Obesity, Diabetes, and Cardiovascular Diseases Compendium

Obesity and Cardiovascular Disease

Francisco B. Ortega, Carl J. Lavie, Steven N. Blair

Abstract: **The prevalence of obesity has increased worldwide over the past few decades. In 2013, the prevalence of obesity exceeded the 50% of the adult population in some countries from Oceania, North Africa, and Middle East. Lower but still alarmingly high prevalence was observed in North America (≈30%) and in Western Europe (≈20%). These figures are of serious concern because of the strong link between obesity and disease. In the present review, we summarize the current evidence on the relationship of obesity with cardiovascular disease (CVD), discussing how both the degree and the duration of obesity affect CVD. Although in the general population, obesity and, especially, severe obesity are consistently and strongly related with higher risk of CVD incidence and mortality, the one-size-fits-all approach should not be used with obesity. There are relevant factors largely affecting the CVD prognosis of obese individuals. In this context, we thoroughly discuss important concepts such as the fat-but-fit paradigm, the metabolically healthy but obese (MHO) phenotype and the obesity paradox in patients with CVD. About the MHO phenotype and its CVD prognosis, available data have provided mixed findings, what could be partially because of the adjustment or not for key confounders such as cardiorespiratory fitness, and to the lack of consensus on the MHO definition. In the present review, we propose a scientifically based harmonized definition of MHO, which will hopefully contribute to more comparable data in the future and a better understanding on the MHO subgroup and its CVD prognosis. (*Circ Res*. 2016;118:1752-1770. DOI: 10.1161/CIRCRESAHA.115.306883.)**

Key Words: cardiovascular diseases ■ metabolically healthy obesity ■ morbidity ■ mortality ■ obesity

There is overall agreement in the scientific and clinical community that obesity is one of the major public health problems of this century. The first documented reports on obesity date from the end of the 19th century and the beginning of the 20th century.[1–3] From these days to date, >57 000 articles have been published in PubMed including the term obesity in the title, with these figures being 3× larger when searching by obesity also in the abstract. Figure 1 graphically illustrates the overwhelming amount of investigations focused on obesity in the past decades, with a marked increase starting from the end

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From the PROFITH "PROmoting FITness and Health through physical activity" Research Group, Department of Physical Education and Sports, Faculty of Sport Sciences, University of Granada, Granada, Spain (F.B.O.); Department of Biosciences and Nutrition at NOVUM, Karolinska Institutet, Huddinge, Sweden (F.B.O.); Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School-the University of Queensland School of Medicine, New Orleans, LA (C.J.L.); and Departments of Exercise Science and Epidemiology and Biostatistics, University of South Carolina, Columbia (S.N.B.).

Correspondence to Francisco B. Ortega, PhD, Department of Physical Education and Sports, Faculty of Sport Sciences, University of Granada, Carretera de Alfacar s/n, Granada 18071, Spain. E-mail ortegaf@ugr.es

Nonstandard Abbreviations and Acronyms

ACLS	Aerobics Center Longitudinal Study
BF%	percent body fat
BMI	body mass index
CHD	coronary heart disease
CV	cardiovascular
CVD	cardiovascular disease
FFM	fat-free mass
FM	fat mass
FMI	fat mass index
HF	heart failure
LV	left ventricular
MAO	metabolically abnormal obese
MetS	metabolic syndrome
MHNW	metabolically healthy normal-weight
MHO	metabolically healthy but obese
NHANES	National Health and Nutrition Examination Survey
PA	physical activity
WC	waist circumference

of the 1990s. Many of these studies reported the prevalence of obesity problem in different parts of the world. Without any shade of doubt, the biggest and more powerful study describing the current prevalence of obesity worldwide in adults and in children, as well as how this prevalence has changed over the past decades, is the systematic review conducted by Ng et al.[4] These authors reported data from 188 countries of individuals aged 2 to ≥80 years, separately by sex, age group, world region, and development status (developed versus developing countries). This unique study concluded that in some countries from Oceania, North Africa, and the Middle East, the prevalence of obesity (body mass index [BMI] ≥30 kg/m^2) in 2013 exceeded 50% of the adult population, which is extremely alarming. The prevalence of obesity was lower but still very high in other parts of the world, such as in North America, where one third of the adult population is obese, or in Western Europe, where one fifth of the adults are obese. These figures are more than doubled when considering the percentage of people with either overweight (BMI ≥25 kg/m^2) or obesity. The prevalence of obesity in children and adolescents is about half than that reported in adults. A worldwide increase in obesity has taken place from 1980 to 2013 in both developed and developing countries, men and women, and children and adults. The authors found no single country in which obesity has been successfully and significantly reduced over the past 33 years. However, there is evidence supporting that the obesity epidemic seems to have peaked in developed countries, suggesting that the prevalence of obesity, yet still high, is not currently increasing.[4] As an exception among the developed countries, Japan is not considered to have an obesity epidemic, with only 3.8% of its population being obese. It is thought that this might be at least partially explained by it traditional dietary patterns (rice, vegetable, fish, and lower caloric diet), together with a lower use of the car because of its excellent public transportation, which leads to more walking per day. Both the low obesity prevalence and these healthier behaviors might contribute to explain why Japan is the country in the world with the highest life expectancy.

The prevalence and trends in obesity observed in most of developed and developing countries would not be so serious if not because of the harmful effects of obesity on many different physical and mental health outcomes. In the present review, we will discuss in depth how obesity is not only related with cardiovascular disease (CVD) in the general population but also, as a complex condition, is associated with CVD differently depending on certain relevant factors. Particularly, we will comment on how the number of years that a person lives with obesity affect CVD outcomes, as well as on other important concepts, such as the fat-but-fit paradigm, the metabolically healthy but obese (MHO) phenotype and the obesity paradox in patients with CVD.

What Does Obesity Really Mean and How Is Associated With CVD?

This may seem to be a simple and irrelevant question, but actually it is not. Many would answer that obesity means an excess of adiposity, measured for instance by percent body fat (BF%), whereas others would say that most of what we currently know

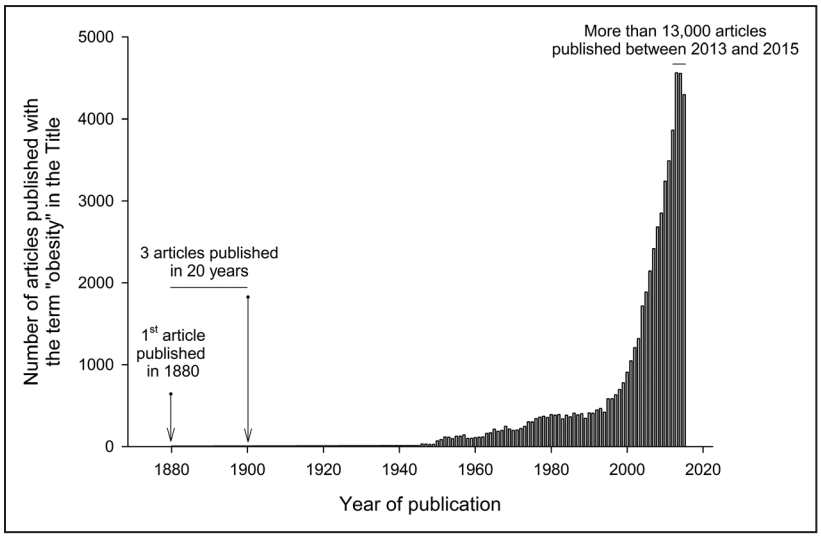

Figure 1. Number of publication focused on obesity (ie, term obesity included in the title) over the past decades.

about the adverse effects of obesity on health is actually based on BMI-defined obesity, and, therefore, obesity could as well mean an excess of body weight, which is what BMI directly measures.

The meta-analysis conducted by Flegal et al[5] concluded that compared with normal-weight, overweight and mild obesity (class I, BMI=30–34.9) was associated with lower CVD mortality. These findings have been extremely controversial, and some have blamed that BMI as an inaccurate measure of total adiposity to be responsible for these unexpected results. We agree that BMI includes an estimation error when assessing adiposity because by definition BMI is a height-normalized sum of fat mass (FM) plus fat-free mass (FFM; ie, total body weight divided by squared height [m]). Based on this and on the assumption that it is the excess of adiposity that predicts mortality, it would be expected that an accurate measure of adiposity, such as BF%, would be a stronger predictor of death than BMI. However, studies directly comparing BMI and BF% (ie, categorizing both of them in an identical way so that results are comparable) are scarce. The reason for the limited information is that few cohort studies focused on CVD mortality have included an accurate assessment of BF% in their baseline examination because these methods are more complex, expensive, and time consuming than to measure weight and height and to calculate BMI.

It is well known that high levels of FM worsen most of CVD risk factors, such as plasma lipids, blood pressure, glucose/insulin resistance, and inflammation. However, it is less known by the general population than high levels of FFM might also have some detrimental effects on CV health. Obese individuals (as defined by a BMI>30 kg/m^2) do have high levels of not only FM but also FFM, as an adaptation of carrying an extraload, ie, high body weight, in daily activities.[6–8] It has been previously reported that higher FFM largely explains the higher circulating blood volume that has been observed in obese individuals. This increases the left ventricular (LV) stroke volume, which in turns increases the cardiac output. These changes place an extra heavy burden on the heart, resulting in ventricular (both left and right) alterations that ultimately lead to ventricular (both left and right) hypertrophy and enlargement, predisposing to heart failure (HF). More detailed information the pathophysiology and hemodynamics of CVD is provided elsewhere.[9–11] This notion is supported by recent studies that have observed a positive association between FFM/lean mass and CVD risk factors in young people.[12–15] Bigaard et al[16] observed a reversed J-shape association between FFM index (FFM in kg divided by squared height [m]) and all-cause mortality, using bioelectrical impedance to assess body composition and additionally adjusting by FM index (FM in kg divided by squared height [m]) what could have attenuated the association because it is known that obese people have both high FM and high FFM. Recently, Moreno et al[17] have demonstrated that lean mass, rather than FM, is an independent determinant of carotid intima media thickness in obese subjects. Pooling all these evidence together, the accumulated physiological consequences of high FFM and high FM for CVD can explain why BMI, which includes both FFM and FM (in fact, BMI is mathematically the sum of FM index+FFM index), has consistently shown to be a strong predictor of CVD. Supporting this hypothesis, we have recently observed that the simple and inexpensive measure of BMI was a stronger predictor of CVD mortality than total adiposity measures assessed by the gold standard methods, and also, that high FFM index is a strong predictor of CVD mortality.[18] Perhaps BMI is not so bad metric as has been blamed by many for years. This notion is also in line with thoughts from Dr Wells, a well-known expert on body composition analysis, who recently pointed out that "BMI is not a good index of adiposity, but might be a good index of cardio-metabolic risk."[19] Despite many criticisms, BMI is still the most used anthropometric index in the literature and persists as a strong predictor of CVD mortality,[20,21] with recent findings discussed above providing further support to the use of BMI and novel physiological explanations about its link with CVD.[18]

Duration of Obesity and CVD

Most of epidemiological evidence supporting a link between obesity and CVD incidence and CVD mortality are based on one time point assessment. However, the prognosis of a patient who just became obese might be different from another who has been obese for the past 20 years, as an example. In 1985, Nakajima et al[22] studied 2 groups of obese people with the same degree of obesity and cellularity (number and size) of adipose tissue, but with different duration of obesity, ie, <15 and ≥15 years. The authors studied their cardiac performance using several noninvasive methods (ie, echocardiography, carotid arterial pulse tracing, and phonocardiography) and found significant differences in different cardiac performance markers, concluding that alterations of cardiac performance in obese patients with LV enlargement and wall thickening is attributed not only to the excess of body weight but also to the duration of obesity. Several investigations have addressed this hypothesis over the past decades. A major contribution to this topic was made by the study conducted by Abdullah et al,[23] in which 5036 participants of the Framingham Cohort Study were followed up every 2 years for ≤48 years. The authors concluded that the risk of all-cause mortality increased as the number of years lived with obesity increased, independent of a set of potential confounders and even independent of current BMI. This association was particularly strong for CVD mortality and with a clear dose–response pattern. For every 2 years additionally lived with obesity, the risk of CVD mortality significantly increased 7%. Reis et al[24] (data from the Coronary Artery Risk Development in Young Adults [CARDIA] study) confirmed these findings using coronary artery calcification as a subclinical predictor of coronary heart disease (CHD) and extended the conclusions to abdominal obesity. The authors concluded that longer duration of overall and abdominal obesity was associated with subclinical CHD and its progression through midlife independent of the degree of adiposity. In this line, the same authors have recently reported, also using data from the CARDIA study, that excess BMI and waist circumference (WC) years are better predictors of the risk of CVD than BMI or WC only,[25] results in line with other recent studies.[26] On the contrary, others found evidence supporting that current BMI is a stronger predictor than duration of obesity.[27,28] Regardless of which metric is a stronger predictor of CVD, collectively, these findings suggest that delaying the onset of obesity can contribute to lower the risk of developing future CVD. Public health policies aiming to prevent obesity

should start as early in age as possible, being of special concern the increase in the prevalence of pediatric obesity over the past 3 decades that has been discussed above.[4]

Fat-but-Fit Paradigm and CVD

Physical activity (PA) and physical fitness, particularly cardiorespiratory (or aerobic) fitness, are closely related to obesity, and any comprehensive study focused on obesity should take them into account. More than 60 years ago, Dr Morris and coworkers published a work that is considered by many as the beginning of the PA epidemiology field.[29] In 1953, Dr Morris studied a large number of men (n=31 000) working at the London Transport Service to compare the risk of incident CVD and early death between the bus drivers (who spent many hours sitting) and the ticket controllers (who spent many hours walking up and down in the double-floor busses, the so-called red busses).[30] The results from this study clearly showed for the first time that being more active was related to a marked reduction in the risk of incident CVD and early mortality. Some years later, Paffenbarger[31,32] published another landmark report showing shorter longevity in sedentary Harvard alumni when compared with their more active counterparts. Moreover, Paffenbarger et al[33] showed for first time that individuals who increased their level of PA (ie, >1500 kcal/wk) had a 28% lower risk of mortality than their peers who remained less active. Currently, there is strong evidence supporting that being physically active is related to lower risk of CVD and longer life expectancy.[34–36] This evidence applies not only to healthy individuals but also to patients with CVD, in whom exercise, particularly aerobic exercise, has shown to have multiple health benefits.[37]

Closely related with PA, obesity and health is cardiorespiratory fitness as assessed by maximal (or submaximal) exercise tests (typically on a treadmill or cycle-ergometer) and usually expressed in terms of maximal oxygen consumption (mL/kg per minute). In this context, the Aerobics Center Longitudinal Study (ACLS) has been one of the major contributors to consistently demonstrate the power of cardiorespiratory fitness as a predictor of CVD morbidity and mortality. The classical study published in 1989, with its nearly 2,000 citations, is generally considered a landmark work for cardiorespiratory fitness in relation with of all-cause mortality and CVD mortality.[38] Later ACLS studies showed that moderate to high cardiorespiratory fitness was associated with a reduced risk of CVD mortality (compared with low cardiorespiratory fitness) in smokers and nonsmokers, in those with and without elevated cholesterol levels or elevated blood pressure, and in healthy and unhealthy individuals.[39] ACLS reports also demonstrated that regardless of the initial cardiorespiratory fitness level, those individuals who maintained or improved their cardiorespiratory fitness level over a 5-year follow-up period also had a marked reduction in CVD and all-cause mortality.[40] From these early studies to date, an enormous amount of additional studies have consistently confirmed that cardiorespiratory fitness is a powerful marker of CV health at any age, sex, or health/disease condition.[36,37,41–43]

Fat-but-Fit and CVD Prognosis

Given this strong and consistent evidence supporting that higher levels of cardiorespiratory fitness are associated with a lower risk of incident CVD, as well as a lower risk of CVD mortality, in this section, we discuss the extent to what a higher cardiorespiratory fitness level can attenuate the adverse effects of obesity on CV health. In this context, we will focus on the fat-but-fit paradigm, which refers to those individuals whom in spite of being obese have a relatively good cardiorespiratory fitness level. Although the name fat-but-fit was established later, the 2 key studies supporting this concept were published in 1999, ie, the study conducted by Wei et al,[44] and the one conducted by Lee et al,[45] both using data from the ACLS. These 2 studies can be considered as the foundation of the fat-but-fit concept.

Wei et al[44] followed up 25 714 men for 10 years, a period in which 439 deaths occurred because of CVD. Men were stratified into BMI groups using the internationally accepted cut-points, ie, normal-weight when BMI was between 18.5 and 24.9 kg/m^2 (underweight individuals, BMI<18.5 kg/m^2, were excluded from the analyses), overweight when BMI was between 25 and 29.9 kg/m^2, and obese when BMI was ≥30 kg/m^2. Because previous ACLS studies showed that the risk of CVD was markedly higher in the first quintile (least fit) of cardiorespiratory fitness than in the second, third, fourth, and fifth quintiles,[38] individuals were categorized into 2 cardiorespiratory fitness groups: unfit when belonging to the first age-specific quintile from the original publication[40] and relatively fit when belonging to the second to fifth age-specific quintiles from the original publication.[40] The main findings from this study are illustrated in Figure 2A. Men who were obese but fit had a higher risk of CVD mortality than normal-weight and fit men although this risk difference was of borderline significance. On the contrary, this risk was 50% lower than that observed in normal-weight and unfit men and was also dramatically lower than the risk observed in obese and unfit men. These data support 2 relevant public health messages: (1) within obese men, being at least relatively fit (ie, not falling in the bottom quintile of age-adjusted cardiorespiratory fitness level) reduced >3× the risk of CVD mortality, suggesting that improving cardiorespiratory fitness even without reduction in weight might have important long-term benefits; and (2) an obese man who is fit might have a lower risk of CVD mortality than a normal-weight but unfit man, suggesting that being thin per se might not be as safe condition as many would expect to ensure an optimal CV health. Improving cardiorespiratory fitness through PA and physical exercise should therefore be a public health recommendation in any case.

A few months later, Lee et al[45] published additional evidence supporting the fat-but-fit paradigm, but using accurate methods for assessing body composition, ie, skinfold thicknesses or hydrostatic weighing, instead of BMI. Lee et al[45] followed up 21 925 men over an average period of 8 years and divided male participants into 3 groups according to their BF% (Figure 2B). In addition, they aimed to test whether the fat-but-fit concept persisted when considering abdominal adiposity instead of overall adiposity or body weight. For this purpose, men were categorized into 3 groups according to their WC (Figure 2C). Finally, cardiorespiratory fitness

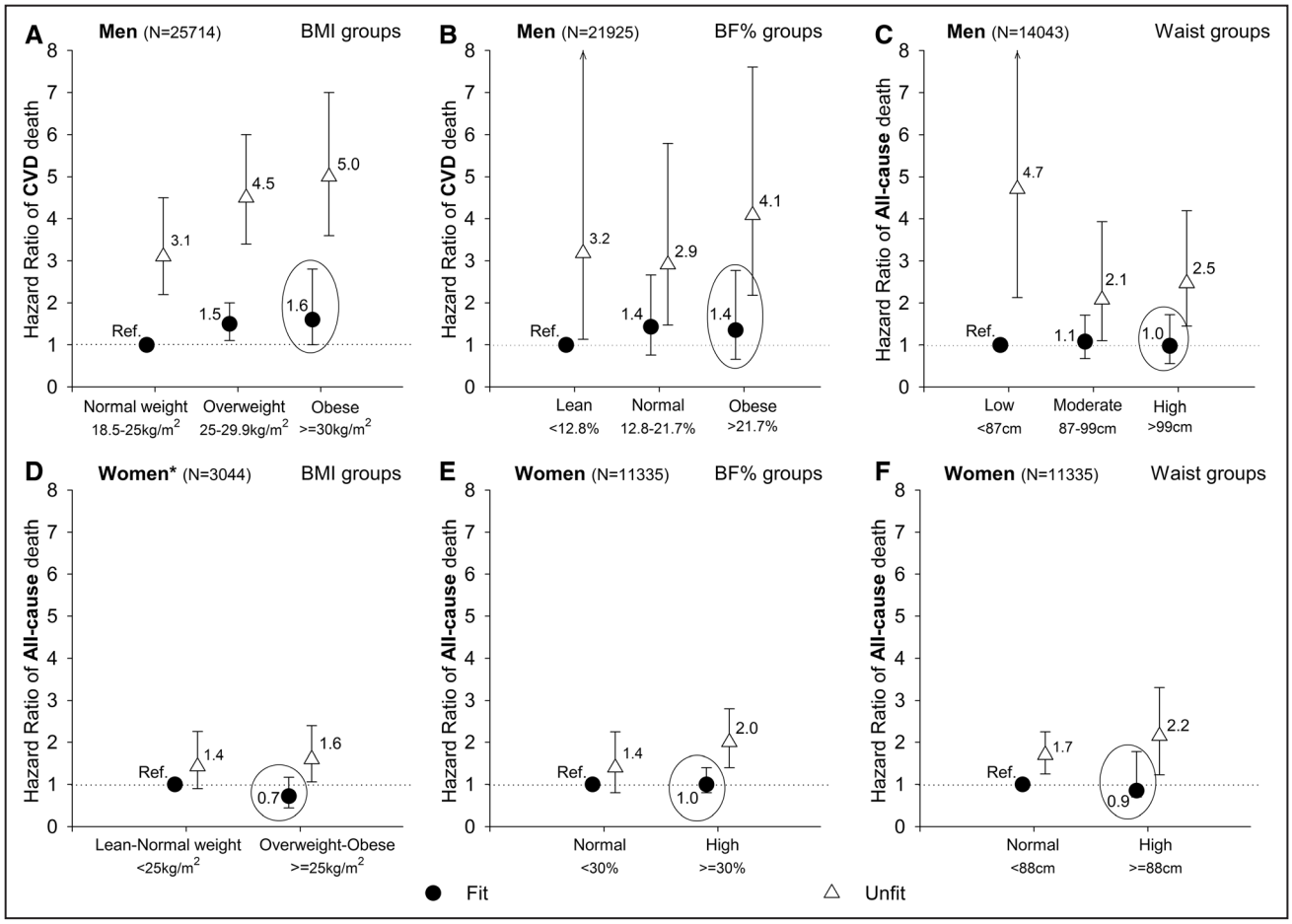

Figure 2. Graphical illustration about the fat-but-fit paradigm, based on data from the pioneer studies on this topic. *Women with impaired fasting insulin or undiagnosed type 2 diabetes mellitus (**D**), the rest of women (**E** and **F**) were apparently healthy women. Classification into cardiorespiratory fitness groups for both men and women was done using the sex- and age-specific quintiles from the Aerobics Center Longitudinal Study[38,40] and categorized as follows: unfit when belonging to the first quintile and fit when belonging to the second to fifth quintiles. The group circled highlights the fat-but-fit group. The figure show how this group is not at a significantly higher risk of cardiovascular disease (CVD) or all-cause death than the reference group (ie, normal-weight/low-fat and fit) with any of the adiposity measures used, neither in men nor in women. BF% indicates percent body fat; and BMI, percent body fat. This figure has been crafted by the authors of this review retrieving data from tables and figures from the following 4 articles: **A**, Adapted from Wei et al[44]; (**B** and **C**) adapted from Lee at al[45]; (**D**) adapted from Lyerly et al[49]; and (**E** and **F**) adapted from Farrell et al[47] with permission of the publishers. Copyrights ©1999, American Medical Association; ©1999, American Society for Nutrition; ©2009, Elsevier; ©2010, Lippincott Williams & Wilkins, respectively.

groups were defined using the same categorization than explained above: unfit if belonging to the first quintile, fit otherwise.[38,40] Overall, the results when using BF% groups are nearly identical to those from Wei et al[44] using BMI groups. Obese men (based on BF%) who were fit had a markedly lower risk of CVD mortality than those who were obese and unfit and even lower than those who were normal-weight and unfit, all compared with the lean and fit referent group (Figure 2B). Likewise, men with a high WC but fit had a markedly lower risk of mortality than those with a high WC and unfit and also than those with a low WC and unfit (Figure 2C). This study, using valid and accurate measures of body composition (including a gold standard method, hydrostatic weighing), strongly supports that cardiorespiratory fitness might counteract the adverse effects of an excess of total and abdominal adiposity on the CV system in men.

It was not until 10 years later that Lyerly et al[46] and Farrell et al[47] tested a similar hypothesis in women. Lyerly et al[46] studied 3044 women with impaired fasting insulin or diagnosed type 2 diabetes mellitus, and Farrell et al[47] studied 11 335 apparently healthy women. Because these sample sizes were smaller than the ones used in the studies in men mentioned above, the main outcome used for these analyses was all-cause mortality instead of CVD mortality. Lyerly et al[46] studied the fat-but-fit paradigm using BMI groups, whereas Farrell et al[47] additionally focused on BF% and WC groups. Unfit and fit groups were defined using the same procedures as for men, the first age-specific quintile for defining unfit women, and the remaining second to fifth quintiles for defining fit women, based on the reference cardiorespiratory fitness data from women participating in the Aerobics/Cooper Center Longitudinal Study.[47,48] The main findings of these 2 studies conducted in women are summarized in Figure 2D, 2E, and 2F, for BMI, BF%, and WC groups, respectively. The pattern of the association was exactly the same in women as in men. Fat-but-fit women had a markedly lower risk of mortality than

fat and unfit women and also lower mortality than normal-fat but unfit women, independently of the adiposity marker used, ie, BMI (D), BF% (E), or WC (F).

The fat-but-fit paradigm has also been tested in individuals with pathological conditions related to CVD, such as type 2 diabetes mellitus or hypertension. As an example, the study mentioned above by Lyerly et al[49] was conducted in women with impaired fasting insulin or diagnosed type 2 diabetes mellitus and clearly supported the fat-but-fit concept. Similar evidence has also been provided for men with type 2 diabetes mellitus or hypertension, as shown in the studies by Church et al[50] and McAuley et al,[51] respectively. Recently, Kim et al[52] used a gold standard measure of visceral adipose tissue and concluded that viscerally lean but unfit individuals had a higher risk of having metabolic syndrome (MetS) than more viscerally obese but fit subjects, further supporting the fat-but-fit paradigm. The fat-but-fit paradigm has also been studied in older adults (≥60-year olds).[48] Sui et al[48] observed that being obese but fit (men and women analyzed together) was associated with a markedly lower risk of mortality than being obese and unfit, and also than being normal-weight and unfit, supporting that the fat-but-fit paradigm occurs also in later stages in life.

The physiological explanation for the fat-but-fit paradigm is that fitter people have lower levels of most of CVD risk factors, and this remains true within the obese individuals, so that fitness is able to counteract the adverse effects of obesity on CVD risk factors reducing therefore the risk of CVD mortality.[36,53] As an example of this, for the present review, we have conducted an analysis in the obese sample of the ACLS and tested whether the risk of having CVD risk factors according to the MetS definition[54] was reduced in fit individuals (using the same definition of fit/unfit used in this section). The results from these analyses are shown in Table 1 and consistently support that obese but fit individuals have a markedly reduced risk (ranging between 25% and 46% lower) of having CVD risk factors and a reduced risk of having MetS compared with obese unfit individuals, contributing to explain the fat-but-fit paradigm in relation with CVD mortality.

Table 1. Associations Between High Levels of Cardiorespiratory Fitness (ie, Fit vs Unfit) and Risk of Having Cardiovascular Disease Risk Factors as Defined by the Standard Definition of Metabolic Syndrome[54] in a Sample of Obese Individuals (n=5959) From the Aerobic Center Longitudinal Study (ACLS)

Meeting Metabolic Syndrome Criteria	OR*	95% Confidence Intervals	
		Lower	Upper
High glucose	0.66	0.59	0.74
High blood pressure	0.75	0.67	0.84
High triglycerides	0.65	0.58	0.72
Low HDL	0.71	0.64	0.79
Metabolic syndrome	0.54	0.48	0.61

Classification into cardiorespiratory fitness groups for both men and women was done using the sex- and age-specific quintiles from the Aerobics Center Longitudinal Study (ACLS)[38,40] and categorized as follows: unfit when belonging to the first quintile and fit when belonging to the second to fifth quintiles. HDL indicates high-density lipoprotein; and OR indicates odds ratio.

*All models are adjusted for age, sex, examination year, smoking, alcohol consumption and family history of cardiovascular disease. Unfit was set as reference group, so that ORs are interpreted as how is the risk of having high glucose levels, for example, in fit individuals compared with unfit individuals. ORs <1 indicate high fitness is beneficial.

The ACLS has been the major project providing evidence for the fat-but-fit paradigm in relation with CVD mortality. Nevertheless, results from other studies seem to be in line with those from the ACLS. As an example, the fat-but-fit concept was also tested in men (n=2860) and women (n=2506) from the Lipid Research Clinics Study and obtained the following conclusion: although obese and unfit men and women had a significantly higher risk of CVD mortality (hazard ratios, 1.7 and 2.0 in men and women, respectively, $P<0.05$) than their normal-weight and fit counterparts, obese but fit men and women did not (hazard ratio, 1.4 in men and women; $P\geq0.05$).[55] Another report also derived from the Lipid Research Clinics Study separately studied a sample of Russian and US men and obtained identical conclusions: while obese and unfit men had a significantly increased risk of CVD mortality ($P<0.05$), obese but fit did not ($P\geq0.05$).[56]

We found 1 study in which the results did not support the fat-but-fit paradigm.[57] This study is based on the National Health and Nutrition Examination Survey (NHANES) data and examined the combined effect of obesity and cardiorespiratory fitness level on CVD risk factors, particularly dyslipidemia, insulin resistance, and elevated C-reactive protein.[57] However, these results should be interpreted cautiously because of several reasons: (1) they are based on cross-sectional data, instead of longitudinal prediction models as the studies discussed above; (2) the study outcomes were CVD risk factors (cholesterol, glucose, etc.), whereas the studies mentioned above mostly used CVD mortality.

Interestingly, the fat-but-fit hypothesis also seems to be valid when evaluating changes in cardiorespiratory fitness and fatness in relation with CVD. It has been shown that maintaining or improving cardiorespiratory fitness over time counteracts some of the adverse effects of fat gain, such as eliminating the significant link between fat gain and hypertension or hypercholesterolemia, and reducing by half the risk of developing MetS.[58] Likewise, it has been shown that individuals (men) who gain fat are at a significantly higher risk of CVD mortality only if they also lose cardiorespiratory fitness, but not if their cardiorespiratory fitness level was maintained or improved.[59] These studies further support the fat-but-fit paradigm on a longitudinal (changes in fitness/fatness levels) basis.

Cardiorespiratory fitness is mainly determined by PA habits, but genetics also influences cardiorespiratory fitness. Another important lifestyle factor related with CVD health is nutrition. Data from the ACLS support that an unhealthy dietary pattern is a modest risk factor for all-cause mortality; however, this association was largely confounded by cardiorespiratory fitness.[60] Literature about fatness and cardiorespiratory fitness in relation to mortality has mostly included poor data on dietary patterns, because of the methodological difficulties to accurately assess nutrition, particularly in cohorts studies designed many years ago. Consequently, it cannot be discounted to have a stronger role in these

relationships. Future studies with improved methods to assess dietary patterns will increase our understanding about nutrition and disease.

In summary, it is important to highlight that in all the studies discussed above, obese individuals who were fit did not have a significantly higher risk of CVD mortality than the theoretically healthy group, normal-weight, and fit. Obesity was associated with a significantly increase in risk of CVD mortality only when combined with a low cardiorespiratory fitness level, but not when combined with a moderate to high cardiorespiratory fitness level. Of note is also that being fat-but-fit was in most of cases related to a lower risk of CVD mortality than being normal-weight and unfit, suggesting that being normal-weight per se might not be enough to preserve an optimal CV health.[61] In spite of the fact that all these evidence is based on longitudinal observational studies and causality cannot be confirmed, currently available data strongly support the hypothesis that cardiorespiratory fitness seems to largely, if not completely, reverse the negative consequences of obesity on CV health. This notion is supported by a recent meta-analysis that analyzed the results from 10 studies examining the combined effect of obesity and cardiorespiratory fitness level on all-cause mortality.[42] This meta-analysis concluded that fat-but-fit individuals had similar mortality risks than normal-weight and fit individuals. Figure 3 illustrates the findings from this meta-analysis and shows how obesity is associated with an averaged 2.5 (confidence interval, 1.9–3.1) higher risk of mortality when the obese individuals are unfit, whereas this risk was reduced to 1.2 (confidence interval, 0.9–1.5) when the obese individuals were fit.

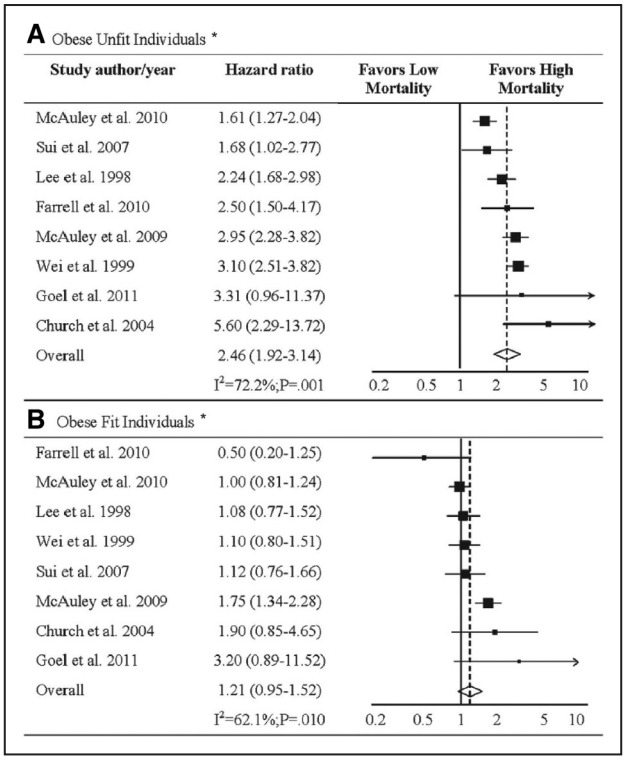

Figure 3. Meta-analysis of studies examining the fat-but-fit concept in relation with all-cause mortality. *Compared with normal-weight fit individuals. Adapted from Barry et al[42] with permission of the publisher. Copyright ©2014, Elsevier.

How Many? Prevalence of Fat-but-Fit

In the previous section, we discussed in-depth the CVD prognosis of fat-but-fit individuals, but many might wonder how many people are actually considered fat-but-fit. It is well known that heavier people usually perform worse on average in cardiorespiratory fitness tests, particularly when cardiorespiratory fitness is tested in a treadmill or any other weight-bearing activity (see the study by Wang et al[62] for cardiorespiratory fitness reference data in US adults). Consequently, it could be that few obese people achieve the cardiorespiratory fitness level required to be considered fit. This research question has been addressed by Duncan using the US nationally representative sample of 4675 adults aged 20 to 49 years from the NHANES.[63] Considering the sampling and weighing methods used in NHANES, this analytic sample size (n=4675) was equivalent to a population-based sample size of 143 million of US adults. Duncan categorized the individuals according to the sex- and age-specific cardiorespiratory fitness standards from the ACLS into low (lowest 20%), medium (medium 40%), and high (top 40%).[38,40] Duncan defined fit as having a high cardiorespiratory fitness level (top 40%); however, this is different from the definition used in all the studies discussed above,[44,45,47,49–51,55–57] in which unfit was considered when having a low cardiorespiratory fitness level (20% least fit or bottom quintile in age- and sex-based cardiorespiratory fitness) and fit when having a medium or high cardiorespiratory fitness level (80% most fit). Taking the standard definition used in the fat-but-fit literature[44,45,47,49–51,55–57] together with the figures provided by Duncan from the NHANES,[63] we can calculate that the prevalence of fat-but-fit individuals in United States would be ≈17%, which within the whole adult population would be equivalent to ≈24 million people. In our opinion, this is a sizeable number of people who, because of their higher cardiorespiratory fitness level, are at a markedly decreased risk of CVD mortality, even if they are obese. It should be emphasized, however, that the estimation of 24 million refers only to US adults aged 20 to 49 years, so the actual number of fat-but-fit individuals in United States would be considerably larger if the remaining age groups would be taken into account, ie, adults aged ≥50 years and children/adolescents. When these figures are scaled to the obese population, we can say that ≈20% of the obese adults in the United States can be considered fit, which means that approximately one fifth of adult obese would be considered fat-but-fit and would have a risk of CVD mortality similar or even lower than to normal-weight unfit individuals, regardless of the patient's sex, age, or healthy/disease condition.

MHO Phenotype and CVD

It is well known that obesity is associated with poorer health in general and with higher risk of CVD, in particular, as it is comprehensively discussed in this Compendium Review series. However, it has been identified that in a subset of individuals that in spite of being obese, they have a fully normal/healthy metabolic profile; and it has been proposed that they might have a better CVD prognosis, the so-called MHO phenotype (also uncomplicated obesity or metabolically benign

obesity).[64,65] The origins of this concept dates from 2001, when Brochu et al[66] published the first original article on this topic. Later that year, Sims[67] published a review article. After reviewing the existing evidence at that time, Dr Sims concluded that this subset of individuals must be taken into consideration in both clinical and research work, and also that future prospective research would clarify the significance and mechanisms underlying this subset. In 2004, Karelis et al[69] published another landmark work on this topic. This study used the term metabolically healthy but obese as such and also its abbreviation MHO, as well as proposed a set of markers based on MetS criteria and insulin resistance cut-points, which would allow for first time to define MHO individuals. From that study to date, Karelis et al[64,65,68–76] have published some of the most relevant studies on this topic. Opposite to MHO, individuals who are obese and have an unhealthy metabolic profile are mostly named in the literature as having a metabolically abnormal obesity (MAO).

Current Definitions of MHO and Proposal of a Harmonized Definition

After the first definition of MHO proposed by Karelis et al,[69] several definitions have been used in the literature. Overall, individuals are considered MHO if meeting 2 requirements: (1) being obese and (2) being metabolically healthy. Although the definition of obesity is rather consistent and widely accepted as BMI≥30 kg/m^2, the definition of what is a healthy/abnormal metabolic profile is much less consistent and controversial. The use of different definitions of MHO is a major problem that leads to different prevalence data, makes difficult the comparison of the existing data, and limits the potential of future meta-analyses to examine the prognosis of MHO individuals. The body of literature on the MHO topic has grown so much in the past years that there is an urgent need for a standardized definition of the MHO phenotype in adults and in youth. In the present article, we proposed a harmonized definition of the MHO based on a thorough review of the literature and opinions from leading groups on this topic. This proposal is based on a logical thinking and takes advantage of the previous consensus efforts made by major international organizations and large collaborative projects. Finally, for a definition to be useful and feasible in clinical and public health settings, it needs to be based on markers that are relatively simple, inexpensive, and quickly measured. To make this proposal, we have addressed 7 different questions that are the rationale and scientific platform for this proposal. All these information are summarized in Table 2, and the final proposal for a harmonized MHO definition is presented in Table 3. In short, our proposal for harmonization of the MHO definition is to consider an adult person as MHO if he/she has a BMI≥30 kg/m^2 and meets 0 of the MetS criteria[54] (excluding WC) shown in Table 3. In youth, MHO will be defined if (1) being obese according to the BMI cut-points proposed by Cole and Lobstein[77] and (2) if meeting 0 of the 4 MetS criteria (WC excluded) proposed by Jolliffe and Janssen[78] because they are equivalent to those proposed for adults (Table 3). In both adult and youth individuals, the opposite group to MHO would be named as non-MHO and would be defined as being obese and meeting 1 to 4 MetS criteria (WC excluded). The definition of non-MHO is as important as the one for MHO because the results from studies on MHO prognosis depend on how the referent groups are defined (Table 2, question 6).

Prevalence of MHO

The percentage of MHO in a certain population logically differs depending on the definition of MHO used. In addition, factors such as lifestyle, ethnicity, sex, or age can also influence the prevalence of MHO.[79,80] Single studies that examined the MHO topic have provided the prevalence of MHO in their sample; however, in many of the cases, samples were small and with little representativeness of the target population. Reviews on this topic have reported that the prevalence of MHO in adult population ranges between 10% and 40%, depending on the definitions used.[65]

In the United States, the largest and more representative estimates about the prevalence of MHO have been reported by Wildman et al[80] using data from the NHANES. They defined MHO as being obese plus meeting 0 or 1 of the MetS criteria, and observed that 31.7% (≈20 million) of obese adults were metabolically healthy. Although this was the definition of choice in that study, in agreement with our current proposal of harmonization of the MHO definition (Table 2), the authors additionally reported that when MHO was defined using a more strict concept of healthy, ie, meeting 0 criteria, the prevalence of MHO was reduced by half, ie, 16.6% (≈10 million).

In Europe, the greatest effort done to date to understand the current prevalence of MHO in this continent has been done by the Healthy Obese Project, under the umbrella of the BioSHaRE-EU consortium (Biobank Standardisation and Harmonisation for Research Excellence in the European Union; www.bioshare.eu).[81] This study published by van Vliet-Ostaptchouk et al[81] included participants from 10 population-based cohort studies in 7 European countries as listed below. Data from 163517 individuals were available from the following cohort studies (in some countries, 2 studies were available): Estonia, n=8930[82]; Finland, n=3685[83] and n=6,022[84]; Germany, n=2987[85]; Italy, n=117 and n=1060[86]; the Netherlands, n=63 995[87] and n=7216[88]; and Norway, n=61 199[89]; and United Kingdom, n=7306.[90] Only obese individuals (BMI≥30 kg/m^2) were selected for this analysis, leading to an analytic sample size of 28007 obese participants.[81] The authors defined MHO as meeting 0 of the MetS criteria, in accordance with our current proposal of definition (Table 3). The authors reported the prevalence of MHO separately by sex and study, providing accurate information in each case. For the purpose of this review, we have used the sex- and study-specific data reported and computed an averaged and weighted (based on sample size) estimation of the prevalence of MHO in this large and geographically diverse sample of European adults. The result of our calculation shows that ≈12.1% of obese individuals were MHO. This estimation suggests that the prevalence of MHO in Europe could be slightly smaller than in the United States. To put these figures into perspective, we used the official EU statistics about number of adults living in Europe in January 2014,[91] together with the pooled prevalence of obesity (17%) and the prevalence of MHO (12%) derived from the BioSHaRE study just mentioned, and estimated that ≈7 million of European

Table 2. Scientific Rationale Behind the Proposed Harmonized Definition of the MHO Phenotype

Question 1: Definition of obesity based on BMI, BF%, or WC?
Facts 1: It is internationally accepted by researchers, clinicians, and major organizations, such as the World Health Organization,[139] that obesity must be defined as having a BMI≥30 kg/m^2. Nearly all previous studies focused on the MHO phenotype have defined obesity using this index and cut-point. On the contrary, a few studies have referred to MHO but have actually included not only obese but also overweight individuals (ie, BMI≥25 kg/m^2).[111] This would be a different concept because overweight is not so strongly related to CVD as it is obesity. In fact, a large meta-analysis showed that overweight individuals could have even a reduced risk of CVD mortality compared with normal-weight individuals.[5,140] Although these findings have been controversial and not everybody agrees with the methods used and therefore with the conclusions obtained in that meta-analysis, we strongly recommend to keep the MHO term linked exclusively to obese individuals (not overweight), otherwise results on prevalence and prognosis of MHO would be largely affected. Similarly, Plourde and Karelis[75] recently recommend, in relation with the MHO definition, that obesity should be defined using WC cut-points (particularly those proposed by the IDF, ie, 94/80 cm for men/women, respectively) instead of BMI≥30 kg/m^2. Although we agree with the authors that abdominal obesity is a powerful predictor of metabolic disorders and CVD even within BMI categories,[141–143] this would be a new concept and new phenotype that could be termed as metabolically health but abdominally obese. However, from a clinical and public health point of view, obesity as such (based on BMI) is targeted for interventions and treatments, and it is needed to standardized a definition so that obese individuals can be classified into risk groups based on their metabolic profile (ie, MHO and MAO). Finally, obesity can also be defined using BF%. In line with this, our previous study with the ACLS data examined the MHO phenotype defining obesity based on both BMI and BF%.[105] The use of BF% instead of BMI in this context has some drawbacks: First, methods for assessing BF% are more expensive, take more time and evaluators need to be more trained. Second, there is no consensus on which is the cut-point in BF% to define obesity. Although some authors have used 25%/30% for men and women, respectively,[45,105] other have proposed age and ethnic-specific cut-points.[144] In addition, the estimated BF% values largely differ depending on the methods used, even among reference methods such as air-displacement plethysmography (eg, Bod-Pod) vs dual-energy x-ray absorptiometry.[145] Weight and height used to calculate BMI are more simple and estable measures, increasing the comparability of the data and the use of a standardized cut-point. BMI remains as a powerful predictor of CVD mortality,[146] being perhaps an even stronger predictor of CVD than BF%.[18]
Recommendation 1: From a research point of view, it is interesting to test the same hypothesis using different adiposity markers. However, from a clinical and practical point of view, we recommend to keep definitions as simple and consistent as possible, which means to define obesity based on BMI≥30 kg/m^2 when studying the MHO phenotype
Question 2: MHO definitions based on MetS criteria versus insulin resistance/sensitivity cut-points?
Facts 2: Although many definitions have been used, they can be organized into 2 groups: (1) those based on MetS criteria, and (2) those based on insulin resistance/sensitivity cut-points. Recent reviews on this topic concluded that most of previous studies focused on MHO used definitions based on MetS criteria.[104,111] In addition, the markers of insulin resistance/sensitivity normally used are more costly than the markers included in the MetS definition, which reduces the feasibility and potential usefulness of the MHO in clinical and other settings. This is also the reason why fasting glucose is used for the MetS definition, instead of more expensive measures such as fasting insulin (or indexes derived from it, eg, homeostatic model assessment or quantitative insulin sensitivity check index) or the gold standard diagnostic test, the hyperinsulinemic euglycemic glucose clamp. This test is particularly costly, labor intensive for the investigator, and largely uncomfortable for the participant/patient
Recommendation 2: To limit the definition of MHO to those criteria included in the MetS definition, which are simple, inexpensive and quick to be measured
Question 3: Which definition of MetS should be used for defining MHO?
Facts 3: Although different definitions of MetS are available, the one published by Alberti et al[54] is no doubt the most accepted by the scientific and clinical community, and it is the result of a consensus from major International Organizations: the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Many authors have used this definition but with small modifications in its cut-points, as well as adding other criteria to the definition (eg, inflammation markers).[65,100]Any small deviation from the most internationally accepted definition of MetS[54] goes against current and future comparability of the data. Likewise, Plourde and Karelis[75] suggested to use the cut-points of 120/80 mm Hg for systolic/diastolic blood pressure instead of the 130/85 suggested in the harmonized definition of MetS.[54] Plourde and Karelis[75] based this decision on the fact that prehypertension (also predicts CVD mortality.[147] We agree that pre- hypertension is a risk factor, perhaps also prehypercholesterolemia and other lower cut-points in the rest of MetS criteria, but modifications from the most consensused and accepted definition of MetS hampers future comparability of the data. Likewise, there is evidence supporting than other factors such as hepatic fat markers and low inflammation markers are also important characteristics of the MHO concept.[111] However, we think that for the MHO concept to be clinically useful must be kept simple and relatively cheap to be assessed and interpreted
Recommendation 3: To strictly stick to the latest and most accepted MetS definition proposed by major international organization, which is the one published by Alberti et al.[54] We recommend not using additional criteria, nor modifying the cut-points established for the MetS definition, to increase the comparability of existing and future data
Question 4: Should WC be included as criteria when defining MHO?
Facts 4: As indicated by its name, MHO individuals are obese and consequently most of them meet the MetS criterion of high WC. Specifically, 80 to 95% of the MHO individuals, depending on the cut-points used (102/88 vs 94/80 cm[54]), meet the criteria of a high WC.[81,105,148]
Recommendation 4: In accordance with previous MHO literature,[65,81,105,148–151] we suggest to exclude WC among the criteria to be considered for MHO
Question 5: How many MetS criteria should be met to be considered MHO?
Facts 5: Existing literature is diverse on this point. Many have considered healthy as equivalent to the absence of MetS, so that a patient would be considered MHO when meeting <2 or <3 (depending on whether WC was excluded or not from the counting of criteria) of the MetS criteria. As an example, Wildman and colleagues with the US representative data from National Health and Nutrition Examination Survey[80] and our study using the ACLS data[105] defined MHO as meeting 0 or 1 of the MetS criteria (WC excluded). However, it has been argued that a person that has hypertension or diabetes, for instance, is not healthy, and therefore the MHO concept should be restricted to those individuals who are obese, but otherwise fully healthy from a metabolic point of view.[152] This more restricted MHO concept would be then defined as meeting 0 MetS criteria. Plourde and Karelis have recently supported this concept.[75] This concept has also obtained the strong support from the largest collaborative project focused on MHO, the EU-funded Healthy Obese Project, which also defined MHO as meeting 0 MetS criteria (WC excluded).[81]

(*Continued*)

Table 2. Continued

Recommendation 5: Based on the latest evidence on this topic, we recommend defining MHO when meeting 0 MetS criteria (WC excluded).
Question 6: How to define and name those obese individuals who are not MHO?
Facts 6: We find two options to answer this question. Option 1: Obese individuals who meet the MetS definition, ie, meeting 2–4 of the criteria (WC excluded for the reasons explained in question 4). Based on this definition and using term/abbreviations already used in the literature, this group could be named as MAO[65,66,104,105,153–155] or MUHO.[75,94,101,111,117,156] This definition would be problematic from both a clinical and analytic point of view, how would be considered/treated those individuals who meet only 1 criteria and are therefore left out from the MHO group and also from the MAO/MUHO group? Option 2: To define this group as all those obese individuals who are not MHO. Based on this definition a more appropriate name would be non-MHO, which has already been used in the literature.[157–160] The definition of the opposite group to MHO is extremely important because this would largely influence the analysis/results as well as clinical practice.
Recommendations 6: Our recommendation is to define as non-MHO every obese person who does not meet the requirements to be considered MHO, ie, individuals meeting 1 to 4 of the MetS criteria (WC excluded). Future analyses would then compare the prognosis of MHO with non-MHO individuals. To avoid confusion to readers, we recommend using the terms and abbreviations proposed in the present harmonized definition (ie, MHO vs non-MHO) from now on
Question 7: How to define MHO in youth?
Facts 7: It is internationally well accepted that obesity in youth should be defined based on the sex- and age-specific cut-points proposed by Cole and Lobstein[77] and supported by the World Obesity Federation (formerly the International Obesity Task Force). These cut-points are equivalent to the adults' cut-point of BMI≥30 kg/m^2, but adapted to be specific by age and sex based on growth curves derived from a large and internationally diverse pooled data set. The definition of metabolically healthy in youth is particularly complicated because abnormalities in the metabolic profile became more apparent in adulthood and there is less consensus about how to define MetS in youth. Nevertheless and for consistency with adults, the MetS cut-points published by Jolliffe and Janssen[78] seem to be a good choice because they are equivalent to those proposed for adults by the IDF and ATP-III, and are adjusted to age and sex based on population growth curves in youth. Other definitions for MetS in youth have been proposed, but they are not sex and age specific, which can be a problem because of the marked physiological changes occurring during puberty and growth in general. Therefore, a young patient would be classified as MHO if meeting 0 of the 4 MetS criteria[78] (ie, after excluding WC), and as non-MHO if meeting 1 to 4 MetS criteria
Recommendations 7: (1) To define obesity based on BMI and using the age- and sex-specific cut-points proposed by Cole and Lobstein[77] that are internationally accepted. (2) To define MHO as meeting 0 of the 4 MetS criteria (WC excluded) proposed by Jolliffe and Janssen[78] which are sex and age specific and equivalent to those proposed in Table 2 for adults. A young patient would be considered as non-MHO if being obese and meeting 1 to 4 MetS criteria (WC excluded)

ACLS indicates Aerobics Center Longitudinal Study; BF%, percent body fat; BMI, body mass index; CVD, cardiovascular disease; IDF, International Diabetes Federation; MAO, metabolically abnormal obesity; MetS, metabolic syndrome; MHO, metabolically healthy but obese; MUHO, metabolically unhealthy obese; and WC, waist circumference.

adults at working age are MHO. We think that although the percentage of MHO reported for the United States and Europe might seem to be smaller than expected (ie, 12%–17%), when these percentages are translated into number of individuals, we can see that millions of obese individuals have a healthy metabolic profile, which supports the notion that the one-size-fits-all approach should not be used with obese individuals. These findings might have important clinical and public health implications, and future estimations of the burden associated with obesity should take this into account.

The largest population-based studies have consistently reported that the prevalence of MHO is higher in women than in men.[80,81] This higher prevalence of MHO in women is most likely just a reflex of the lower prevalence of MetS in women, which according to the latest NHANES data (2009–2010) is 22% and 24% for US women and men, respectively.[92] It has been suggested that sex differences in the MetS factors can be explained by differences in (1) glycemic indices, (2) body fat distribution, (3) adipocyte size and function, (4) hormonal regulation of body weight and adiposity, and (5) the influence of estrogen decline on risk factor clustering.[93] Likewise, there is a overall agreement that there are less MHO individuals as age increases.[79–81] In line with this, it has been reported that the MHO phenotype exists also in elderly (ie, ≥80-year olds), yet with a lower prevalence (ie, 14% meeting 0–1 MetS criteria) of MHO than in younger adults.[94] Information about the prevalence of MHO in youth is scarce, partially because of the lack of consensus on the definition of MetS in children and adolescents and consequently lack of consensus on the MHO definition (Table 3, proposal of standardized definition of MHO in youth). We anticipate that if an equivalent (to adult) definition of MHO is used, the prevalence of MHO in youth will be higher than in adults because children and adolescents are expected to be healthier and metabolic abnormalities are known to increase with age. Several large-scale studies in youth have examined the prevalence of MetS (using different definitions) in children and adolescents in the United States[95–97] and Europe[98,99]; however, the prevalence of MHO was not provided nor could be calculated from the data reported.

Characteristics of MHO Individuals

The first study directly addressing the question of which are the characteristics of the MHO individuals is the one by Brochu et al[66] published in 2001. In this study, the authors observed that despite having no difference in total adiposity or in abdominal subcutaneous adiposity, MHO individuals had significantly lower amounts of visceral adipose tissue. The authors concluded that this might be one of the key characteristics of the MHO phenotype,[66] a notion that remains valid nowadays. From this study to date, many investigations have focused on the MHO phenotype and its key features. In 2011, Primeau et al[65] reviewed the literature available on this topic and concluded that preliminary evidence suggested that differences in visceral fat accumulation, birth weight, adipose cell size, and gene expression-encoding markers of adipose cell differentiation may favor the development of the MHO phenotype. In 2014, Blüher and Schwarz[100] reviewed and updated the characterization of the MHO individuals and concluded

Table 3. Proposal of a Harmonized Definition of MHO in Adults and Youth

Adults	
Definition of MHO	
Based on the facts and recommendations discussed in Table 2, a patient would be classified as MHO if (1) being obese (BMI≥30 kg/m²); plus (2) meeting 0 of the 4 MetS criteria (WC excluded), which are the following[54]:	
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 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 Non-MHO	
A patient would be classified as non-MHO if (1) being obese (BMI≥30 kg/m²); plus (2) meeting 1–4 of the MetS criteria indicated above (WC excluded)	
Youth	
Definition of MHO	
A young patient would be classified as MHO if (1) being obese (based on international BMI cut-points for youth[77]); plus (2) meeting 0 of the 4 MetS criteria (WC excluded) proposed by Jolliffe and Janssen,[78] which are equivalent to adults' criteria indicated above	
Definition of Non-MHO	
A patient would be classified as non-MHO if (1) being obese (based on international BMI cut-points for youth[77]); plus (2) meeting 1–4 of the criteria indicated above (WC excluded)	

BMI indicates body mass index; HDL-C, high-density lipoprotein-cholesterol; MetS, metabolic syndrome; MHO, metabolically healthy but obese; and WC, waist circumference.

*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 ω-3 fatty acids presumes high triglycerides.

†Most patients with type 2 diabetes mellitus will have the MetS by the proposed criteria.

that the most important factors and conditions that contribute to have a MHO phenotype are low inflammatory markers, preserved insulin sensitivity and lower amount of visceral adipose tissue. In addition, Blüher and Schwarz[100] additionally included novel characteristics that have recently shown to be present in MHO when compared with MAO individuals, such as higher hepatic and muscle fat contents, higher adiponectin and lower intima media thickness, and higher levels of PA and cardiorespiratory fitness (Figure 4);[100] in agreement with other studies.[101–103] Our group has recently reviewed the role of cardiorespiratory fitness in the MHO phenotype and concluded that the existing literature on this topic consistently support that MHO individuals have a higher cardiorespiratory fitness level than the rest of obese individuals (Figure 5).[104] The largest study supporting this notion was the one from the ACLS (n=43 265 men and women, 5649 of them obese), in which cardiorespiratory fitness was significantly higher in MHO than in MAO, when obesity was defined based on either BMI or BF%.[105]

Nutrition might also play an important role in the MHO phenotype. The body defends from excessive caloric intake by increasing the storage of the white adipose tissue, resulting in obesity. However, when the increase in body weight stabilizes, the excessive caloric intake persists and the oxidative capacity of fat and lean mass cannot buffer the excess in caloric intake, ectopic fat will accumulate in muscle, liver, and other tissues,[106] which is well known to be a major determinant for MetS, and therefore for the MHO phenotype.[100] Strong support for the role of energy intake on the metabolic profile comes from bariatric surgery studies,[106] which have shown marked reductions in metabolic abnormalities (ie, people eat less after surgery) even in the presence of residual obesity.[107,108]

MHO and CVD Prognosis

After discussing in depth the origins, definition, prevalence, and characteristics of the MHO phenotype, the most relevant question from a clinical and public health point of view, is how is the CVD prognosis of MHO individuals compared with the rest of obese individuals and with their metabolically healthy normal-weight (MHNW) counterparts? In other words, is there really a benign obesity, or on the contrary, an excess of adiposity is per se associated with an increased risk of CVD regardless of the metabolic profile?

Studies have provided mixed results about these questions, and there is to date no consistent and solid answer to it. It is well known that conclusions from observational studies (either cross-sectional or longitudinal studies) might change completely depending on whether the analyses are adjusted or not for key confounders. As discussed in the section immediately above, there is strong and consistent evidence supporting that cardiorespiratory fitness is a powerful predictor of CVD mortality, and consequently it should be accounted for in any study focused in CVD mortality whenever cardiorespiratory fitness data are available.[36] To the best of our knowledge, only 2 studies, both from the ACLS, have adjusted the analyses for cardiorespiratory fitness when examining the CVD prognosis of MHO individuals.[105,109] Interestingly, the conclusion was different when cardiorespiratory fitness was not included versus included the model. When it was not included, the results suggested that obesity per se (either MHO or MAO) was associated with higher risk of CVD morbidity (nonfatal) and mortality compared with MHNW individuals. However, the conclusion was modified when cardiorespiratory fitness was entered into the model, resulting in no difference in the prognosis between MHO and MHNW individuals. This result persisted when obesity was defined based on BMI (standard definition) or on BF% assessed by accurate methods including hydrostatic weighing.[105] These findings have been acknowledged by recent reviews, which have now (not before[65]) considered a higher cardiorespiratory fitness level as a trait of MHO individuals.[53,61,100,101] On the contrary, the meta-analysis published by Kramer et al[110] did not mention in the whole article that cardiorespiratory fitness can be a key

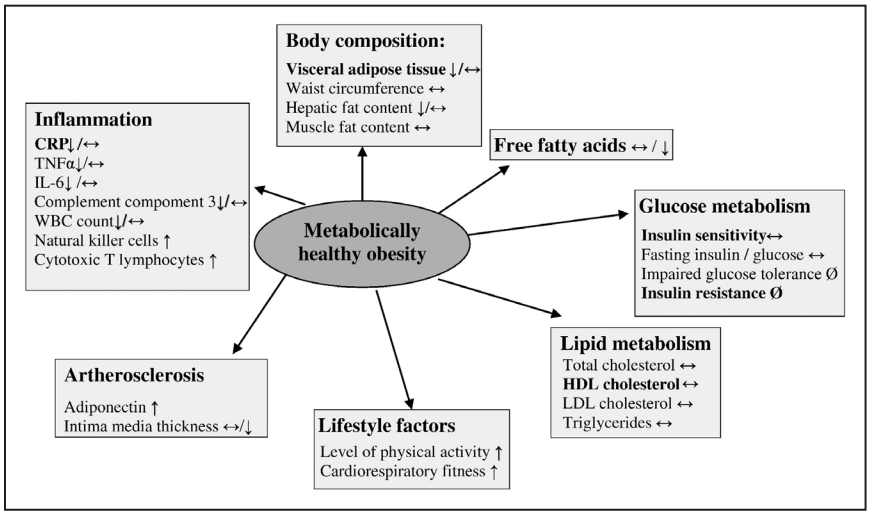

Figure 4. Factors and conditions that have been suggested to determine the metabolically healthy obese (MHO) phenotype. CRP indicates C-reactive protein; HDL, high-density lipoprotein; IL, interleukin; LDL, low-density lipoprotein; TNF, tumor necrosis factor; and WBC: white blood cell. Reproduced from Blüher et al[100] with permission of the publisher. Copyright ©2014, Elsevier.

confounder in these analyses, as discussed just above. These authors concluded that MHO individuals had an increased risk of CVD mortality than their normal-weight counterparts. However, this conclusion should be taken with caution because none of the studies included in the analyses accounted for cardiorespiratory fitness or even PA. In addition, the rationale for including/excluding studies into this meta-analysis is questionable. As an example, the authors excluded those articles that did not include overweight individuals, so that some of the largest studies on the topic, like the one from the ACLS (total n=43 265 men and women, 5649 with obesity),[105] which focused on the risk of mortality in MHO compared with MAO and with the referent group (MHNW) were excluded. On the contrary, a more recent systematic review conducted by Roberson et al[111] examined the prognosis of MHO individuals and concluded that there are mixed findings, and it is not known whether that is because of the differences in MHO definitions, confounders included in the analyses or that the association between this phenotype and CVD mortality is just not consistent. Overall, they observed that MHO individuals did not have a significantly higher risk of incident CVD nor of CVD mortality in most of studies reviewed; ie, 66% and 71% showed null results, respectively. However, yet not significant, the MHO group pointed toward a higher risk of CVD morbidity and mortality in many of the studies reviewed. Interestingly, of the 7 studies that adjusted the analyses for either PA/exercise[112–116] or cardiorespiratory fitness,[105,109] all of them but one (ie, significant difference in incident CVD yet not in CVD mortality)[112] showed that MHO individuals were not at a significantly higher risk of incident CVD or CVD mortality than their MHNW counterparts. These findings support the notion that exercise and cardiorespiratory fitness might counteract the adverse effects of obesity on CVD.

Several authors have suggested that MHO is a transition phase to MAO.[75,117,118] This idea is supported by the fact that the prevalence of MHO is reducing with age.[79–81] On the

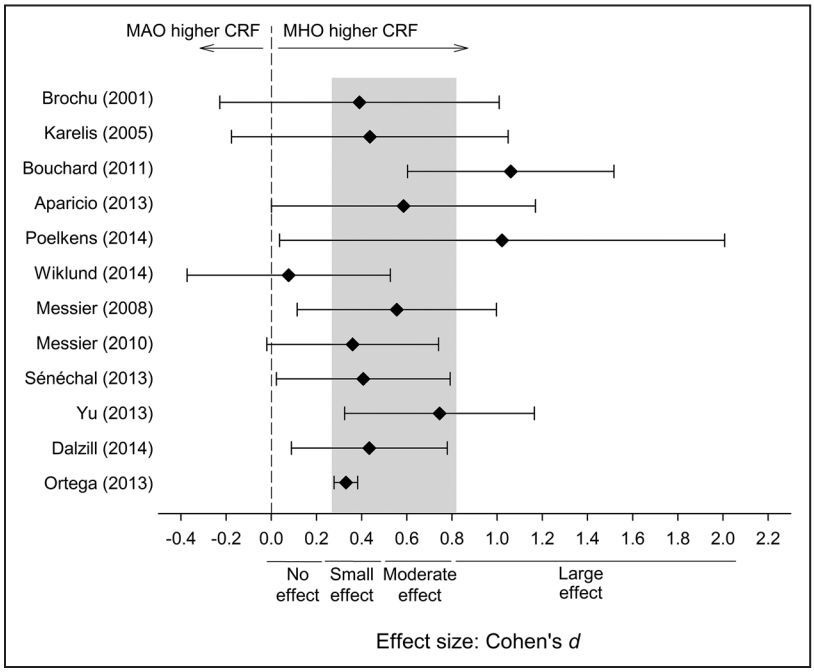

Figure 5. Standardized mean differences (effect size: Cohen) between metabolically healthy but obese and metabolically abnormal obese (MAO). Error bars represent means and 95% confidence intervals. Effect size: Cohen's *d* was computed from the data provided in each study (ie, n, mean, and SD or SEM). According to Cohen effect size, an Cohen *d* value of less than 0.25 is considered trivial, 0.25 to 0.5 small, 0.5 to 0.8 moderate, and >0.8 large.[161] Reproduced from Ortega et al[104] with permission of the publisher. Copyright ©2015, Elsevier. CRF indicates cardiorespiratory fitness.

contrary, it is known that the prevalence of MetS increases with age in everyone,[119] including normal-weight individuals, so that it could be that the transition to a worse metabolic status is not something specific of obesity, but mainly related to aging. The meta-analysis conducted by Kramer et al[110] concluded that MHO was associated with a higher risk of CVD events only when selecting studies with follow-up longer than 10 years, suggesting than in a long-term obesity increase the risk of CVD. However, none of the studies included in this meta-analysis accounted for cardiorespiratory fitness, which as shown above seems to eliminate this significant association.

In summary, the literature on the MHO phenotype and CVD is broad and mixed. Solid conclusions about the CVD prognosis in MHO versus MAO cannot be drawn at the moment. Nevertheless, it seems that when cardiorespiratory fitness or even PA (together with other classical confounders) has been accounted for, MHO individuals are not at a significantly higher risk of CVD morbidity or mortality than MHNW. The use of the harmonized definition of the MHO proposed in the present article, together with adjustment for key confounders in the analyses such as cardiorespiratory fitness or lifestyle factors (PA and caloric intake), will provide a better understanding of this phenotype.

Obesity Paradox in Patients With CVD

In spite of what has been discussed in the 2 previous sections about the fat-but-fit and the MHO concepts, it is well accepted that, in the general population, obesity has adverse effects on most of the major CVD risk factors, including worsening plasma lipids, raising levels of arterial blood pressure and plasma glucose, increasing levels of inflammation, and being associated with lower average levels of cardiorespiratory fitness.[9,10,120,121] In addition, obesity adversely affects CV structure and function, including increasing the prevalence of LV structural abnormalities, including causing concentric remodeling and LV hypertrophy, increasing left atrial enlargement, and leading to abnormalities in both systolic and, especially, LV diastolic function (Figure 6).[10] Therefore, it is not surprising that almost all CVD is increased in a setting of obesity, including CHD, HF, hypertension, and atrial fibrillation.[9,10,120] However, despite these adverse effects on CVD risk factors and increasing the prevalence of CVD, now numerous studies and meta-analyses have demonstrated a strong obesity paradox, where CVD patients with overweight and obesity (at least mild obesity) seem to have a better prognosis than do their leaner counterparts with the same CVD.[9,10,120,121]

The obesity paradox was first shown in patients with end-stage renal failure, in whom obesity was shown to be related to a more favorable prognosis.[122] In the end of the 1990s and beginning of 2000, several pioneer investigations observed similar findings in CVD patients, what leaded to the proposal of the obesity paradox term and concept.[123–127] Probably the most and earliest evidence of an obesity paradox occurred in HF.[10] Because overweight and obese develop more CHD and hypertension, 2 major risk factors for HF, not surprisingly, these patients develop HF much more commonly than do lean patients. For the past 15 years, however, many studies and meta-analyses have demonstrated that overweight and obese HF patients have a better prognosis than do leaner HF patients.[9,10,120,121] A recent meta-analysis of 6 studies (n=22 807) has shown that the highest risk of adverse events, including CVD mortality, all-cause mortality, and rehospitalizations, during a mean follow-up of 2.9 years occurred in those systolic HF patients with low BMI, whereas the lowest risk occurred in overweight patients.[128] Another recent study of 6142 patients with acutely decompensated HF from 12 prospective studies (pooled analysis) also demonstrated an obesity paradox, but this effect was mostly confined to older subjects and those with reduced systolic function, less cardiometabolic illness, and more recently diagnosed HF.[129]

Many studies have also demonstrated a strong obesity paradox among patients with CHD.[9,120,121,130] A recent meta-analysis of 89 studies in >1.3 million patients with CHD, by far the largest of such studies, by Wang et al[131] confirmed information from previous meta-analyses and provided important information about short-term versus long-term prognosis and regarding obesity severity. In their analysis, the obesity paradox was more evident during early follow-up and seemed to disappear after 5 years. In addition, patients with CHD with moderate to severe obesity (class II/III) have a higher mortality during long-term follow-up although these patients still had a better prognosis during the short-term follow-up. These data indicate a higher long-term mortality among those with CHD and BMI≥35 kg/m^2, certainly suggesting that moderate-severe obesity takes a heavy toll on the cardiovascular system long-term.[132] In this context, Flegal et al[5] did a systematic review and meta-analysis including 97 studies and 2.9 million individuals and concluded that the best survival occurred in the overweight group, and a trend for better survival was present in the class I obese patient than in those in the normal-BMI group. Therefore, avoiding more severe obesity and moving the class II/III obese patients into the overweight/class I obese category should be a long-term goal.

Considerable data discussed in this review indicate the important impact of cardiorespiratory fitness over fatness for predicting prognosis. In the obesity paradox, data in both patients with CHD and HF indicate that cardiorespiratory fitness markedly alters the relationship between adiposity and subsequent prognosis.[9] In a study of ≈10 000 patients with CHD followed for close to 15 years, McAuley et al[133] using ACLS data demonstrated that those with moderate to high levels of cardiorespiratory fitness, defined as not being in the bottom tertile of cardiorespiratory fitness for age and sex, have a good prognosis, regardless of BMI, WC, or BF%, whereas in those with low cardiorespiratory fitness, an obesity paradox was present during long-term follow up, meaning that those with low cardiorespiratory fitness and the lowest categories of body composition (BMI, WC, and BF%) have a worse CVD- and all-cause mortality than did heavier CHD patients.[134]

Likewise, Lavie et al[135] demonstrated the same impact of cardiorespiratory fitness to alter the obesity paradox in 2066 patients with systolic HF during 3-year follow-up and those with poor cardiorespiratory fitness, defined as peak Vo_2 < 14 mL/kg per minute, a strong obesity paradox was present, meaning that those with BMI≥30 kg/m^2 had the best survival, followed by overweight HF patients, and the worst survival occurred in those with normal BMI (18.5–25 kg/m^2; underweight patients, who almost have the worst survival, were

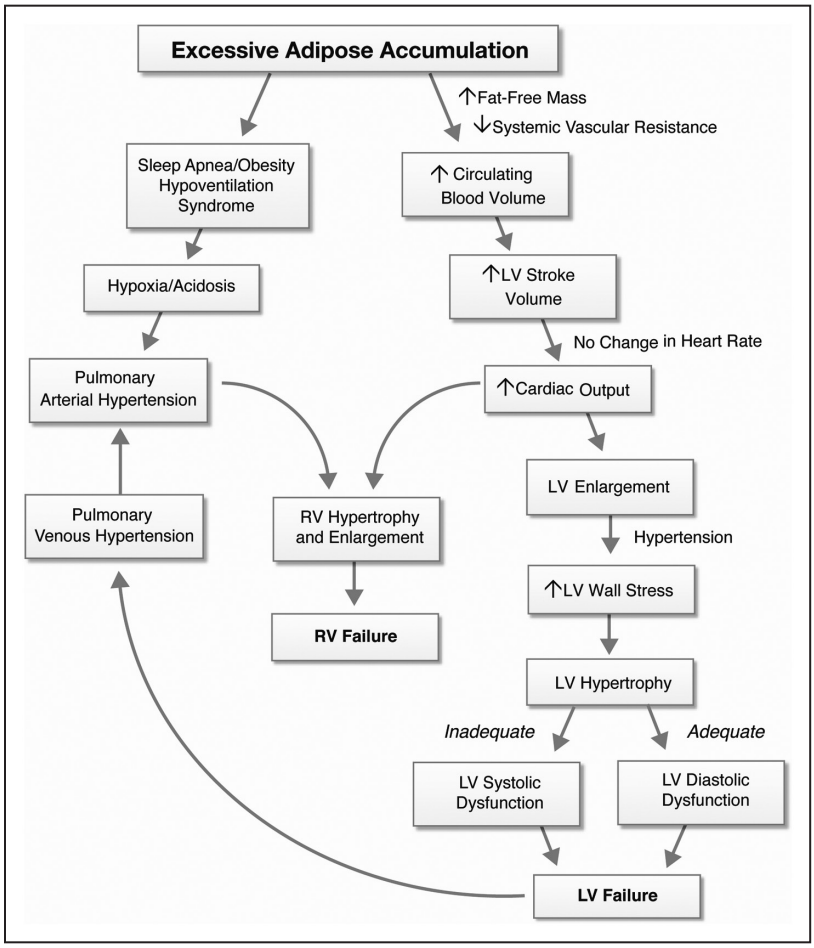

Figure 6. Pathophysiology of obesity cardiomyopathy. This diagram shows the central hemodynamic, cardiac structural abnormalities, and alterations in ventricular function that may occur in severely obese patients and predispose them to heart failure. Left ventricular (LV) hypertrophy in severe obesity may be eccentric or concentric. In uncomplicated (normotensive) severe obesity, eccentric LV hypertrophy predominates. In severely obese patients with long-standing systemic hypertension, concentric LV hypertrophy is frequently observed and may occur more commonly than eccentric LV hypertrophy. Whether and to what extent metabolic disturbances such as lipotoxicity, insulin resistance, leptin resistance and alterations of the renin–angiotensin–aldosterone system contribute to obesity cardiomyopathy in humans is uncertain. RV indicates right ventricular. Reproduced from Lavie et al[10] with permission from the publisher. Copyright ©2013, Elsevier.

excluded). On the contrary, the HF patients with relatively preserved cardiorespiratory fitness (peak $Vo_2 \geq 14$ mL/kg per minute) had a good prognosis regardless of their BMI.

Although most of the evidence on obesity paradox has been reported in HF and CHD, this obesity paradox has been noted in other CVD, including hypertension, atrial fibrillation, and peripheral arterial disease. Likewise, and obesity paradox has been noted in many other chronic diseases, including patients with end-stage renal disease, chronic obstructive pulmonary disease, rheumatoid arthritis, and patients with human immunodeficiency virus infections, as well as in general elderly populations, where leaner weight is associated with worse prognosis in general and, particularly, when combined with other chronic diseases.[9,120,121,136–138]

As previously described,[9,10,121] potential reasons for the obesity paradox are multiple: unintentional weight loss before study entry; younger age at presentation (although age is generally adjusted for in multivariable analyses); lower prevalence of smoking, greater metabolic reserve; less cachexia; lower levels of atrial natriuretic peptides, which could lead to obese presenting earlier with volume accumulation and dyspnea at less advanced stages of disease; attenuated response to hormones involved in the renin–angiotensin–aldosterone system; higher blood pressure, leading to use of more cardiac medications; different causes, including genetic factors, which may be associated with a better prognosis; increased muscle mass and muscular strength; implications regarding cardiorespiratory fitness; and unmeasured confounding factors.

Therefore, considering the obesity paradox, current efforts in patients with CVD and other chronic diseases include increasing levels of cardiorespiratory fitness, especially in overweight and mildly obese patients, where data on weight loss are extremely limited.[132,136] Although improving cardiorespiratory fitness may also be important for heavier patients, moving class II/III patients with CVD into the overweight and class I BMI ranges may also considerably improve long-term prognosis.[132,136]

Concluding Remarks

Several conclusions can be drawn from the present literature review on obesity and its relationship with CVD:

1. Prevalence of obesity has increased worldwide over the past few decades regardless of sex, age, and development status of the country. In the general population, obesity and, especially, severe obesity (BMI≥35 kg/m^2) are consistently and strongly related with higher risk of incident CVD and CVD mortality.
2. Not only does the degree of obesity influence CVD prognosis but also how long a person has been obese, supporting the notion that delaying obesity onset might have important CV health benefits and that efforts on preventing obesity should start as early as possible, ie, in young children.

3. The one-size-fits-all approach should not be used with obesity. Identification of subgroups with different CVD prognosis will improve clinical practice. In this context, it has been consistently shown that moderate to high levels of cardiorespiratory fitness attenuate, if not completely, reverse the negative consequences of obesity on cardiovascular health. This concept is known as the fat-but-fit paradigm and it is more common than would be expected among obese individuals, ie, one fifth of them.
4. Likewise, it should not be assumed that any obese person has a deteriorated metabolic profile. A relatively large proportion (ie, between ≈15% and ≈30% depending on the definition, meeting 0 or 0–1 MetS criteria, respectively) of obese individuals have a fully healthy metabolic profile, which is known as the MHO phenotype. The CVD prognosis of MHO individuals has shown to be clearly better compared with the rest of obese individuals. On the other hand, it is controversial whether MHO individuals have as good CVD prognosis as their MHNW counterparts. According to the most recent systematic review on the topic, nearly all the studies (ie, 86%) where analyses were adjusted for PA or cardiorespiratory fitness found no differences on CVD outcomes between MHO and MHNW individuals. The different MHO definitions used in the literature, however, make it complicated to draw solid conclusions on this topic. In this context, the present review provides a scientifically based proposal for a harmonized definition of MHO (Tables 2 and 3), which will hopefully contribute to more comparable data in the future and a better understanding on the MHO subgroup and its CVD prognosis.
5. Finally, there is strong and consistent evidence supporting that, in patients with CVD, overweight and mild obesity (ie, BMI <35 kg/m^2) protect against new CVD events, what has been named as the obesity paradox. Moving severely obese patients into overweight or mild obesity by means of healthy diet, PA and improved cardiorespiratory fitness would be an ideal long-term goal.

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Dr Lavie has served as a consultant and speaker on fitness/obesity for the Coca-Cola Company and has published a book on the obesity paradox with potential royalties. S.N. Blair has served as consultants for weight loss and fitness companies and for the Coca-Cola Company, which has also provided them unrestricted research grants. F.B. Ortega reports no conflicts.

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