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JACC FOCUS SEMINAR: CV HEALTH PROMOTION

JACC FOCUS SEMINAR

Healthy Weight and Obesity Prevention

JACC Health Promotion Series

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ABSTRACT

Overweight and obesity have reached epidemic levels in the United States and worldwide, and this has contributed to substantial cardiovascular and other health risks. However, controversy exists concerning the causes of obesity and effective modalities for its prevention and treatment. There is also controversy related to the concept of metabolically healthy obesity phenotype, the "obesity paradox," and on the importance of fitness to protect individuals who are overweight or obese from cardiovascular diseases. In this state-of-the-art review, the authors focus on "healthy weight" with the emphasis on the pathophysiologic effects of weight gain on the cardiovascular system; mechanistic/triggering factors; and the role of preventive actions through personal, education/environment, and societal/authoritative factors, as well as factors to provide guidance for caregivers of health promotion. Additionally, the authors briefly review metabolically healthy obesity, the obesity paradox, and issues beyond lifestyle consideration for weight loss with medications and bariatric surgery. (J Am Coll Cardiol 2018;72:1506–31) © 2018 by the American College of Cardiology Foundation.

Overweight and obesity have reached epidemic levels in the United States and worldwide, affecting nearly three-fourths of adults in the United States (1,2). In 2016, the prevalence of obesity on the basis of body mass index (BMI) ≥30 kg/m^2 was 39.6% in the U.S. adults, and the prevalence of Class III obesity (BMI ≥40 kg/m^2) was 7.7% (3). Obesity is also among the largest health care costs in the United States, from 147 billion to nearly 210 billion dollars per year (4). In addition, obesity is associated with other costs, including reduced job production, costing employees over $500 per obese worker per year (5,6). Clearly, obesity has many adverse effects on health, particularly on cardiovascular disease (CVD) risk factors and CVD prevalence and severity (1). More discerning is that obesity independently increases risk for almost all of the CVD risk factors, including hypertension (HTN), dyslipidemia, glucose abnormalities, including metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM), as well as levels of inflammation. Consequently, almost all CVD is increased in obesity, especially heart failure (HF) (7), but also HTN, coronary heart disease (CHD), atrial fibrillation (AF), as well as most other CVD (1,2,7,8).

Typically, normal weight is defined by BMI of 18.5 to 24.9 kg/m^2, but there remains considerable controversy on the impact of various other measures of body composition/adiposity, including body fat (BF), waist circumference (WC), waist-to-hip ratio, and lean mass. Although BMI ≥30 kg/m^2 represents obesity in U.S. Caucasians and African Americans,

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values ≥25 kg/m^2 generally represent obesity in Asians, Middle Eastern, and Mediterranean populations. At any given BMI, high WC and waist-to-hip ratio may lead to a further increase in risk (9). A WC ≥94 cm in men and ≥80 cm in women (cutpoints of 90 cm in men and 80 cm in women in Asian/Middle East/Mediterranean populations) indicates increased risk, and values ≥102 cm in men and ≥88 cm in women (corresponding values of 94 cm in men and 80 cm in women in Asian/Middle East/Mediterranean populations) are particularly associated with increased risk of chronic diseases. The corresponding values for waist-to-hip ratio associated with substantially increased risk are ≥0.9 and 0.85 for men and women, respectively. Clearly the impact of cardiorespiratory fitness (CRF) and the importance of the metabolically healthy obesity (MHO) phenotype, as well as the "obesity paradox," remain areas of considerable controversy.

As recently reviewed in the *Journal* (10), a major emphasis is making "Health Promotion a Priority" with an 8-part Focus Seminar series on the behavioral factors that impact CV health. In this state-of-the-art review, we focus on "healthy weight" with the emphasis on the pathophysiologic effects of weight gain on the CV system; mechanistic/triggering factors; and the role of preventive actions through personal, education/environment, and societal/authoritative factors, as well as factors to provide guidance for caregivers of health promotion (**Central Illustration**). Additionally, we also briefly review MHO, the obesity paradox, and issues beyond lifestyle consideration for weight loss with medications and bariatric surgery.

PATHOPHYSIOLOGICAL AND PSYCHOSOCIAL EFFECTS OF OBESITY

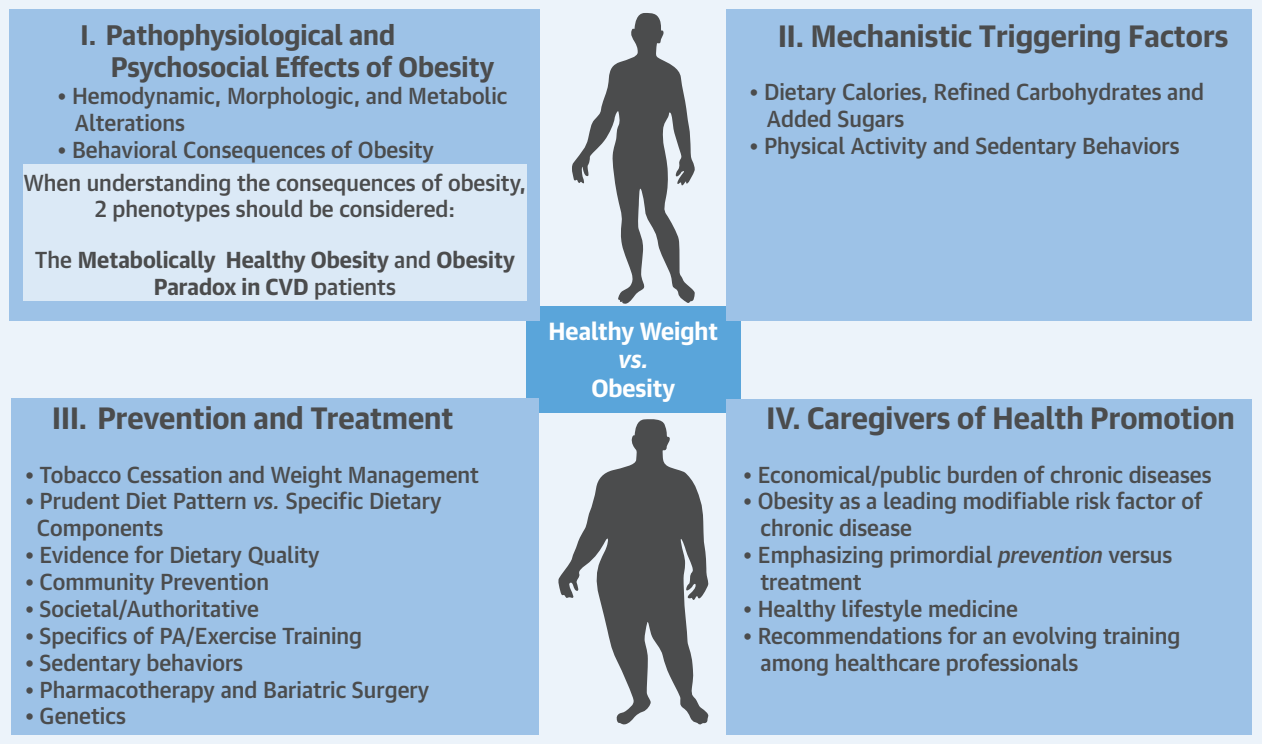
ROLE OF HEMODYNAMIC, MORPHOLOGIC, AND METABOLIC ALTERATIONS AND EFFECTS ON VENTRICULAR FUNCTION. Obesity is capable of producing a variety of hemodynamic, neurohormonal, and metabolic alterations that may adversely affect cardiac morphology and ventricular function (11–16), as described in **Table 1 and Figure 1**. These changes are most pronounced in severe obesity (Class III, BMI ≥40 kg/m^2), but may occur to a lesser extent in mild (Class I, BMI: 30.0 to 34.9 kg/m^2) and moderate (Class II, BMI: 35.0 to 39.9 kg/m^2) obesity (11–14). Obesity-related changes in cardiac structure and function have also been reported in children and adolescents (11–13). Early studies suggested that changes in cardiac morphology and ventricular function associated with obesity are primarily attributable to hemodynamic alterations (11–13). However, in recent years, it has become increasingly clear that various neurohormonal and metabolic factors commonly associated with obesity may also contribute to cardiac remodeling and abnormal ventricular function. Thus, it is now evident that the effects of obesity on cardiac performance and morphology evolve from a complex, multifactorial process of adaptation and maladaptation to excess fat accumulation.

Most studies assessing hemodynamic alterations in individuals with obesity have described a high cardiac output (CO) state (11–15). The presence of excessive adipose accumulation in association with increased fat-free mass, together with a decrease in systemic vascular resistance produce an increase in circulating blood volume that leads to an increase in myocardial oxygen consumption and augmentation of CO. Because heart rate rises little, if at all with obesity, the elevation in CO is attributable predominantly to increased left ventricular (LV) stroke volume. In this model, augmented CO predisposes to the development of LV enlargement. Secondary (eccentric) left ventricular hypertrophy (LVH) may occur in part due to increased LV wall stress. Adequate hypertrophy may reduce LV wall stress; however, LV diastolic dysfunction may ensue (11–13). If LVH is inadequate, LV wall stress will remain elevated and over time, LV systolic dysfunction may accompany LV diastolic dysfunction (11,12). The presence of LV dysfunction (diastolic, systolic, or both) may lead to elevation of LV end-diastolic pressure, increased left atrial pressure (and volume), pulmonary venous hypertension, and increased pulmonary capillary pressure. Clinical manifestations of left-sided HF may ensue, and in the absence of comorbidities such as CHD or HTN are most likely to occur in patients with severe obesity (11–13). The increase in pulmonary capillary pressure is the predominant cause of pulmonary arterial hypertension in these patients, facilitated in some cases by severe hypoxemia from sleep apnea and obesity-induced hypoventilation (11,12,15). It is not unusual to detect a diastolic pressure gradient across the pulmonary vascular bed in patients with severe obesity (11,12). Pulmonary arterial hypertension may contribute to the development of right ventricular hypertrophy and enlargement and an increase in right atrial pressure and volume (facilitated by high CO) (11,12). This

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
AHA = American Heart Association
BF = body fat
BMI = body mass index
CHD = coronary heart disease
CO = cardiac output
CRF = cardiorespiratory fitness
CV = cardiovascular
CVD = cardiovascular disease
DASH = Dietary Approaches to Stop Hypertension
GI = glycemic index
HF = heart failure
HLM = healthy living medicine
HLP = Healthy Living Practitioner
HTN = hypertension
LV = left ventricle
LVH = left ventricular hypertrophy
MetS = metabolic syndrome
METs = metabolic equivalents
MHNW = metabolically healthy normal weight
MHO = metabolically healthy obesity
MUO = metabolically unhealthy obesity
OSA = obstructive sleep apnea
PA = physical activity
SSB = sugar sweetened beverages
T2DM = type 2 diabetes mellitus
WC = waist circumference

CENTRAL ILLUSTRATION **Healthy Weight and Obesity Management**



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A schematic for the management of obesity to optimize long-term prevention and treatment. CVD = cardiovascular disease; PA = physical activity.

sequence of events may lead to right-sided HF (11,12,14,15). In fact, HF due predominantly or entirely to obesity, generally severe obesity, is referred to as obesity cardiomyopathy (11,12). However, the previously described alterations in cardiac structure and function may also occur to a lesser extent in those with mild to moderate obesity (11–14). Such individuals are often free from HF symptoms.

Studies assessing LV morphology using a variety of diagnostic techniques have consistently demonstrated that LV mass is significantly greater in patients with obesity (all classes) compared with those who are normal weight (11–13). The aforementioned pathophysiological model suggests that in patients with obesity with increased LV mass, eccentric LVH should predominate. However, evidence is accumulating to indicate that concentric LV remodeling or LVH occurs more frequently than eccentric LVH in obese patients with abnormal LV geometry (12,16–18). A key factor relating to LV geometry is HTN (19,20), which is typically associated with concentric LV remodeling or LVH (19,20). Messerli et al. (20) described "dimorphic cardiac adaptation" to obesity and HTN, a hybrid form of LVH previously referred to as eccentric-concentric LVH (now classified as a form of concentric LVH). In this model, LV chamber size is larger than that observed with pure concentric LVH, but smaller than that associated with eccentric LVH (19,20). LV wall thickness in this model is greater than that of eccentric LVH, but less than that observed with pure concentric LVH (19,20). It is important to take into consideration both duration and severity of obesity and HTN in reference to LV geometry (21). For example, a patient with long-standing, poorly controlled HTN and mild obesity might be expected to develop concentric LVH, whereas a patient with severe obesity of long duration, but mild or controlled HTN, might be expected to develop eccentric LVH. Most, but not all studies, reporting a high prevalence of concentric LV remodeling or LVH in obese subjects

TABLE 1 Impact of Obesity on Hemodynamics and Cardiac Structure and Function

Hemodynamics
Increased blood volume
Increased stroke volume
Increased arterial pressure
Increased LV wall stress
Pulmonary artery hypertension
Cardiac structure
LV concentric remodeling
LV hypertrophy (eccentric and concentric)
Left atrial enlargement
RV hypertrophy
Cardiac function
LV diastolic dysfunction
LV systolic dysfunction
RV failure
Neurohumoral
Insulin resistance and hyperinsulinemia
Leptin insensitivity and hyperleptinemia
Reduced adiponectin
Sympathetic nervous system activation
Activation of renin-angiotensin-aldosterone system
Overexpression of peroxisome proliferator-activator receptor
Inflammation
Increased C-reactive protein
Overexpression of tumor necrosis factor
Cellular
Hypertrophy
Apoptosis
Fibrosis

LV = left ventricular; RV = right ventricular.

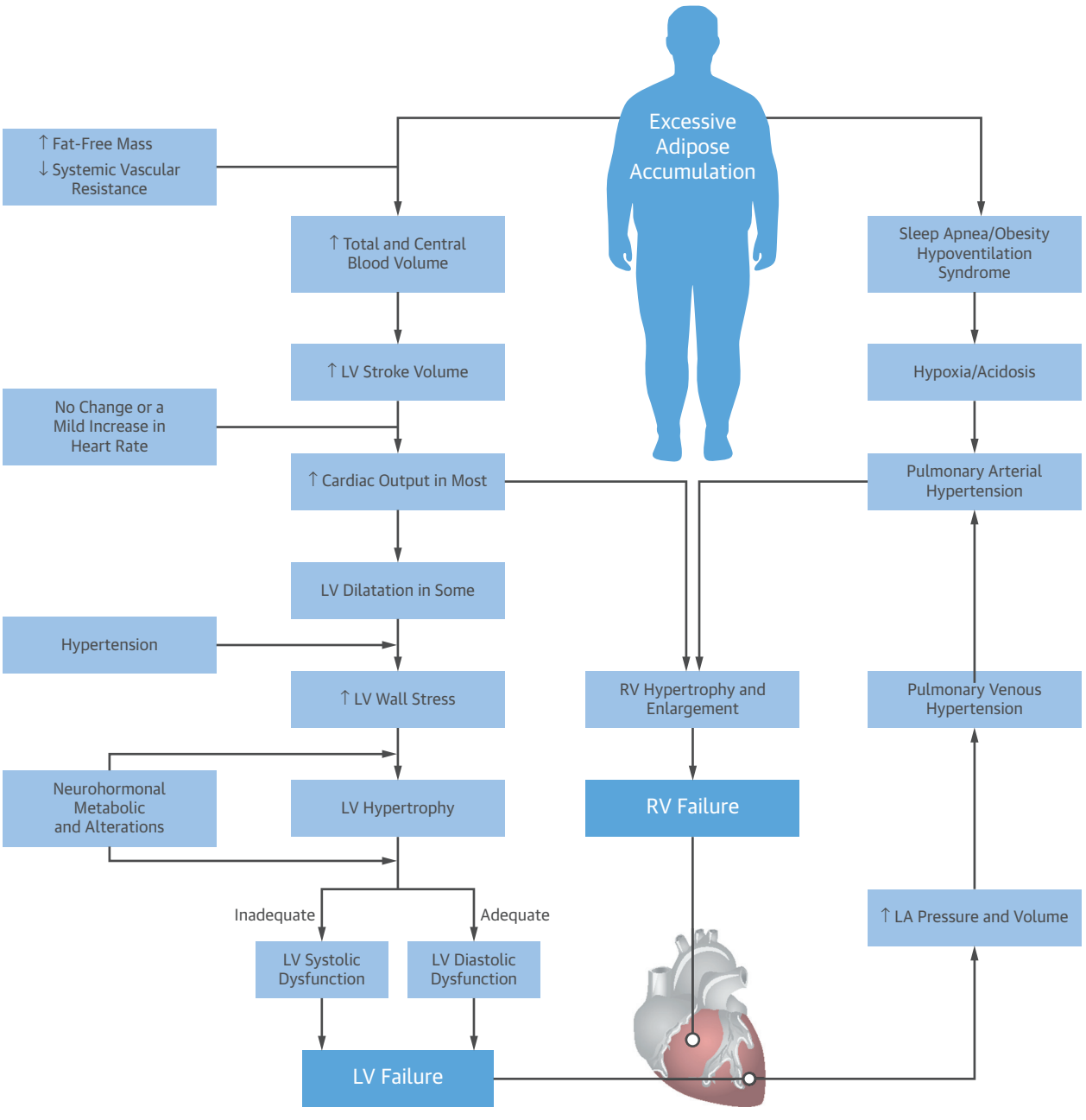
did not exclude patients with HTN or adjust for its presence. Another important factor in determining LV geometry may be fat distribution. Neeland et al. (21) reported the results of a study that showed that central (visceral) obesity was more commonly associated with concentric LV remodeling or LVH, whereas peripheral obesity was more commonly associated with eccentric LVH. In their study, central obesity was also associated with lower CO and higher systemic vascular resistance, whereas peripheral obesity was associated with higher CO and lower systemic vascular resistance (21).

LV diastolic dysfunction has been reported in all classes of obesity (11-13). In patients with severe obesity, LV end-diastolic pressure is often elevated at rest and may increase substantially with exercise (15). Impairment of LV diastolic filling or relaxation has been reported in subjects with obesity relative to normal weight patients using load-dependent noninvasive diagnostic techniques (11,12). LV diastolic dysfunction occurs commonly in patients with obesity and LVH, but has also been described in those with normal LV mass (11,12). Studies employing tissue Doppler imaging, a technique thought to be less dependent on LV loading conditions, have shown reduced early diastolic mitral annular velocities in asymptomatic obese subjects, suggesting the presence of subclinical LV diastolic dysfunction in this population (11-13).

In the absence of comorbidities, such as CHD, LV systolic function assessed using LV ejection phase indices is usually normal or supranormal (11-14). LV systolic dysfunction has been reported in uncomplicated obesity, predominantly in those with long-standing severe obesity. Even in this population, severe impairment of LV systolic function is rare and should elicit a search for other etiologies (11-13). Studies utilizing tissue Doppler imaging have reported reduced systolic mitral annular velocities in asymptomatic obese patients, even when LV ejection phase indices are normal (11-13). More recently, studies employing LV strain rate imaging have reported reduced global longitudinal strain and in some cases decreased radial strain in such patients (12,17). This suggests the presence of subclinical LV systolic dysfunction in obesity.

In addition to HTN and fat distribution, there are a variety of other factors that may contribute to the development of cardiac remodeling and ventricular dysfunction in obesity (11-13,22-24). These include insulin resistance with hyperinsulinemia, activation of the renin-angiotensin-aldosterone system, stimulation of the sympathetic nervous system, hyperleptinemia due to leptin resistance, low levels of adiponectin, myocardial fibrosis, and lipotoxicity (11-13,23,24). Obesity is commonly associated with insulin resistance with compensatory hyperinsulinemia (11,12,23). Insulin resistance is thought to contribute to the development of LVH by promoting binding of insulin to insulin-like growth factor 1 receptors, which are plentiful in myocardium and by stimulation of the sympathetic nervous system, resulting in increased afterload (14,23). In animal models, insulin resistance increases myocardial fatty acid uptake and creates an imbalance between fatty acid uptake and oxidation, which causes accumulation of ceramides and other fatty acid intermediates that impair myocardial function and promote apoptosis of cardiomyocytes (13,23,24). Obesity is associated with activation of the renin-angiotensin-aldosterone system (11,13). Adipocytes are actually a source of angiotensinogen and angiotensin-converting enzyme. Activation of this system stimulates sympathetic nervous system activity that may predispose to HTN and increase afterload in normotensive persons with obesity (11-13). Volume

FIGURE 1 Obesity and CVD: Proposed Pathophysiology of Obesity Cardiomyopathy



This diagram shows the central hemodynamic alterations that result from excessive adipose accumulation in severely obese patients and their subsequent effects on cardiac morphology and ventricular function. Left ventricular (LV) hypertrophy in severe obesity may be eccentric or concentric. Factors influencing LV remodeling and geometry include severity and duration of obesity; duration and severity of adverse LV loading conditions (particularly hypertension); and, possibly, neurohormonal and metabolic abnormalities such as increased sympathetic nervous system tone, activation of the renin-angiotensin-aldosterone system, insulin resistance with hyperinsulinemia, leptin resistance with hyperleptinemia, adiponectin deficiency, lipotoxicity, and lipoapoptosis. These alterations may contribute to the development of LV failure. LV failure, facilitated by pulmonary arterial hypertension from sleep apnea/obesity hypoventilation, may subsequently lead to right ventricular (RV) failure. LA = left atrial.

expansion may increase preload in such individuals. Angiotensin II is a potent growth factor that promotes myocardial hypertrophy (11–13). Aldosterone stimulates myocardial fibrosis (13,14). These sequelae form the substrate for the development of LVH and LV diastolic dysfunction. Obesity is frequently associated with leptin resistance and hyperleptinemia (11–14). Animal studies have reported an association between hyperleptinemia and LVH (11–14). Elevated leptin levels stimulated matrix metalloproteinase 2, which increased synthesis of collagen III and IV in human pediatric myocytes (14). Adiponectin is a cardioprotective adipokine (12–15). Obesity is associated with low adiponectin levels that reduce the activity of tissue metalloproteinase inhibitors, thus impairing its antifibrotic effect in obese subjects. Myocardial lipotoxicity is characterized by fatty acid and triglyceride accumulation in cardiomyocytes leading to cellular dysfunction and death and eventually to myocardial dysfunction (11,12,23,24). The accumulation of fatty acids and triglycerides in these cells creates an imbalance between uptake and metabolism of these substances (11,12,23,24). Increased myocardial triglyceride accumulation has been associated with LVH in humans and both LVH and LV dysfunction in genetically obese rats (11,12,16). Transgenic murine models of lipotoxicity have been developed involving stimulation or inhibition of various enzymes or proteins that modulate lipid uptake or turnover (11,24). Several of these models have demonstrated LV diastolic and systolic dysfunction. Cardiac remodeling and myocardial dysfunction associated with lipotoxicity in animal models are thought to be mediated by long chain fatty acids and their metabolic products such as diglycerol or ceramides (11,12,23,24). As previously noted, this process has been described with insulin resistance in animal models (23). Whether lipotoxicity is responsible for the development of LV dysfunction in humans is uncertain. High levels of tumor necrosis factor alpha, reactive oxygen species, and C-reactive protein in adipocytes have stimulated conjecture that apoptosis, oxidative stress, and inflammation may play an important role in cardiac remodeling in obesity, but confirmatory data are lacking (13,14).

BEHAVIORAL CONSEQUENCES OF OBESITY

Even though it is well-established that obesity serves as a potent risk factor for various cardiometabolic comorbidities, discussions focusing on obesity's relationship to behavioral and psychosocial morbidities, which may otherwise hinder obesity treatment strategies, have been relatively limited. Concurrent with the growing global obesity epidemic, there has been a similar risk in breathing-related sleep disorders, particularly those characterized by the recurrent collapse of the pharyngeal airway during sleep (25). Although sleep apnea may result from or be worsened by obesity, it can also lead to adverse consequences. Most notable of the subtypes of sleep disorders is obstructive sleep apnea (OSA), because of its relationship to various CVD and metabolic comorbidities (26,27). Whereas sleep disorders are suggested to be causal in the pathway leading to weight gain, obesity is considered as the most potent demographic risk factor for the development and progression of OSA (25,26). Current estimates posit OSA prevalence rates of >40% in patients who are overweight, but otherwise healthy, and nearly 50% to 98% in patients with severe obesity (BMI ≥40 kg/m^2) (25,27). Physiologically, obesity's effect on OSA susceptibility can be explained, in part, by the differentiating effects of fat patterning and fat distribution, the inflammatory responses elicited from these fat depots, and the anatomic alterations such as excessive adiposity around the pharynx and chest as well as fat deposited around the upper airway that predispose to upper airway obstruction during sleep (27). Notably, the pathogenic effects of central (visceral) obesity on OSA development have specifically been shown to increase mechanical loading in the upper airway, contributing to airway collapsibility and/or decreased compensatory neuromuscular responses (27). Inherent differences in fat distribution also explain why OSA predominates in men versus women (26); whereas men typically carry greater central fat deposition and subscapular skin fold thickness (26,27), leading to increased resistive load of the upper airway, greater peripheral adiposity in women may be a factor that protects them from developing OSA (26). Other studies have shown OSA correlates with neck size, which also increases with central obesity (25).

Without argument, weight loss is implicated as the most important and effective component of healthy living medicine (HLM) (28), with the goal of reversing an obesity classification and the severity and burden of its behavioral consequences, including breathing-related sleep disorders. However, curtailing weight loss efforts are a host of psychological disorders that manifest as a consequence of obesity, and therefore challenge long-term success of weight loss in populations with obesity. Theories underlining the health psychology model suggest weight stigma and internalization of weight bias are psychological stressors that beget weight gain/regain by perpetuating the body's central stress-response hypothalamic-pituitary-adrenocortical axis, and activating the

TABLE 2 Proposal of a Harmonized Definition of MHO and MUHO or MUO in Adults

Definition of MHO	
Based on the 7 fundamental points and recommendations discussed elsewhere (8) (see Online Table 1 for more detailed information), a person would be classified as MHO if they are obese (BMI ≥30 kg/m^2) plus they meet 0 of the 4 MetS criteria (WC excluded), which are the following (34):	
Elevated triglycerides (Drug treatment for elevated triglycerides is an alternate indicator.*)	≥150 mg/dl (1.7 mmol/l)
Reduced high-density lipoprotein cholesterol (Drug treatment for reduced HDL-C is an alternate indicator.*)	<40 mg/dl (1.0 mmol/l) in men <50 mg/dl (1.3 mmol/l) in women
Elevated blood pressure (Antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator.)	Systolic ≥130 and/or diastolic ≥85 mm Hg
Elevated fasting glucose† (Drug treatment of elevated glucose is an alternate indicator.)	≥100 mg/dl (5.6 mmol/l)
Definition of MUHO or MUO	
A person would be classified as MUHO or MUO if they are obese (BMI ≥30 kg/m^2) plus they meet 1 to 4 of the MetS criteria indicated (WC excluded).	

*The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking 1 of these drugs can be presumed to have high triglycerides and low HDL-C. High dose of omega-3 fatty acids presumes high triglycerides. †Most patients with type 2 diabetes mellitus will have the MetS by the proposed criteria.

BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; MetS = metabolic syndrome; MHO = metabolically healthy obesity; MUHO = metabolically unhealthy obesity; MUO = metabolically unhealthy obesity; WC = waist circumference.

endocrine stress hormone, cortisol. Consequently, hypercortisolemia, which promotes central obesity and is implicated in a myriad of obesity-related comorbidities (29), is also hypothesized to drive maladaptive eating behaviors (binge eating, night eating) (30) by sensitizing the food-reward system. Hence, increased eating behavior in obesity is often seen as a response to coping with psychological stress induced by weight stigma (30). Accordingly, higher levels of psychological stress are suggested as mediators of anxiety (31) and depression (32) in adults and possibly in childhood and adolescent obesity (33). These data together suggest that whereas lifestyle and behavior modification remains the gold standard approach to treating obesity, it is imperative that clinicians understand potential behavioral responses to obesity and psychological sequelae of obesity that may undermine weight loss goals and further increase risk of clinical comorbidities. In terms of alleviating the medical burdens associated with obesity, applying a more comprehensive obesity treatment approach that prioritizes behavioral and psychological challenges of obesity is warranted. This multidisciplinary approach may help guide clinicians to identify patients who are less likely to respond to traditional lifestyle intervention and provide avenues for more effective primary, secondary, and tertiary prevention and treatment strategies.

METABOLICALLY HEALTHY OBESITY

DEFINITION, PREVALENCE, AND CHARACTERISTICS OF MHO.

Definition. MHO is defined as a subset of individuals who are obese but have otherwise a totally normal and healthy metabolic profile, that is, absence of HTN, glucose abnormalities, and dyslipidemia. The discrepancies in the definition of MHO have hampered comparability among studies and contributed to the controversy about the prognosis of these individuals. As a step toward the standardization of the MHO concept, we have recently proposed a harmonized definition of the MHO phenotype (**Table 2**) based on 7 fundamental points (Online Table 1) (8,34). Probably the most significant change in the MHO definition since the origins of the concept to date has been to move from the concept of MHO if meeting 0 or 1 MetS criteria (35,36) to the concept of MHO if meeting 0 MetS criteria, due to the rationale that a person with HTN or T2DM cannot be considered "healthy" and, therefore, MHO should be considered only in the presence of 0 MetS criteria (8). Large and recent studies (37,38) have used the 0 criteria/metabolic abnormalities definition (WC excluded), confirming, therefore, this definition in the study of MHO. In opposition to MHO, the rest of individuals with obesity have been named using different terms (e.g., metabolically abnormal obesity), yet the term metabolically unhealthy obesity (MUO) seems to be the most accepted/used in the last years.

Prevalence. Following the strict definition of meeting 0 MetS criteria and evaluating the largest representative studies conducted in Europe (37) and the United States (35), the prevalence of MHO seems to range from 12% to 17% of all adults with obesity. Caleyachetty et al. (38) have recently published the largest study in this field, including 3.5 million men and women representative from the United Kingdom and observed that 68% of the participants with obesity were MHO (2 of every 3 obese patients). This markedly higher prevalence of MHO than in the

previous studies is due to the fact that they did not use blood pressure or glucose/lipids blood cutpoints (i.e., criteria) from the MetS definition as usually is done in this field; they used only physician-diagnosed or -treated T2DM, HTN, and/or dyslipidemia. Regardless of the definition used, it is clear that the MHO is not a rare condition. Therefore, the prevalences discussed should inform clinicians that they can expect from one-sixth to two-thirds of their patients with obesity clinically managed to be MHO.

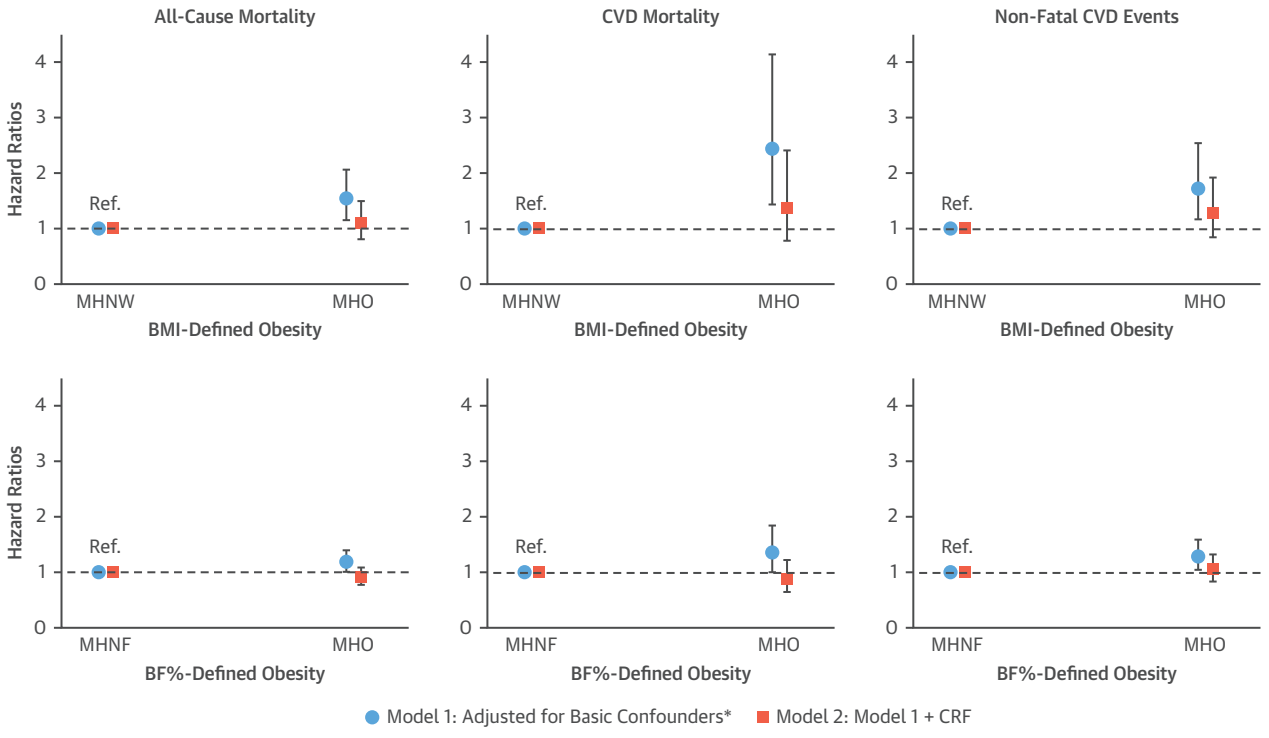
Characteristics. A number of physiological and phenotypic differences between MHO and MUO have been identified, including lower levels in markers of inflammation, insulin resistance, visceral adipose tissue, fatty liver and atherosclerosis in individuals with MHO compared with individuals with MUO. Our study using data from the ACLS (Aerobics Center Longitudinal Study) was the largest study showing that individuals with MHO have a significantly higher CRF level than the individuals with MUO, something that, together with higher physical activity (PA), has been recognized as a novel characteristic of the MHO phenotype in later reviews of published reports (39,40). Recently, a meta-analysis has confirmed that MHO, compared with MUO, have higher levels of PA, lower levels of sedentary behavior, and higher levels of CRF (41).

IMPACT ON CVD. Numerous studies have focused on this phenotype and have provided conflicting findings about its prognosis, with some studies suggesting that MHO was a benign condition with similar risk of fatal and nonfatal CVD mortality than metabolically healthy normal weight (MHNW), and others supporting the opposite. In spite of this, accumulating evidence overall suggests that individuals with MHO have a better CVD prognosis than do their MUO counterparts, but worse than individuals with MHNW, supporting the notion that obesity, even if metabolically healthy, has long-term negative consequences on CV health. Along these lines, 5 systematic reviews and meta-analyses have concluded that individuals with MHO are at a higher risk of CVD mortality and morbidity than individuals with MHNW (42–46). This idea has been further supported by the recent and powerful study from Caleyachetty et al. (38) including 3.5 million participants. There is much agreement (47) that this study, together with previous meta-analyses, has definitively demonstrated that individuals with MHO have a higher risk of overall and specific CVD than MHNW. However, whether the differences in CVD risk observed between these 2 phenotypes are due to differences in adiposity levels (i.e., obesity per se), as assumed by others (38,47) or are due to the differences in CRF that exist between these 2 groups of individuals has yet to be clarified (48).

ROLE OF CRF IN THE CVD PROGNOSIS OF MHO. Observations that individuals with MHNW have, on average, higher CRF levels than age-matched individuals with MHO is clear and well established (36,39,41,48,49). The question that remains unanswered is whether the differences in CVD risk observed in the individuals with MHO compared with the individuals with MHNW could be partially or completely explained by the existing differences in CRF between these 2 groups (50). Data from the ACLS was the first and the largest of its kind (>43,000 participants), demonstrating that the CVD prognosis of individuals with MHO differed depending on whether CRF was or was not included in the models as a confounder. Our findings concur with those observed in the present study by Caleyachetty et al. (38) and most of the existing publications (42–46); however, when CRF is included as a covariate in the models, the differences in the risk of CVD mortality and nonfatal CVD incidence between individuals with MHO and MHNW completely disappeared (**Figure 2**) (36). These findings suggest that cohort studies on MHO lacking information on CRF should acknowledge that as a limitation. Caleyachetty et al. (38) highlights as a limitation another aspect, the fact that in their study obesity was defined using BMI, which does not distinguish between fat and lean mass. Yet this might not be a limitation, because in a recent study (51), we showed that BMI could be a similar if not stronger predictor of CVD mortality and morbidity than BF percentage or fat-mass index (fat mass expressed in kilograms divided by height expressed in meters squared) accurately measured using a gold standard method. Likewise, a study on MHO prognosis (36) was able to overcome this potential limitation, by testing the same hypothesis using BMI-defined obesity and BF percentage (accurately measured)-defined obesity, and obtained identical conclusions (**Figure 2**).

The notion that CRF may explain differences in CVD risk observed between MHO and MHNW was also supported by a systematic review that observed that 6 of the 7 existing studies that controlled for PA or CRF found no differences between MHO and MHNW in the risk of nonfatal CVD incidence, and 7 of the 7 studies found no difference between MHO and MHNW in the risk of CVD mortality (44). Our group has recently meta-analyzed the existing publications that have accounted for the potential confounding effect of PA and identified 10 unique cohorts (41). Our findings suggest that MHO individuals, compared with MHNW

FIGURE 2 Role of CRF on the CVD and All-Cause Prognosis of MHO Versus MHNW or MHNF Individuals From ACLS



Role of cardiorespiratory fitness (CRF) on the cardiovascular disease (CVD) and all-cause prognosis of metabolically healthy obesity (MHO) men and women compared with metabolically healthy normal-weight (MHNW) or normal-fat (MHNF) men and women from the ACLS (Aerobics Center Longitudinal Study) (N = 43,265 adults). *Model 1 is adjusted for age, sex, examination year, smoking, alcohol consumption, and parental history of CVD. Nonfatal CVD events include myocardial infarction, stroke, and coronary revascularization (i.e., bypass, coronary angioplasty); data available in a subsample of 18,430 participants. Reproduced with permission from Ortega et al. (41). BF% = body fat percentage; BMI = body mass index; Ref. = reference.

individuals, have a 24% to 33% higher risk of all-cause mortality and CVD mortality/morbidity. This risk was borderline significant/nonsignificant, independent of the length of the follow-up and lower than that reported in previous meta-analyses in this topic, including all type of studies, which could be indicating a modest reduction in the risk estimates as a consequence of accounting for PA. In addition, our meta-analysis identified only 1 study (36) that examined the role of CRF in the prognosis of MHO individuals; this study suggested that the differences in the risk of all-cause mortality and CVD mortality/morbidity between MHO and MHNW are largely explained by differences in CRF between these 2 phenotypes. Therefore, the main take-home message from the landmark study by Caleyachetty et al. (38) and from most of the currently existing evidence (42–46) that there is no benign obesity should be taken cautiously, given support from these studies indicating that CRF, versus obesity per se, explains the higher risk observed in MHO versus MHNW populations (**Figure 2**) (8,36,41). In addition, there is consistent evidence supporting that a sizeable subset of the individuals with obesity can actually have a moderately to high CRF level, the so-called fat but fit paradox, which has consistently shown that being fit counteracts the negative consequences of obesity on CVD (52,53).

OBESITY PARADOX IN CVD

A detailed discussion of the obesity paradox is beyond the scope of this review and has been extensively discussed elsewhere (1,2,7,8,53–59), but in brief, despite the mark adverse effect of obesity to worsen almost all of the CVD risk factors, especially HTN, MetS/T2DM, dyslipidemia, and inflammation, and to increase the prevalence of almost all CVD, including HTN, HF, CHD, and AF, and almost all other CVD, studies have demonstrated that overweight and at least mildly obese individuals have a better short- and moderate-term prognosis than do thinner

patients with the same CVD. Although this is particularly present with the high-risk underweight CVD patients, normal weight patients also tend to have a worse prognosis then do their heavier counterparts with the same CVD. Although this has mostly been shown with BMI assessments of body composition, in CHD this is also evident with BF percentage and WC in addition to BMI.

A major factor impacting prognosis in CVD and strongly influencing the obesity paradox and CHD, HF, and AF, however, is CRF (1,2,7,8,53-59). In fact, in CHD (57), and systolic HF (58,59), there is evidence that the obesity paradox only exists in the low-fit patients with thin unfit CHD and HF patients having a particularly poor prognosis. However, in CHD and systolic HF, those with relatively preserved fitness (e.g., not in the bottom quintile or tertile for age- and sex-related CRF), prognosis is excellent regardless of the level of body composition. Additionally, improving CRF and weight loss has been shown to improve prognosis in patients with AF (56). Although there is little data on weight loss in CHD or HF on improving survival, purposeful weight loss is associated with reductions in CVD events in patients with CHD (60) and improved symptoms and functional capacity in HF (2,7). However, in a large recent study of 3,307 patients (1,038 women) with CHD from Norway who were followed for a median of 15.7 years (61), we observed no mortality risk reductions with weight loss and reduced mortality associated with weight gain among those with normal weight at baseline. On the other hand, sustained PA was associated with substantial mortality reductions (61). Therefore, PA and exercise training to improve levels of CRF should be strongly encouraged for patients with CVD and may be even more important than weight loss, at least for overweight and mildly obese CVD patients (1,2,7,8,53-61).

GENETIC FACTORS

Certainly, some individuals have a pre-existing genetic predisposition to excess adiposity (62). Additionally, genetic factors may not only affect the development of obesity but may also influence the location of fat deposition, with some areas of fat deposition being clearly associated with greater risk than others (e.g., visceral adipose tissue, epicardial fat, pericardial fat, and hepatic fat are associated with higher risk than subcutaneous adipose tissue is), but also genetic factors may influence the risk that obesity and various fat depots have on the risk of adverse health consequences, which have been reviewed in detail elsewhere (62).

MECHANISTIC TRIGGERING FACTORS

There is considerable controversy regarding the fundamental cause of weight gain and the relative influence of caloric intake and type of calories consumed versus PA and caloric expenditure. Although clearly the etiology of obesity depends on both of these factors, the relative importance of these factors remains an area of hot debate. Regardless of this debate, it is generally accepted that increments in body weight and overall adiposity, at the most fundamental level, are the result of chronic positive energy balance (i.e., energy expenditure > energy intake) (54).

DIETARY CALORIES, REFINED CARBOHYDRATES, AND ADDED SUGARS. Mounting evidence has suggested that energy and poor dietary choices are largely, if not completely, responsible for the obesity epidemic (54,63-65). Although conventional dogma treats all calories the same (e.g., a calorie is a calorie), alternative views suggest the quality of diet indirectly results in obesity. Certainly, in the United States, there is ample evidence that weight gain and obesity rates parallel the increasing consumption of refined carbohydrate intake and, most notably, added sugars, particularly in the form of sugar sweetened beverages (SSB) (66,67). Specifically, excess intake of refined carbohydrates and, especially, added sugar leads to altered physiology and hormonal imbalance leading to insulin resistance and leptin resistance, or internal starvation. Decreased PA/exercise and time spent in leisure-time PA and behavioral characteristics, such as increased sedentariness are also known contributors of excess weight gain (68-70) and further suggest obesity is solely due to an excessive energy or caloric intake reference (54,68). The various aspects of time spent in leisure-time PA and dietary choices, including SSB, are discussed in more detail next.

PA AND SEDENTARY BEHAVIORS

Leisure time PA represents a relatively small portion of total time per week, which is much more affected by occupation-related PA (68) and household management energy expenditure (69). Recently, we demonstrated very marked declines in both occupation-related PA (68) and household management (69) energy expenditure during the last 5 decades along with marked increase in sedentary time and reductions in PA time in mothers during this period (70). Although these declines were more marked in women not working outside the home than in employed women, realizing that currently two-thirds of women are now employed outside the

home, still dramatic declines in energy expenditure are noted in almost all groups of women during the last 5 decades. For example, we demonstrated that currently, the typical woman had a household management energy expenditure of approximately 1,700 to 1,800 calories per week less than the typical woman did 5 decades previously. Considering the fact that generally approximately 100 calories are burned for each mile traveled by foot, the typical woman or mother would have to walk/run 17 or 18 more miles currently to make up for this reduced caloric expenditure. These data suggest that reductions in PA and energy expenditure may largely explain the marked increased prevalence in obesity noted in recent decades. Additionally, there is considerable evidence that PA is the major determinant of CRF, a major factor in prognosis.

Time spent in sedentary behaviors has been recently proposed as separate construct from PA (71) and an independent risk factor for a number of health outcomes, in other words, all-cause mortality, CVD incidence and mortality, and T2DM incidence (72). Ekelund et al. (73) observed that the amount of sitting time was positively related with a higher mortality risk, yet this increased risk could be counteracted and become nonsignificant when combined with high levels of PA. However, the increased risk associated with television watching was not fully eliminated by high levels of PA (73), suggesting that this could be a more harmful sedentary behavior than others. Concerning sedentary behavior and obesity, a recent meta-analysis observed a 33% higher risk of overweight or obesity in the highest categories compared with the lowest categories of sedentary behavior (74). However, this same meta-analysis and other recent narrative reviews, systematic reviews, and meta-analyses agree that the current evidence regarding the link between sedentary behavior and obesity, once PA have been controlled for, is limited and inconclusive (74–77). Further research is certainly needed in this field.

GENETIC FACTORS. In addition to biological and behavioral determinants, multiple genetic determinants or correlates of obesity have been identified to date (77). In fact, genome-wide association studies have contributed to the identification of over 100 obesity-associated genetic variants, but their roles in causal processes leading to obesity and its consequences remain largely unknown. A more detailed discussion of genetic factors, in addition to those mentioned herein and in Walley et al. (62), is beyond the scope of this review and is reviewed in detail elsewhere (77).

PREVENTION AND TREATMENT

BEHAVIORAL FACTORS. Tobacco cessation and weight management. Cigarette smoking and obesity are noted as being the leading causes of preventable death in the United States (78), as well as in developing countries (79). Therefore, it is no surprise that the combination of smoking and overweight or obesity status pose substantial public health burden (80). Whereas current estimates posit significant declines in the global prevalence in tobacco smoking rates (81) over the last 30 years, obesity rates have moved in the opposite direction, reaching historically high levels (80).

At present, there is burgeoning evidence consistently showing an inverse association between smoking behavior and weight status. Review of epidemiological and clinical studies suggest that current smokers, on average, weigh 4 to 5 kg less than nonsmokers do (78,82,83) and have a lower likelihood of becoming obese (79). To this degree, the robust association between smoking cessation and weight gain is not unfounded (79,82,84). Reports of weight gain in both clinically treated quitters (81) and quitters derived from population-based cohorts (79) average 4 to 5 kg, with the greatest increases of weight gained observed 3 to 12 months after quitting (79,82,83). Biologically, increases in appetite, a common side effect of nicotine withdrawal (81) in conjunction with declines in energy expenditure in the range of 4% to 16%, are suggested to contribute to the cessation-related weight gained observed in former smokers (79). Furthermore, there is some evidence that suggests smoking cessation is positively associated with abdominal adiposity, as greater absolute WC (85) and larger increases in WC have been previously reported in former versus current and never smokers (79,84). It has been suggested that post-cessation gains in WC are due to greater gains in subcutaneous fat relative to visceral fat (79,84). However, additional research is needed to confirm the effects of smoking cessation on changes in fat distribution, particularly as it relates to future chronic disease risk.

Given that weight gain is an unwelcomed but expected outcome of smoking cessation, a number of interventions have been designed to promote smoking cessation while simultaneously curtailing weight gain (86). Such intervention approaches have included pharmacotherapy, weight management education, cognitive behavior therapy, and lifestyle recommendations. Among the various smoking cessation and weight management interventions

evaluated in a recent Cochrane review, overall clinical efficacy from all intervention types aimed to jointly affect smoking cessation and weight gain remained modest yet insufficient. Only exercise interventions showed some promise in attenuating long-term (i.e., 12 month) post-smoking cessation-related weight gain, whereas benefits were not observed at shorter time points (i.e., ≤6 months) (86). Other studies have shown that the amount of PA engaged while smoking, as well as PA performed after quitting smoking, significantly reduce the magnitude of weight gained following cessation (79). Nonetheless, these data further underscore the need for clinically effective weight management intervention strategies that can be easily implemented in smoking cessation programs (86).

Implications for a prudent diet pattern versus specific dietary components. Treatment of obesity through various forms of dietary intervention requires achieving a state of negative energy balance through decreased energy consumption. Whereas prior nutrition reports have focused on reducing portion sizes, or isolating or eliminating specific food groups and/or nutrients, more recent evidence has suggested that poor dietary quality and excess diet quantity (e.g., calories) are drivers of energy imbalance and hence, obesity· (87). Thus, recent dietary recommendations have shifted away from theories based on single dietary/nutrient components and diet restriction/elimination tactics and moved toward empirical evidence examining foods consumed in combinations and the overall diet composition consumed by individuals (87). As such, larger emphasis on dietary patterns have been endorsed by the Dietary Guidelines for Americans (88) and The Obesity Society/American Heart Association (AHA)/American College of Cardiology (89), as they offer the opportunity to characterize the overall nutritional density and thus dietary quality of eating behaviors in a population rather than providing recommendations about the quantity of calories or macronutrients to consume (88). With regard to facilitating behavioral counseling, focusing on diet patterns versus single nutrients or food groups may permit greater flexibility and smaller, incremental changes in eating behavior, thereby increasing potential adherence, patient mindfulness of selecting healthful eating choices, and overall effectiveness of the diet recommendations (87).

The most well-studied dietary patterns include the Mediterranean- and Dietary Approaches to Stop Hypertension (DASH)-style diets (88,89), both of which emphasize plant-based foods (fruits and vegetables, whole grains, nuts, legumes, seeds), whole grains (cereals, breads, rice, or pasta), low fat dairy, and low amounts of red meat. With respect to obesity, Mediterranean and DASH diet types have been praised for their effectiveness in safely promoting weight loss and reducing long-term weight gain (when combined with energy restriction) (88,90), while consistently being associated with reduced CVD risk factors and metabolic outcomes (91,92). Importantly, adoptions to DASH or Mediterranean-style diets have been proposed for sociocultural feasibility (87), underscoring their generalizability to various populations, and greater likelihood of either diet pattern to promote weight loss/maintenance as well as attenuation of the presumably inevitable weight gain "rebound" following weight loss success.

Obesity treatment strategy: Evidence for dietary quality aggregate quality. In line with recommendations of healthy dietary patterns, evidence-informed dietary priorities include adherence to a low energy-dense dietary prescription (88). Data pooled from 3 population cohort studies in middle-aged and older adults have consistently demonstrated that higher consumption of whole grains, nuts, fruits and vegetables, specifically higher fiber and lower glycemic index ([GI], i.e., better carbohydrate quality) vegetables, and yogurt are each associated with less weight gain over a 4-year follow-up (93–95). Coincidently, these findings overlap with the primary identified dietary components of Mediterranean and DASH diet patterns. On the contrary, increased intake of starchy, higher GI vegetables, such as corn, peas, and potatoes, is associated with weight gain in these populations (95). Biological mechanisms regarding how specific dietary components may reduce weight gain are commonly explained in terms of their effect on hunger and satiety (96). For example, the satiating properties of fruits and vegetables and whole grains, for example, higher water content per volume and fiber content, may displace the intake of more energy-dense foods from the diet (96) and reduce energy absorption from the gastrointestinal tract (97). Additionally, the higher fiber content and lower GI of these foods may further moderate energy intake by slowing down starch digestion or absorption, reducing postprandial glucose concentrations (98), and in turn, eliciting lower insulin and glucose responses that favor fat oxidation and lipolysis rather than its storage (99). Higher resting energy expenditures during isocaloric low GI versus low fat feeding following weight loss have also been reported in adults who are overweight or obese, suggesting reduced GI diets may be advantageous for sustaining weight loss in this highly vulnerable population (100).

Not surprising are observations of greater weight gain associated with increased intakes of refined carbohydrates (93,94), which are often higher in starches, fats, and added sugars, that are hypothesized to elicit an immediate insulinemic response, followed by a hypoglycemic period; this combined effect leads to reduced satiety and increased hunger signals and may in turn drive overconsumption of energy-dense foods, increased total caloric intake, and consequently weight gain over time. Adverse metabolic consequences imposed by higher intakes of refined grains and starches reported in overweight and obese individuals suggests that these highly palatable, rapidly digested, low GI/low fiber carbohydrates are aggravated by underlying insulin resistance (101) and may further drive obesogenic pathways (101,102).

ADDED SUGARS. Conventional wisdom posits that added sugar (i.e., sweeteners added to processed and prepared foods including those sugars and syrups added at the table) is a key driver of the obesity epidemic (103). The most compelling evidence of added sugars effect on weight gain derives from studies evaluating consumption of SSB, which account for almost one-half of the added sugar consumed in the United States (104) and remains to be a consistent dietary feature associated with obesity, T2DM, and CVD rates (105). Notably, greater visceral and liver fat accumulation, regardless of body weight, have been reported in individuals consuming daily amounts of SSB (105-107), suggesting a mechanistic pathway linking SSB consumption to abdominal obesity and cardiometabolic risk factors. In response to the growing concerns of added sugars on the escalating obesity rates, the AHA and the 2015 Dietary Guidelines Advisory Committee have recommended reducing added sugar intake to <10% of total caloric intake (88) or consume ≤9 teaspoons per day (or 150 calories per day) in men and ≤5 to 6 teaspoons per day (or 100 calories per day) in women (108).

It is important to note, however, that the assertion of added sugars in obesity continues to be debated, as evidence for this association has primarily been supported by epidemiological and animal studies (109). Whether this association is causal to the development of obesity remains to be proven in randomized control studies (110). Arguably, eating more or less of any 1 food or nutrient may change the total amount of energy consumed, but the magnitude of this effect may vary, depending on what else is consumed in the same meal (111). In the context of SSB consumption, which is linked to poor overall dietary quality (105), there are notable confounding dietary characteristics, including the Westernized diet, reliance on processed foods, and increased eating behaviors out of the home, not to mention lifestyle behaviors, such as smoking and a sedentary lifestyle. Coincidently, eating outside the home and take-away meals and snacks have independently been associated with higher energy intakes, increased portion sizes, long-term weight gain, and a higher risk of obesity (105). In this regard, targeting SSB, or other dietary metrics (e.g., fat, calories, carbohydrates), may elicit divergent relationships with long-term weight gain and thus may not accurately identify how specific dietary factors influence obesity (87,94). Given that diet quality presumably affects energy intake (i.e., total calories), aggregate changes in dietary metrics that contribute to an overall improved dietary pattern remains to be a key dietary priority for obesity prevention, treatment, and cardiometabolic health (105). Also, if PA and exercise levels are high, the importance of dietary GI and sugar contents may be considerably lessened.

Community prevention. Success in reducing obesity risk through lifestyle and behavioral modification has been demonstrated in numerous clinical intervention trials (90,112,113). However, utilization of structured protocols have limited the generalizability of clinical findings to "real-world" settings, and overall, sustainability of lifestyle modification efforts outside "investigator-controlled" conditions has yet to be proven. Leveraging community input in clinical studies may be the key to ensuring successful implementation, dissemination, and translation of evidence-based clinical approaches to broader, more diverse, vulnerable populations. This notion of partnering researchers with multiple stakeholders, including community members who live with the problem being investigated, are foundational to community-based participatory research (113). The premise of meaningful involvement by members of a community has recently been woven into multilevel cross-disciplinary health paradigms that aim to link community prevention efforts with clinical services.

Integrated partnerships between clinical research and the community have offered both progress and promise to obesity prevention research. Most notable of these "clinic-to-community" strategies has been the translation of the landmark national Diabetes Prevention Program to various community settings, including the Young Men's Christian Association (114), churches (115), local health care facilities (116), underserved communities (117), and on American Indian reservations in the United States (118). Collectively, lifestyle protocols modeled after the Diabetes Prevention Program have shown success in

improving various obesity and cardiometabolic metrics, with evidence showing sustained improvements at least 12 months after intervention completion (119,120).

More system-wide approaches that are likely to cripple the current obesity epidemic have been heralded by larger foundations (e.g., Kaiser Family Foundation, Robert Wood Johnson Foundation, California Endowment, and W. K. Kellogg Foundation) (121). A core focus of these programs has been to implement more sustainable, policy-, system-, and environmental-wide interventions that transform local environments and remove barriers (environmental and social) that may otherwise hinder individual health behavior decision making. Many of these funded programs have successfully demonstrated that changes in community environments (i.e., creating walkable and safe environments and more green space; increasing affordability, proximity, and availability of nutritious foods; and increasing access to health services and wellness programs in schools) can lead to substantive, desirable, and sustainable public health outcomes (121,122). More exemplar obesity prevention strategies implemented by the Centers for Disease Control's Communities Putting Prevention to Work initiatives have elicited a greater obesity reduction affect at the community- and state-wide levels, specifically by targeting the community environment (i.e., where an individual lives), and by modifying multiple contexts within the community environment that directly affect many individuals (121). The overall effect size and long-term sustainability of these policy-, system-, and environmental-wide initiatives to reduce obesity in various community settings has yet to be determined and will likely vary by community factors. Nonetheless, leveraging cross-collaborations among community members, health care systems, policy makers, and other environmental stakeholders appears to be essential to maximize the future investment in obesity prevention and to facilitate more timely improvements in the health of populations (123).

Societal/authoritative. In the task of obesity prevention, efforts have been (strategically) hurdled by the debate of responsibility, and more specifically, whether obesity truly should be accepted as an individual responsibility or an environmental/public liability (124,125). Consequently, discussions on obesity prevention strategies have been propelled into the political arena (110,124,125). The views of personal responsibility, for example, stem from the belief that obesity is caused by an individual's irresponsibility to avoid unhealthy lifestyle behaviors (e.g., diet and inactivity, sedentariness) and is therefore premised on individual's choice to practice sensible dietary and lifestyle practices. Generally, personal responsibility patrons view any form of government interference as being intrusive, demanding, and paternalistic, in other words, a clear obtrusion to their first amendment rights and freedom of choice (124,125). Individuals who align with this view favor industry to tackle the perceived problems of obesity (124). Coincidently, these arguments represent a disturbing echo of the vices used by tobacco industry, which coined personal responsibility as their first line of defense against regulation (125). In response to what can only be seen as successful campaigning, the government has taken on more of a supportive versus reactive role by pushing solutions that are viewed as "laissez faire" in nature; that is, developing sanctioned nutrition education and encouraging PA/exercise through propaganda. As is evident with our nation's current obesity statistics, such conservative measures have yet to show any significant affect in slowing down obesity in this country.

The notion that obesity is both caused and exacerbated by our obesogenic environment falls in line with those advocating for environmental/governmental responsibility. Environmental responsibility proponents, therefore, encourage regulatory responses by government (125). Through much perseverance, local- and state-wide progress in increasing obesity awareness, detoxifying our environment, and "healthifying" the general public has been made by lobbying activists (e.g., Obesity Society, Center for Science in the Public Interest, American Diabetes Association, AHA, and Academy of Nutrition and Dietetics). Although some initiatives, such as calorie/nutrition menu labeling and regulation of food ingredients (i.e., transfats in restaurants), have shown resiliency against industry and public opposition, other, more controversial, strategies, such as curtailing food advertisements (particularly those targeting youth) or SSB taxation, have been limited to regional successes, but with the potential to reach national influence. Regardless of whether successes have been long-term or short-lived, each of these public health initiatives has been instrumental in raising the salience of obesity as a national threat to our society.

However, if government is going to intervene, insights can be obtained from the North Karelia Project experience (126,127). In the 1960s and 1970s, CVD mortality in Finland was perhaps the highest in the world. In 1972, the North Karelia Project was established to reduce the extremely high CHD mortality through behavioral change and reductions in the major CVD risk factors among the whole population of North Karelia, targeting smoking, cholesterol, and

TABLE 3 Recommendations for Physical Activity

- Maintaining and improving health: 150 min/week
- Prevention of weight gain: 150 to 250 min/week
- Promote clinically significant weight loss: 225 to 420 min/week
- Prevention of weight gain after weight loss: 200 to 300 min/week

blood pressure, leading to impressive declines in CHD mortality (127). Therefore, some of the governmental aspects of the success of this type of program could also be transferred to obese in the United States and worldwide.

WHERE TO GO FROM HERE?

With differing opinions regarding responsibility, it is not surprising that discussions on obesity solutions have inspired divergent policy recommendations (125). The primary question regarding how our legislation will respond to the obesity problem remains unanswered. Treating obesity through medical interventions (i.e., surgical to pharmaceutical) has significantly escalated in recent years, whereas obesity prevention, the most cost-effective, commonsense approach to reversing the inevitable obesity forecast of our nation and globally (128) has remained lost amid the politics of obesity. Clearly, stronger initiatives are needed to affect the world's discerning obesity trajectories. For example, any proposed strategies that address the U.S. obesity crisis will require common ground between public health lobbyists; however, creating approaches that provide personal and public collective benefit remains a challenge. Leveraging personal responsibility by "rehabbing" all sectors of our environment (i.e., school programs, food industry and marketing practices, food taxation) has been a central theme in proposals suggested by special interest groups, with the premise being that creating these healthier "defaults" in our environment will help foster more responsible decision making, bridging the divide between individualistic and environmental views shared by policy makers (125). Solutions of this manner will undoubtedly depend on successful public advocacy (124) and more judicious authority by all government sectors to better regulate individual behavior and promote public health (110,125). Ultimately, reconciling the frontier of our obesity crisis will require a greater commitment from individuals and environmental policy makers and lobbyists (i.e., government and food industry) to create a proactive culture of health and wellness that aspires to prevent chronic disease rather than treating it. Certainly, global efforts to increase PA/exercise and CRF across the life span would go a long way to promote these efforts (129).

Specifics of PA/exercise training. As reviewed earlier, as well as elsewhere in this Seminar Series, there is substantial evidence that low PA is a significant, possibly the most significant, contributor to weight gain and obesity (68–70). Certainly, PA and exercise training is better to prevent weight gain than it is to promote marked levels of weight reduction in more severe obesity (130). However, PA/exercise is critical to prevent further weight gain in overweight/obese individuals and to prevent overweight individuals from becoming obese and to prevent mildly obese from progressing to severe and morbid levels of obesity. Researchers have speculated on the amount of PA necessary to prevent weight gain, promote clinical significant weight loss, and to prevent weight regain after successful weight loss (130). The American College of Sports Medicine recommends 150 to 250 min/week of moderate to vigorous PA, with an energy equivalent of 1,200 to 2,000 kcal/week to prevent weight gain. To induce weight loss in overweight and obese patients, the requirement is considerably higher, with prevention of weight gain after successful weight loss being in between (**Table 3**). Although many weight loss studies defined clinically significant weight loss as ≥5%, we have demonstrated considerable improvements in insulin resistance with modest weight loss (3% to 4.9%) with exercise training, which is similar to that obtained with more significant weight loss and may represent a reasonable initial weight loss target with exercise training (131). Clearly, improvements in CRF with PA and exercise training are extremely important and may be more important than weight loss per se, as considerable evidence suggests that fitness may be more important than fatness for predicting prognosis (47,113).

SEDENTARY BEHAVIORS. Concurrent with efforts to increase PA engagement, targeting excessive sedentary behavior has been a focal point of obesity and chronic disease prevention strategies (132). However, sedentariness represents a construct distinct from physical inactivity (57) and is therefore considered to be a unique determinant of health consequences (133). Sedentary behavior specifically refers to time spent in a sitting, reclining, or lying down position (e.g., watching television, playing computer games, driving a car, sitting, or reading) during waking hours, resulting in an energy expenditure of ≤1.5 metabolic equivalents (METs) (71,134). Accordingly, the amount of time spent in sedentary behaviors is associated with increased risk of weight gain (135) and is

therefore considered to be a putative risk factor for obesity, a variety of other chronic conditions (135), and ultimately higher mortality (136); the risks associated with obesity are independent of body weight, PA, and eating behaviors (137). The highest risk of obesity and comorbidities are among inactive individuals with higher levels of sedentariness (132) and are thus in greatest need of lifestyle interventions. Notwithstanding, even individuals who are otherwise physically active but engage in prolonged periods of sedentary behavior are subject to adverse cardiometabolic alterations (132,137). Physiologically, prolonged sitting results in the loss of cumulative energy expended during contractions from the large skeletal muscle groups (e.g., legs, back, and trunk) during the waking hours of the day (135), contributing to the greater propensity to become overweight or obese. A shift of 2 h/day from light-intensity behaviors (i.e., 2.5 METs) to sedentary behaviors (i.e., 1.5 METs) is equivalent to 2 MET-h/day (or 2 kcal/kg/day of energy conserved). In this context, it can be estimated that for someone with a normal body weight and a resting energy expenditure of 67 kcal/h, this increase in sedentary behavior would equate to a 134 kcal/day surplus, equivalent to the amount of energy that is expended during a 30-min episode of brisk walking (3.5 METs). Conversely, in an obese individual, an additional 2 h/day spent sitting is approximately equal to 350 kcal/day surplus (138). This example further highlights the importance of promoting PA in obese individuals. Additionally, a study by Ekelund et al. (73) showed that high PA almost completely abolished the adverse effects of prolonged sitting on all-cause mortality.

Given our contemporary society, and consistent with epidemiological publications, it is apparent that both too little exercise and general PA, coupled with too much sitting, propel weight gain and presumably interfere with weight loss efforts. On average, for a person weighting 72 kg (~158 pounds), every minute of sedentary behavior replaced with light PA would presumably equate to an additional 1 kcal expended (calculated assuming 1.5 vs. 2.3 METs for a person weighing 72 kg) (139). Hence, in regard to obesity treatment, advising patients to reduce prolonged sitting and optimally replace sedentary behavior by moving a little more (133), weight reduction, adequate weight management, and importantly, health improvements are likely, especially among those with substantial disease burden or risk. In support, increasing evidence suggests interrupting sedentary activities with light PA effectively improves various domains of cardiometabolic risk factors in overweight/obese populations and particularly in those with dysglycemia (140) or T2DM (141). Likewise, replacing even modest doses of sedentary time (e.g., 10 min) with equal amounts of PA (142) or interrupting sitting time with 2-min periods of light- or moderate-intensity walks every 20 min (102) has been shown to have clinically significant, favorable effects on BMI and WC, as well as glycosylated hemoglobin, lipids (142), postprandial glucose, and insulin levels (102,140). Ultimately, the evidence, though primarily observational in nature, is promising with regard to reversing health consequences associated with obesity. In the contention of obesity treatment, engaging in strategies that break up or replace sedentary time with modest amounts of light PA is a prudent, yet feasible approach to promoting weight reduction and optimizing behavioral lifestyle therapy compliance over time (139,142).

PHARMACOTHERAPY AND BARIATRIC SURGERY

Similar to other chronic diseases in which lifestyle modification alone may not be effective enough to control symptoms and/or adverse outcomes, pharmacotherapy and bariatric surgery are 2 evidence-based treatments that can be used to intensify therapy for obesity. The goal of using these interventions is to enhance weight loss and improve the associated comorbid conditions, such as hyperglycemia, hypertension, and dyslipidemia. According to U.S. Food and Drug Administration, anti-obesity medications are approved for patients with a BMI $\geq$30 kg/m^2 or with a BMI $\geq$27 kg/m^2 who also have concomitant obesity-related risk factors or diseases and for whom dietary and PA therapy has not been successful. Anti-obesity medications require the implementation of lifestyle modification as a foundation for drug action due to the importance of the drug-behavior interaction, in other words, by pharmacologically modifying the sensation of hunger and/or satiety, patients must deliberately and consciously alter their eating behavior for weight loss to occur, thus producing a negative energy (calorie) balance.

Among the 6 U.S. Food and Drug Administration-approved medications used today (**Table 4**), 5 are approved for weight loss and maintenance of weight loss (orlistat, lorcaserin, phentermine/topiramate, naltrexone sustained release, bupropion sustained release, and liraglutide), and 1 is approved only for short-term use (phentermine). Except for orlistat, which acts peripherally as a competitive gastrointestinal lipase inhibitor, the other 5 medications function centrally, targeting sites in the appetite center of the hypothalamus, the nucleus tractus solitarius, or

TABLE 4 Summary of Centrally Acting Anti-Obesity Medications Approved for Long-Term Weight Management

	Phentermine-Topiramate	Lorcaserin	Naltrexone-Bupropion	Liraglutide
Mechanism of action	Sympathomimetic modulation of gamma-aminobutyric acid receptors and/or inhibition of AMPA/kainite glutamate receptors	Selective serotonin (5-hydroxytryptamine)2_C receptor agonist	Opioid antagonist reuptake inhibitor of dopamine and norepinephrine	Glucagon-like peptide-1 agonist
Mean percentage of weight loss: drug vs. placebo*	7.8–10.9 vs. 1.2–1.6	4.8–5.8 vs. 3.0–3.6	6.1–6.5 vs. 1.3–1.9	6.2–8.0 vs. 0.2–2.6
Categorical change in 5% weight loss: drug vs. placebo*	62.0–66.7 vs. 17.3–21.0	47.2–47.5 vs. 20.3–25.0	48.0–50.5 vs. 16.0–17.1	63.2–81.4 vs. 27.1–48.9
Most common adverse events	Dry mouth, paresthesias, headache, insomnia	Headache, dizziness, diarrhea	Nausea, GI complaints, headache, insomnia	Nausea, GI complaints
Dosage and administration	Once daily	Twice a day or once daily extended release	2 tablets twice daily	Once daily by subcutaneous injection

*Mean 1-year outcomes from clinical trials.

AMPA = alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GI = gastrointestinal.

reward centers of the brain. Patients who are responsive to medication experience various perceptions of less hunger, earlier and prolonged satiety, fewer thoughts of food, and diminished cravings. Accordingly, patients are better able to adhere to a calorie-controlled diet.

Excluding phentermine, which was approved in 1959 as a short-term weight loss agent, the other 4 centrally acting medications were approved since 2012 and underwent randomized, placebo-controlled, double-blind trials for efficacy and safety. A summary of the medications, weight loss outcomes, and adverse events is shown in **Table 4** (143–150). Interestingly, phentermine, topiramate, naltrexone, bupropion, and liraglutide have been previously approved for other indications and should be familiar to clinicians. When used either in combination or at a different dose, they are effective as weight loss agents. In contrast, lorcaserin is a new compound that was selectively developed as a serotonergic agonist. Clinical and statistical dose-dependent improvements are seen in intermediate CV and metabolic outcome measurements that are related to the weight loss. The selection of which medication to use is based on several factors, including comorbidities, drug-drug interactions, side effects, route of delivery, dosing frequency, and cost. The Endocrine Society's guidelines on the Pharmacological Management of Obesity emphasizes the importance of shared decision making in the use and selection of agents (151).

Due to its higher risk and cost, bariatric surgery should be considered for patients with severe obesity (BMI ≥40 kg/m^2) or those with moderate obesity (BMI ≥35 kg/m^2) associated with a serious medical condition, such as diabetes, heart disease, sleep apnea, lipid abnormality, or nonalcoholic fatty liver disease. According to the AHA/American College of Cardiology/The Obesity Society guidelines, patients who are motivated to lose weight and who have not responded to behavioral treatment with or without pharmacotherapy with sufficient weight loss to achieve targeted health outcome goals should be advised that bariatric surgery may be an appropriate option to improve health (90).

The 2 most commonly performed procedures are the laparoscopic sleeve gastroplasty and Roux-en-Y gastric bypass. The clinical benefits of bariatric surgery in achieving weight loss and alleviating metabolic comorbidities have been attributed largely to changes in the physiologic responses of gut hormones, bile acid metabolism, the microbiota, and adipose tissue metabolism. Mean weight loss at 2 to 3 years following a surgical procedure ranges from 20% to 34% of initial body weight, depending on the procedure. Significant improvement in CVD outcomes such as myocardial infarction, stroke, CVD risk and events, and mortality have been reported from matched controlled studies (152,153). One of the most significant clinical outcomes is the role of bariatric surgery in the treatment of patients with T2DM, where bariatric/metabolic surgery has demonstrated superior glycemic control in patients with T2DM compared with various medical and lifestyle interventions (154,155). Based on this data, the 2018 Standards of Care for Diabetes from the American Diabetes Association includes bariatric surgery in the treatment algorithm for T2DM. All surgical patients should participate in post-operative programs that support lifestyle modification because obesity is considered a chronic disease.

TABLE 5 Learning Objectives for Behavioral Sciences Knowledge and Skills Development During Undergraduate Medical Training

Domains	Learning Objectives
Knowledge	Describe counseling steps that foster behavioral change.
	Describe a patient-centered approach and core concepts of major behavior change theories.
	Recognize the expertise of the behavioral counselor and distinguish health professionals who have expertise in supporting specific types of lifestyle behavioral change.
Skills	Assess lifestyle behaviors and patients' confidence and readiness to make changes.
	Demonstrate effective patient-centered communication skills to help the patient set behavior change goals and establish a plan.
	Use appropriate behavior change techniques, such as goal setting, self-monitoring, and reinforcement, to support patients in making healthy lifestyle changes.
	Appropriately adapt counseling to patients' age, sex, race or ethnicity, culture, and preferences.
	Refer to a behavioral counselor or other health care professionals with behavioral expertise when appropriate.

Reproduced with permission from Hivert et al. (156).

CAREGIVERS OF HEALTH PROMOTION

Health care in the United States as well as in a majority of countries around the world is undergoing a needed major paradigm shift that entails recognition of 5 salient points. 1) The leading global health care concern is the staggering negative impact chronic disease, both the current crisis as well as future projections, has on health outcome and the economy. 2) Obesity is a leading risk factor for the development of chronic disease. 3) Moving forward, there needs to be a much greater focus on the prevention of chronic disease, ideally before primary risk factors, including excess body mass, manifest. 4) HLM, which includes PA and generally moving more, healthy nutrition, healthy body weight, and not smoking, is vital to the prevention as well as treatment of chronic disease. 5) To shift toward a much greater focus on chronic disease prevention and the needed increase in the delivery of HLM, the way we train health care professionals must evolve.

Recently, the AHA published a scientific statement titled "Medical Training to Achieve Competency in Lifestyle Counseling: An Essential Foundation for

TABLE 6 Learning Objectives for Nutritional Assessment and Counseling During Undergraduate Medical Training

Domains	Learning Objectives
Nutrition assessment	Describe health benefits of recommended dietary patterns and current dietary guidelines for maintenance of health and for the prevention and treatment of diverse medical conditions.
	Assess dietary behaviors and evaluate patients' habitual food intake.
	Recognize the need for detailed nutritional assessment and referral to RD and other health care professionals with nutritional expertise when appropriate.
Nutrition diagnosis	Describe pathogenesis of nutrition-related diagnoses.
	Diagnose nutrition-related problems and prioritize them.
	Recognize and use diagnostic labels for documentation in patients' medical records.
	Communicate effectively with RD, including understanding the information conveyed by the "problem, etiology, signs, and symptoms" statements commonly used by RD.
Nutrition intervention	Assess patients' confidence and readiness to change toward a healthy lifestyle behavior that includes good nutritional practices.
	Counsel patients on the benefits of evidenced-based recommended nutrition practices for the prevention and treatment of diverse medical conditions.
	Use appropriate behavioral skills and tools to help patients initiate and maintain good nutritional practices.
	Demonstrate effective communication skills with patients and other health care professionals with nutritional expertise.
	Appropriately counsel patients according to age, sex, race or ethnicity, culture, and other personal characteristics.
	Recognize the need and appropriate timing for referral to RD or other health care professionals with nutrition expertise with the intent of modifying a nutrition-related behavior.
	Support the implementation of the nutrition intervention with members of the health care team.
Nutrition monitoring and evaluation	Facilitate goal setting and periodic evaluation of dietary recommendations.
	Support behavioral changes by advising the use of monitoring tools in achieving nutrition-related goals.
	Evaluate the health effects of nutrition modifications made by patients.

Reproduced with permission from Hivert et al. (156).
RD = registered dietician.

TABLE 7 Learning Objectives for PA and Exercise Assessment and Counseling During Undergraduate Medical Training

Domains	Learning Objectives
PA assessment	Describe the normal physiological responses to an acute bout of exercise and adaptations to aerobic and resistance exercise training.
	Describe health benefits of PA for health maintenance and in diverse medical conditions, as well as recommended guidelines for an active lifestyle.
	Assess PA behaviors using the appropriate tools for patients who are healthy, have controlled disease, or are living with a disability.
	Recognize the need for additional assessments such as symptom-limited exercise testing and refer to appropriate health care professionals or clinical settings.
PA and exercise prescription	Recognize individuals who do not meet current PA recommendations.
	Develop a safe PA or exercise prescription for apparently healthy people, those at increased risk for developing a chronic noncommunicable disease, and patients with specific medical conditions.
	Recognize individualized constraints/risks and contraindications to performing PA or a structured exercise program and adjust recommendations accordingly.
PA and exercise counseling, behavioral strategies	Assess patients' confidence and readiness to change toward a healthy lifestyle behavior as it relates to PA and exercise.
	Counsel patients on the benefits of PA in health maintenance and for prevention and treatment of specific medical conditions.
	Use appropriate behavioral tools and skills to support patients to initiate or maintain a PA plan.
	Demonstrate effective patient communication skills with regard to PA and exercise assessment and counseling in all clinical settings.
	Appropriately counsel patients according to age, sex, race or ethnicity, culture, and other personal characteristics.
	Recognize the need for individualized or supervised PA programs when referring a patient to appropriate health care professionals with PA or exercise expertise.
	Support the implementation of the PA intervention in close collaboration with other members of the health care team.
	Use behavioral strategies to maintain an active lifestyle, including monitoring, goal setting, and periodic reassessment.
	Evaluate the health effects of PA modifications with patients and reinforce or adjust the plan accordingly.
Physician's personal health	Recognize the importance of an active lifestyle for his or her own quality of life, professional balance, and as a role model for patients.

Reproduced with permission from Hivert et al. (156).
PA = physical activity.

Prevention and Treatment of Cardiovascular Diseases and Other Chronic Medical Conditions" (156). This statement, focused on medical education, recognizes HLM is not frequently delivered in current practice; ≈34% of physicians reporting the performance of lifestyle counseling to their patients during office visits. Interestingly, patients report an even lower frequency of receiving HLM; as an example, obese patients reported their primary care providers provided counseling on PA and nutrition during ≈20% and ≈25% of office visits, respectively (90). This is in contrast to current overweight and obesity guidelines affording lifestyle counseling, primary of which are PA and healthy nutrition counseling, a Class A, Level 1 recommendation (90). A primary mechanism for the current low practice of HLM by physicians is a lack of training in this critical area while receiving their medical education; currently very few medical schools have a well-developed HLM curriculum (156,157). Medical students not made aware of the importance of a healthy lifestyle for the prevention and treatment of chronic disease, or who are not prepared to deliver HLM, have a low likelihood of integrating this important intervention into their medical practice on graduation. Data indicate that when medical training includes content on HLM in a meaningful way, students both comprehend its importance to chronic disease prevention and management (158). The AHA, American College of Cardiology Foundation, American College of Physicians, and the Institute of Medicine have all called for stronger HLM curricula in medical schools (156,159,160). The recent AHA statement on medical training for HLM proposed behavioral science, nutrition, and PA competencies during undergraduate medical training (**Tables 5 to 7**). The authors of this review wholeheartedly support a strong HLM curriculum in all medical schools that incorporate the competencies listed in **Tables 5 to 8**.

Although physicians must play a leading role in delivering HLM, all health professionals (e.g., nurses, pharmacists, dentists, physical and occupational therapists) can and should play important roles. Patients in all practice settings, from primary care to specialized clinics focused on chronic disease management (e.g., cardiology, pulmonology, endocrinology) should receive a consistent HLM message. Unfortunately, akin to medical school curricula, other

TABLE 8 Healthy Living Practitioner Graduate Certificate Curriculum

Course	Learning Objectives	Credit Load
	Fall Courses	
Upstream Prevention: Epidemiology, Economics, and Policy	• Describe the incidence and prevalence of behaviors that lead to disease states and key health measures and how they begin early in the life course. • Describe the relationship between LS7 score and other evidence-based risk calculators (e.g., Framingham, ASCVD risk calculator, Reynolds) and chronic disease risk. • Describe the intersection between unhealthy behaviors, social determinants of health, policy, systems, and environment on population health outcomes and economic ramifications. • Describe policy initiatives centered on improving healthy living characteristics and other preventive measures at a population level.	3
Health Communication and Literacy	• Read as a critical thinker to better translate nutrition and exercise science, both regulated and nonregulated (e.g., supplements for general health and exercise) for a wide and varied audience. • Understand the role of pragmatism to support a 2-way health dialogue. • Appreciate the distinction between scientific and anecdotal evidence as it relates to health and wellness and how this distinction influences the 2-way health dialogue. • Appreciate that there are many forms of literacy that lack hierarchy but can be orchestrated to effectively and respectfully foster a transaction of health information.	3
Preventive Health Screening	• Be able to use perform a basic health screening assessment, using evidence-based tools, to ascertain the risk for or potential presence of 1 or more chronic diseases. • Become familiar with current evidence-based risk prediction tools (e.g., LS7, Framingham, ASCVD risk calculator, Reynolds).	1
Nutrition for Healthy Living	• Understand basic principles of nutrition throughout the life cycle (from embryo to elderly person). • Understand basic concepts of nutrition and chronic disease, for both deficiency and degenerative diseases (arthritis, osteoporosis—non-trauma-related). • Be able to perform a basic nutritional assessment. • Be able to provide basic guidance on healthy nutrition. • Be able to provide common nutrition substitutions for culture-specific foods behaviors and values (food focused).	3
	Spring Courses	
Exercise and Physical Activity for Healthy Living	• Understand basic principles of exercise and physical activity in health and disease states. • Be able to interpret exercise and physical activity assessments. • Be able to provide basic guidance on exercise and physical activity.	3
Behavioral Counseling for Healthy Living	• Understand challenges surrounding adoption of a healthy living behaviors. • Be able to employ basic behavioral counseling strategies focused on improving LS7 scores, mental health, and well-being. • Be able to employ basic behavioral counseling strategies to those facing socioeconomic challenges (e.g., food stamps, government assistance).	2
Use of Technology for Healthy Living	• Understand basic principles of health information systems and informatics with implications for tracking and managing LS7 characteristics. • Be able to effectively utilize technology (e.g., web, social media, mobile applications, wearable devices) to track LS7 characteristics and enhance healthy living interventions. • Understand the role of technology in a citizen science approach (e.g., taking photos of built environment—how does the environment promote/hinder healthy living).	2
Healthy Living Seminar	• Through an interprofessional group project, develop and present a healthy living program proposal in a broad array of settings and environments (e.g., community, workplace, school system, health care organization).	2
	Practical Component	
	Summer Course	
Healthy Living Practicum	• Participate in the development and/or implementation of a healthy living program in a broad array of settings and environments (e.g., community, workplace, school system, health care organization).	3

Reproduced with permission from Hivert et al. (157).
ASCVD = atherosclerotic cardiovascular disease; LS7 = Life's Simple 7.

health professions commonly do not provide sufficient training in HLM (161,162). To address this issue, Hivert et al. (157) and Arena et al. (163) recently proposed the Healthy Living Practitioner (HLP) graduate certificate program. This 22-credit program is a "stackable credential" meant to be taken as an elective sequence in parallel to a student's health profession training; students in any discipline are

eligible for this program, thereby embracing an interprofessional education model. The University of Illinois at Chicago launched the program in the fall of 2017 (164). The University of Tasmania in Australia and University of Belgrade in Serbia are both preparing to launch the HLP program in the next 1 to 2 years. Expansion to other academic institutions globally will follow. AHA has trademarked the HLP brand, ensuring a uniform training model with high academic rigor. **Table 8** lists the HLP graduate certificate program. This model has the potential to train a large number of health professions across all disciplines, creating a health care workforce proficient in the delivery of HLM.

The published reports indicate lifestyle counseling by health professionals can result in significant and clinically meaningful improvements in behaviors and health profile, including weight loss in those who are overweight or obese (165–168). Most research has examined the efficacy of physicians and nurses in lifestyle counseling and subsequent outcomes. Fewer studies have been performed to suggest the potentially important role of other health professionals, including pharmacists (169–172), dentists (162,173), physical therapists (174), and occupational therapists (161). Currently, the publications on the benefits of lifestyle interventions delivered by pharmacists appear to be most robust and promising (169–171). Moreover, using a pharmacy as a community-based platform to deliver HLM holds promise. In a rural Australian community, Kellow (175) demonstrated a lifestyle program that was provided to 40 individuals under 50 years of age with chronic disease risk factors resulted in significant weight loss as well as a significant increase in fruit and vegetable consumption and PA. The year-long program consisted of free nutritional counseling (after hours) by a dietician, a pharmacist-led medication review, and a gym membership, as well as the opportunity to participate in cooking classes and supermarket tours. Overall, research examining the benefits of a broader array of health professionals participating in HLM is currently in its initial stages and must expand to determine optimal roles, messaging, and interventions. Moreover, it appears that lack of training in the delivery of HLM is a barrier for health professionals to appropriately implement HLM into their practice (161,162), an issue that can and should be addressed by changes in academic preparation across all disciplines.

Of significant note, it appears that intensive lifestyle counseling, entailing more contact with health professionals proficient in delivering HLM in an individualized and group format, goal setting, and such, is needed for more significant and lasting improvements (176–178). In a systematic review and meta-analysis of "Lifestyle Weight-Loss Intervention Outcomes in Overweight and Obese Adults With Type 2 Diabetes," Franz et al. (178) concluded that weight loss >5% was required for clinically significant improvements in glycosylated hemoglobin, as well as lipids and blood pressure. To achieve this weight loss goal, it was concluded that intense lifestyle interventions, such as energy restriction, a regular exercise program, and frequent contact with a qualified health professional was needed (178). Given the frequent need for intensive lifestyle interventions in those who are at high risk for or already diagnosed with 1 or more chronic diseases, often the case in those individuals who are overweight or obese, it will be important to train physicians, nurses, and other health professionals, who serve as the initial point of patient contact, on when to refer individuals for intensive lifestyle counseling to optimize long-term compliance and health outcomes.

FUTURE DIRECTIONS AND CONCLUSIONS

Clearly, better long-term studies are needed to determine optimal weight in various groups of patients, especially studies that adequately control for PA, exercise, and CRF. Also, studies are needed that assess the impact of various weight loss strategies on the development of CVD and other chronic diseases, as well as the cost-effectiveness of these strategies. Additionally, weight loss studies are needed in both primary and secondary prevention, including assessing clinical events and survival in patients with CHD in both HF with preserved and reduced ejection fraction. Finally, the impact of various programs in school children and adults, including taxing certain food items, such as SSB, by various governmental programs, needs to be determined. Clearly, a multimodality approach and intervention, as reviewed here (**Central Illustration**), will be required to reduce the devastating consequences of progressive obesity in our society and, especially, for the prevention and treatment of CVD.

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APPENDIX For a supplemental table, please see the online version of this paper.