1.84) 1 (referent) 0.90 (0.83–0.97) 0.77 (0.70–0.86)

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Additionally, investigations performed in patients with hypertension and coronary heart disease showed a paradoxical decrease in mortality in those with higher BMI. In a cohort including 22,576 hypertensive patients, the occurrence of death, non-fatal myocardial infarction, or nonfatal stroke was lower in overweight patients (RR 0.77 [0.70-0.86]), class I obese patients (RR 0.68 [0.59-0.78]), and class II and III obese patients (RR 0.76 [0.65-0.88]) than in patients with normal weight as the referent group (36). The obesity paradox has also been indicated in patients with chronic heart failure (HF). Although obesity as defined by elevated BMI is a major risk factor for the development of HF, a surprising association between BMI and HF has been observed. It was first described by Horwich et al. (39) in a cohort study of 1203 advanced systolic HF patients, where patients with higher BMI (>27.8 kg/m^2) were found to have significantly improved risk-adjusted survival (Fig. 1). A relationship between BMI and in-hospital mortality was analyzed in 108,927 patients with decompensated HF over a 3-year period. Ten percent reduction in mortality rates for every 5-unit increase in BMI (P<0.001) was observed (40). Oreopoulos et al. in a meta-analysis of nine observational studies on HF patients (n= 28,209) during 2.7 years of follow-up found that overweight and obese individuals had reduced cardiovascular (−19% and −40%, respectively) and all-cause (−16% and −33%) mortality, respectively (41).

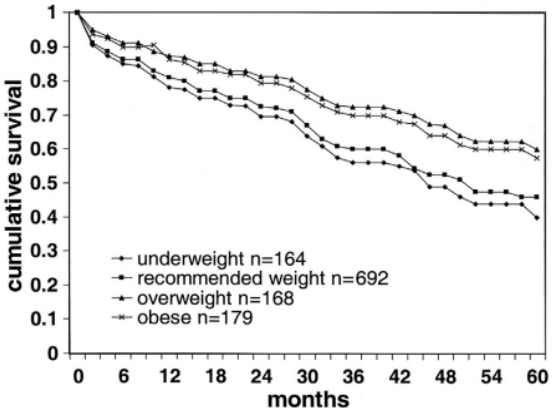

Fig. 1: Risk-adjusted survival curves for the four BMI categories at 5 years. The variables entered into the equation were age, gender, hypertension, diabetes mellitus, left ventricular ejection fraction, hemodynamic variables, peak VO2, mitral regurgitation, tricuspid regurgitation, medications and serum sodium, creatinine and lipid levels. Survival was significantly better for the overweight and obese BMI categories (39).

The obesity paradox was also confirmed in non-CV studies that included patients with end stage renal disease (ESRD) (40-41), diabetes (42) and the elderly (41). Epidemiologic studies have reported an inverse relationship between obesity and mortality rates in patients with chronic kidney disease (CKD). In hemodialysis patients, lower BMI and weight loss have been associated with higher mortality rates (40, 44). Glanton et al. conducted a historical cohort study on 151,027 incident ESRD patients. Obesity (BMI≥30 kg/m^2) was related to reduced mortality and higher two-years survival (44).

Most studies of the obesity paradox have used BMI to identify overweight and obese patients because of widespread acceptance and readily measured. However, this method has been criticized, and the reliability of BMI as a measure of true body fatness has been questioned. Critics of obesity paradox have pointed to the inaccurate diagnosis of obesity by the BMI assessment, and that defining obesity by other methods, including percentage of body fat (BF), waist circumference, and waist/hip ratio may be more accurate. Some investigators have demonstrated obesity paradox in CHD patients, hypertension and HF by using BMI as well as BF assessments. As a consequence, both higher BMI and higher percentage of body fat were independent predictors of better survival in these patients (45-48). However, more data are required to explain the obesity paradox phenomenon. Systematic review of the obesity paradox literature is needed to better synthesize the conflicting results.

Paradox 2: Pre-obesity: Overweight is protective in normal populations

The relationship between pre-obesity (BMI 25-29.9 kg/m^2) and mortality is less clear. Based on scientific evidence, pre-diabetes and pre-hypertension were associated with significant increased risk of CVD mortality and all-cause mortality (49-51). Therefore, a gradual increase in mortality risk from pre-obesity to obesity is expected. Additionally, being overweight has little effect on all-cause mortality rates, or either is beneficial in normal populations. By analysis of data from National Health and Nutrition Examination Survey (NHANES), Flegal et al. reported significantly lower risks for mortality in overweight compared with normal weight individuals (51). In a study from the National Population Health Survey (Canada), during an

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average of 12 years follow-up on 11,326 men and women, it was found that overweight (specifically BMI 27.5 to ≤30 kg/ m^2) was related to the lowest risk of all-cause mortality compared with other BMI categories (52) (Fig. 2).

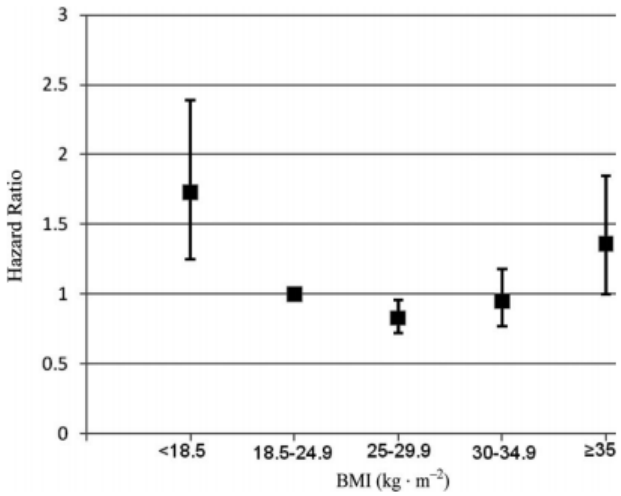

Fig. 2: Multivariate hazard ratios for all-cause mortality by BMI category in 11,326 men and women from the National Population Health Survey (Canada). Each data point represents the relative risk after adjustment for age, smoking status, physical activity frequency, and alcohol consumption, with the relative risk of normal weight (BMI 18.5–24.9 kg/m2) set at 1.0. Error bars represent 95% confidence intervals (24).

In a meta-analysis of 26 observational studies, McGee et al. found summary of the relative risks of all-cause mortality for overweight as 0.97 (95% CI, 0.93-0.99) for women, and 0.97 (95% CI, 0.92-1.01) for men relative to normal weight (51). Recent meta-analysis of 97 studies by Flegal and colleagues with more than 2.88 million individuals and more than 270 000 deaths, estimated the association of all-cause mortality in adults with the current standards of BMI categories. According to the results of this meta-analysis, overweight (BMI 25-29.9 kg/m^2) was associated with significantly lower all-cause mortality (HR 0.94 [0.91-0.96]) compared with normal-weight (52). In this analysis, only the findings related to standard BMI categories were included. Therefore, some high-quality studies were excluded. Also other aspects of body composition such as fitness level, visceral fat, or fat distribution were not included in this analysis. In Feb. 20, 2013, Harvard School of Public Health's Department of Nutrition assembled a panel of health experts to elucidate inaccuracies in this meta-analysis. Dr. Walter Willett explained that the overweight and obese groups in this meta-analysis were compared to the normal weight group included a mix of lean and active people, heavy smokers, patients with cancer or other conditions that cause weight loss. This mix of healthy and ill persons who have a very high risk of death led to the false conclusions. Dr. Hu highlighted another crucial weakness in the study design; many high-quality studies (including approximately 6 million people) were excluded from the primary analysis because they did not use standard BMI categories in the analysis (55).

Paradox 3: Fat-but-fit: Obesity is not a risk factor for mortality in fit individuals

Based on the available evidence, fat-but-fit individuals have considerably lower mortality risk compared to normal-weight but unfit individuals (56). Few studies have been conducted to determine the combined effects of fitness and BMI on mortality. However, available data indicate that fit obese individuals have no greater risk for CVD and all-cause mortality than their normal weight and fit counterparts (26, 56). Many studies dealing with the relationship between adiposity and mortality did not mention physical activity or fitness as possible confounding variables (57-58). A number of studies have indicated that physical activity is independently associated with mortality rates (59-60). Many studies have paid attention to the relationship between BMI and mortality without adjustment for fitness. Assessment of physical activity by self-reported questionnaires is often subject to recall bias. Many studies claim to have proven validity but obese patients often overestimate their physical activity and exercise. Therefore, objective measures of physical activity or BMI–mortality investigation without adjustment for fitness lead to serious misclassification and faulty conclusions; and consequently; this ultimately ends with exaggerated hazards of obesity (24, 57, 61-62).

In contrast, the assessment of cardio respiratory fitness is an objective and reproducible measure of habitual physical activity. Cardio respiratory fitness by definition is *the ability of the circulatory, respiratory, and muscular systems to supply oxygen during sustained physical activity* (63). The first meta-analysis of 33 studies comprising 102,980 participants with 6,910 all-cause deaths, and 84,323 participants with 4,485 CVD events in men and

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women, estimated the association of all-cause mortality and CVD events in healthy individual adults with cardio respiratory fitness. The meta-analysis further showed that each 1-MET increase in cardio-respiratory fitness was associated with 13% and 15% risk reduction of all-cause mortality and CVD events, respectively (64). The results of the Aerobics Center Longitudinal Study (ACLS) revealed that compared to the least-fit women (65) and men (66), the most-fit women and men had 70% and 47% lower risk of CVD mortality, and 53% and 43% lower risk for all-cause mortality, respectively.

A cohort including 9,563 men with 733 deaths (348 of CVDs) during a mean follow-up of 13.4 years in the ACLS reported that men with low fitness had a higher risk of all-cause mortality in the BMI categories of normal weight (HR, 1.60; [1.24-2.05]), obese class I (HR,1.38; [1.04-1.82}), and obese class II/III (HR, 2.43; [1.55-3.80]) compared with those of normal-weight and high-fitness as the referent group (56). Findings of Veterans Exercise Testing Study in men aged 40–70 years showed that if overweight and obese men had a low fitness level, they had higher risk of all-cause mortality (26). In the above mentioned studies, the consistent finding was that higher fitness attenuated or eliminated the detrimental effect of obesity on mortality risk. The primary findings from landmark study of 25,714 men with 10 years of follow-up are summarized in Figure 3 (67).

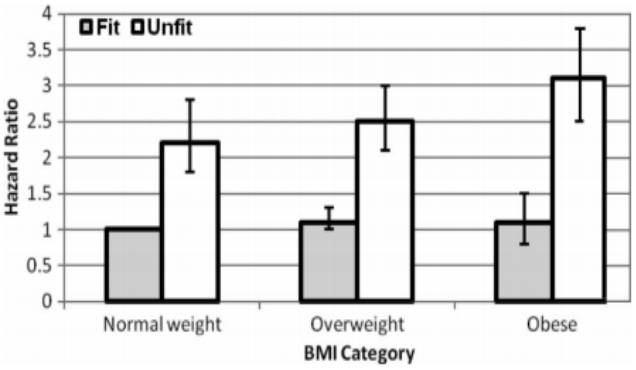

Fig 3: Multivariate hazard ratios for all-cause mortality by BMI and fitness level in 25,714 men from the Aerobics Center Longitudinal Study (ACLS). Each bar represents the relative risk after adjustment for age and examination year, with the relative risk of normal weight (BMI 18.5–24.9 kg/ m2) and fit set at 1.0. Grey bars represent fit (over 80% of age-decade distribution) and white bars unfit (lowest 20% of age-decade distribution). Error bars represent 95% confidence intervals (24).

To summarize, considerable evidence shows that moderate–to-high levels of cardio-respiratory fitness and improvement in cardio respiratory fitness are associated with a lower risk of mortality from all-causes and CVDs. Finally, to understand the obesity paradox, information on the levels of cardio-respiratory fitness beyond BMI is extremely important.

Paradox 4: Healthy obesity: A sizeable population of obese adults has normal cardio metabolic risk profiles

Metabolically healthy obesity (MHO) is defined as *the absence of six common cardio-metabolic risk factors (impaired fasting glucose/diabetes, insulin resistance, high triglycerides, low HDL cholesterol, high blood pressure, and high C-reactive protein) in an individual with a BMI ≥30 kg/m^2*. These individuals are more resistant to the development of metabolic abnormalities associated with obesity. Despite having excessive body fatness, MHO participants display favorable metabolic profile characterized by high levels of insulin sensitivity, a favorable lipid profile, lack of hypertension, inflammation, and as a result, low incidence of type 2 diabetes and cardiovascular disease (68-69). According to data from the NHANES (1994–2004), more than 30% of the nearly 61 million obese American adults are metabolically healthy obese. Wildman et al. reported that 35% of obese women and 29% of obese men in a nationally representative US population are metabolically healthy obese, respectively (70). Evidence from epidemiological data suggests that MHO participants are at lower risk of developing CVDs compared with metabolically unhealthy obese (MUO) participants (68, 71-72). Furthermore, MHO participants are not at increased risk of CVD compared with healthy non-obese people. Hamer and Stamatakis investigated a total of 22,203 participants (45.2% men) without known history of CVD at baseline. The participants were followed up for an average of 7 years. Over this period, the total death numbers were 1,868 (604 from CVD). Also, in 24% of the obese individuals, a metabolically healthy phenotype was observed. The rsults of this well-conducted prospective study showed that metabolically healthy obese participants were not at elevated risk of CVDs (HR, 1.26 [0.74 – 2.13]) compared with the metabolically healthy non-obese participants. Additionally, MUO participants

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were at increased risk of all-cause mortality compared with their metabolically healthy obese counterparts (HR 1.72, [1.23–2.41]) (72).

To better understanding of difference between MHO and MUO, it will be required to compare large samples of metabolically healthy obese individuals with long-term follow-ups. Generally, the recommendations for assessing and treating overweight and obese are same for all obese individuals, and do not distinguish between MHO and MUO.

Traditional weight loss strategies (that mainly include diet therapy, physical activity, behavior therapy and lifestyle modification) identify weight loss as the key component of the intervention's success. Unfortunately, the majority of individuals are unable to maintain the lower body weight over a long term. Concern has arisen that this weight focus is not only ineffective at producing healthier individuals but may also have unintended consequences such as repeated cycles of weight loss and regain, eating disorders, reducing self-esteem, and weight stigmatization and discrimination (12-14). Accordingly, as a different paradigm, the Health at Every Size (HAES) shifts the focus from weight control to health promotion regardless of body weight or fat. The primary intent of HAES is to support improved health behaviors for people of all sizes without using weight as a mediator; weight loss may or may not be a side effect (14, 73). The HAES approach focuses on healthful eating and physical activity for the aim of health versus promotion of dieting and exercise for weight management. HAES includes: 1) Accept body size, 2) Trust internal body systems designed to keep us healthy, 3) Adopt healthy lifestyle habits such as healthy eating behaviors and listen to hunger and satiety body signals and more physical activity, and 4) Embrace size diversity. Humans come in a variety of sizes and shapes. Bacon et al. compared effects of non-diet wellness program to traditional diet program in a randomized clinical trial with 6 month intervention. After 1 year follow up, the HAES participants maintained reduced weight and improved all outcome variables compared with the diet group that regained weight and did not sustain improvements (74). The results of this study indicate that the HAES approach is associated with improvements in physiological measures, health behaviors, and psychosocial outcomes (73,75-76). Overall, in this new paradigm every individual takes personal responsibility in choosing the behaviors that are associated with improved health status including the nutritional quality of the diet and increasing the time spent in daily and regular physical activity; in fact, individuals keep the focus on healthy behaviors inside weight change.

Conclusions: Obesity is definitely a major risk factor for a few chronic diseases and premature disability and death. There are many theories regarding obesity etiology and treatment. Physiological, behavioral and psychological mechanisms have been proposed as the reasons for weight regain and failure in obesity treatment. Some researchers even go beyond the argument on obesity treatment, and believe that obesity might be just a biological adaptation. According to the current evidence and based medical and nutritional information it seems that scientists and practitioners should search for practical recommendations in order to prevent overweight or obesity among the public (healthy or ill). If weight loss is necessary, it should be emphasized that healthy weight loss and prevention of weight regain are preferred to try to reach ideal weight.

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