Healthy obese versus unhealthy lean: the obesity paradox

Carl J. Lavie, Alban De Schutter and Richard V. Milani

Abstract | Overweight and obesity have reached epidemic proportions in the USA and most of the rest of the world. Particularly concerning is the very high prevalence of class III obesity (BMI ≥40 kg/m^2), which has reached ~3% in the USA. In the past few years, controversy has surrounded the idea that some individuals with obesity can be considered healthy with regards to their metabolic and cardiorespiratory fitness, which has been termed the 'obesity paradox'. These controversies are reviewed in detail here, including discussion of the very favourable prognosis in patients with obesity who have no notable metabolic abnormalities and who have preserved fitness. The article also discusses the suggestion that greater emphasis should be placed on improving fitness rather than weight loss *per se* in the primary and secondary prevention of cardiovascular diseases, at least in patients with overweight and class I obesity (BMI 30–35 kg/m^2).

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Introduction

In the USA and most of the rest of the world, overweight and obesity have increased to epidemic proportions in adults and children over the past few decades.[1] Severe obesity (class III obesity [BMI ≥40 kg/m^2]) has now reached a prevalence of ~3% in the US population,[2,3] which is particularly concerning. The exact effect of different degrees of obesity on cardiovascular and overall prognosis[4,5] and whether some classes of obesity can be considered 'healthy'[6] are areas of debate; however, this type of severe obesity is clearly associated with a poor prognosis.[2,3,7] High-profile publications in the past 2 years have suggested that obesity might contribute to nearly 20% of all deaths in the USA,[4] and that patients with overweight or obesity cannot be considered 'healthy'.[6] However, these publications have been highly criticized, which is discussed later in this article.

Total mortality is a very important end point; however, the effect of excessive weight on the development and prognosis of cardiovascular disease is of great concern. Numerous studies have focused on the adverse effects of overweight and obesity on both general and cardiovascular health, and have found that obesity worsens nearly all of the major cardiovascular risk factors. For example, obesity increases blood levels of glucose (leading to the metabolic syndrome and type 2 diabetes mellitus [T2DM]), worsens plasma lipid profiles (raised levels of triglycerides and reduced levels of HDL cholesterol as well as increased levels of LDL cholesterol) and increases arterial blood pressure, as well as increasing the incidence of abnormalities in left-ventricular geometry and left-ventricular hypertrophy and inflammation.[1,8–10] These risk factors, along with abnormalities in left-ventricular systolic and diastolic function, lead to an increased risk of almost every cardiovascular disease.[1,8]

Nevertheless, a considerable number of studies during the past 15 years have demonstrated a strong 'obesity paradox'. This paradox suggests that despite the adverse effects that obesity has on the risk factors associated with cardiovascular diseases and many other chronic diseases, patients with cardiovascular diseases and overweight or obesity often have a better prognosis than leaner patients (underweight as well as patients with a 'normal' BMI) with similar diagnoses.[1,7,8] In addition, some population-level data have suggested that overweight and class I obesity (BMI 30–35 kg/m^2) might not be associated with an increased risk of all-cause mortality.[5]

In this Review, we discuss the controversy regarding metabolically healthy obesity (MHO), as well as the debate regarding the relative importance of fatness versus fitness for overall, and particularly cardiovascular, health. We also review the obesity paradox noted in patients with cardiovascular diseases, highlighting the critical role that fitness has in explaining this puzzling paradox.

Fundamental causes of obesity

To understand the effect of fitness and fatness on subsequent health, particularly the important contribution of physical activity to fitness, it is important to at least briefly discuss the fundamental origin of the obesity epidemic. Many studies suggest that food intake, including our dietary choices and especially the increased general consumption of food, is primarily responsible for the obesity epidemic, arguing that time spent in physical

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Competing interests
C.J.L. has served as a consultant and speaker for The Coca-Cola Company (on fitness and obesity and not on their products) and has published a book on the obesity paradox with potential royalties. A.D.S. and R.V.M. declare no competing interests.

Key points

- The prevalence of obesity has increased in most of the world over the past few decades
- Patients with obesity have more cardiovascular and metabolic risk factors than people of normal weight and have an increased risk of developing cardiovascular diseases
- Data suggest that metabolically healthy obesity, especially when combined with a high level of fitness, is associated with at most a minimal increase in overall risk of cardiovascular diseases and mortality
- In patients with established cardiovascular diseases and other chronic conditions (kidney disease, severe arthritis), those with overweight and class I obesity have a better prognosis than lean patients—the 'obesity paradox'
- Fitness is more important than fatness for long-term prognosis; in the obesity paradox, fitness markedly alters the relationship between adiposity and long-term health outcomes
- Despite accumulating evidence on the obesity paradox, the available data still support purposeful weight loss for long-term health, particularly when combined with increased physical activity, muscular strength and fitness

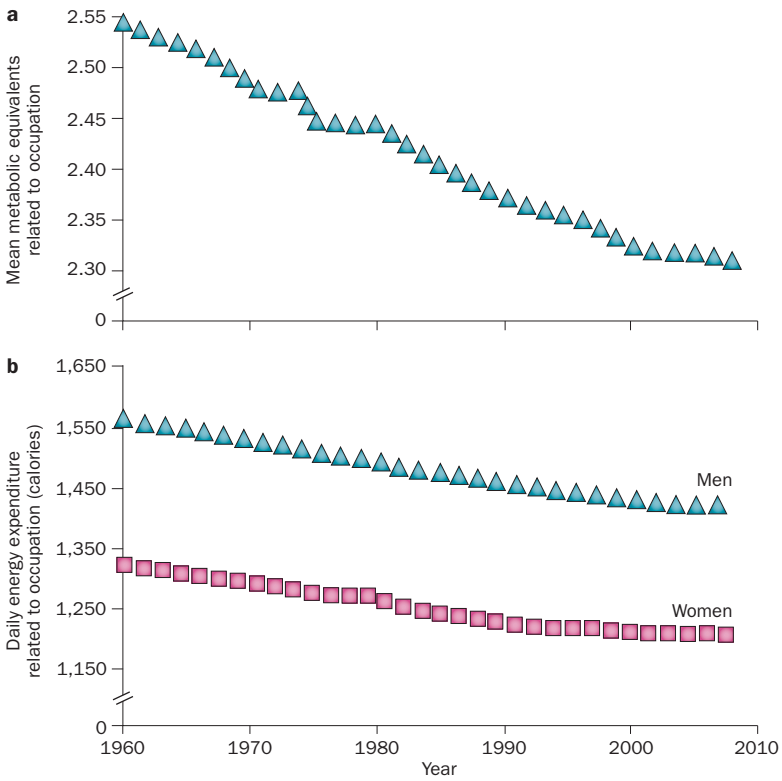

Figure 1 | Physical activity related to occupation from 1960 to 2010. **a** | Mean metabolic equivalents related to occupation since 1960. **b** | Mean daily energy expenditure related to occupation in men and women since 1960. Modified with permission from PLOS © Church, T. S. *et al. PLoS ONE* **6**, e19657 (2011),[14] which is licensed under a Creative Commons Attribution license. To view a copy of this license, visit http://creativecommons.org/licenses/by/3.0/.

activity has remained largely unchanged during the past 3–5 decades.[11–13] Although this assertion might be true for leisure time spent in physical activity, which represents a fairly small portion of total physical activity, data from the past five decades have focused on the contributions of physical activity resulting from occupation and household management, which seems to have decreased.[14–16] This shift in levels of occupational physical activity might be particularly important, as it is widely accepted that most increases in adiposity are the result of a chronic positive energy balance.

A study has demonstrated very marked declines in occupation-related physical activity during the past five decades (Figure 1),[14] which almost completely explained the increased prevalence of obesity during this time span (Figure 2). Similar declines have been demonstrated in the time women with children spend in physical activity related to household management during this same period (Figure 3),[15,16] which might not only affect weight gain in the women themselves but could also affect that of the next generation. In response to the very clear decline in levels of physical activity, similar declines in energy intake would be needed to prevent weight gain. Nevertheless, the primary cause of the weight gain and the obesity epidemic seems to be the striking decline in total time spent in physical activity. Additionally, as discussed later in the article, physical activity is the major nongenetic determinant of fitness, which suggests that the decline in physical activity over time also influences this important determinant of cardiovascular and all-cause mortality.[7]

Can obesity be healthy?

Despite the potential adverse effects of overweight and obesity on cardiovascular risk factors and the incidence and severity of cardiovascular diseases, an important aspect of this Review is discussion of whether obesity can ever be 'healthy'. Considerable controversy exists regarding this issue, as well as regarding the overall concept of MHO.[17] A very large meta-analysis of 97 studies and nearly 2.9 million people (including >270,000 deaths) questions the risk of all-cause mortality associated with overweight and class I obesity.[5] In fact, optimal survival occurred in the group who were overweight (BMI 25–30 kg/m^2). These patients had a 6% lower mortality than patients with a normal BMI (18.5–25.0 kg/m^2), which was statistically significant. As expected, more severe obesity (class II or III or BMI ≥35 kg/m^2) was associated with increased mortality, but class I obesity was associated with a trend for 5% lower mortality than in those with normal BMI. Of note, this analysis only considered all-cause mortality and did not assess the other detrimental aspects of obesity on a variety of chronic diseases or quality of life. Additionally, this analysis did not assess the contributions of MHO or the degree of metabolic healthiness in the control group, which has been criticized,[6] nor did it assess the important contribution of physical activity and fitness to survival.

As discussed above, obesity is known to have many adverse effects on metabolic components associated with an increased risk of cardiovascular disease and mortality, including impaired glucose tolerance or T2DM, plasma levels of lipids and blood pressure.[1,9] Some authors have suggested that most, if not all, of the increased risk associated with obesity could be attributable to its adverse effects on these cardiovascular risk factors, arguing that any adverse effects of obesity beyond these metabolic–cardiovascular abnormalities are negligible.[18,19] Although the exact definition of MHO varies among studies, this term generally refers to obesity without components of

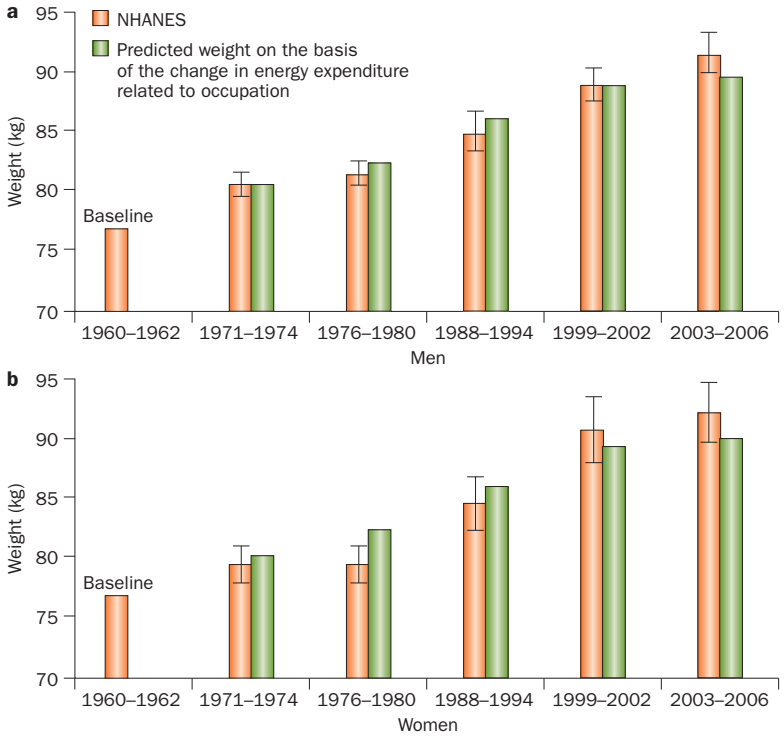

Figure 2 | Change in mean weight in the USA. An energy balance model was used to predict the mean body weight on the basis of the change in daily energy expenditure related to occupation since 1960 compared with the mean weight gain observed in different NHANES examination periods for 40–50-year-old **a** | men and **b** | women. Modified with permission from PLOS © Church, T. S. *et al. PLoS ONE* **6**, e19657 (2011),[14] which is licensed under a Creative Commons Attribution license. To view a copy of this license, visit http://creativecommons.org/licenses/by/3.0/.

the metabolic syndrome (that is, hypertension, dyslipidaemia, high fasting glucose levels and T2DM). However, considerable controversy surrounds this issue, as the results of studies on the effect of MHO on coronary heart disease (CHD) and heart failure have been conflicting.[19–23] Differentiating MHO from 'unhealthy' obesity might be important for public health and clinical management of patients with obesity.

Previous studies concerning CHD events in patients with MHO have reported conflicting results,[6,19–23] as have studies of heart failure in these patients.[19,24] However, most of these studies are limited in their sample size and length of follow-up, and have incomplete information available on key confounding variables, including central obesity, physical activity and fitness.[17,19] A large study from Norway that was published in 2014 suggests that MHO is not associated with an increased risk of acute CHD events but is associated with heart-failure events.[19] This finding is not surprising, as an excess amount of adipose tissue has several adverse effects on cardiovascular structure and function, even when MHO is present.[8,10,17]

By contrast, a high-profile meta-analysis published in 2013 suggests that obesity cannot be truly 'healthy'.[6] Kramer and colleagues[6] assessed eight studies ($n = 61,386$; 3,988 events) and evaluated the effect of metabolic status and BMI on the incidence of all-cause mortality and/or cardiovascular events. When only the studies with ≥10 years of follow-up were considered, patients with MHO had a 24% increased risk of major cardiovascular events compared with lean individuals who were also metabolically healthy. However, all of the metabolically unhealthy groups, regardless of BMI status, had a markedly increased risk of cardiovascular events (2.65–3.14-fold) compared with metabolically healthy participants. Overall, this meta-analysis found that patients with MHO had a slightly higher risk of cardiovascular events than lean individuals who were metabolically healthy; however, patients with MHO had a markedly lower risk of cardiovascular events than lean individuals who were metabolically unhealthy. This meta-analysis has been highly criticized; one of the major limitations of the analysis is the fact that this study did not adequately adjust for many potentially important baseline factors, including age and sex. In addition, information is lacking about the physical activity and fitness of the participants, which will be discussed later in this Review.

Nevertheless, another meta-analysis published in 2013 (14 studies; $n = 299,059$; 12,125 incident cases of cardiovascular disease, 2,130 deaths associated with cardiovascular disease and 7,071 cases of all-cause mortality) reported similar findings. Compared with metabolically healthy participants with a normal weight, patients with metabolically healthy overweight had a 47% increased risk of experiencing any of the events, patients with MHO had a twofold increased risk and metabolically unhealthy participants with a normal weight had an 81% increased risk.[25]

Another study has assessed the effect of fitness on MHO versus metabolically unhealthy obesity (having >1 adverse metabolic component).[20] In this study, patients with MHO had considerably higher levels of fitness than patients with obesity and adverse metabolic profiles. In patients with MHO and high fitness, the prognosis of cardiovascular diseases and cancer and the risk of mortality were 30–50% better than in those with lower fitness. Although fitness did not totally negate the adverse effects of obesity in the setting of adverse metabolic risk factors, a high level of fitness was still associated with a 10–30% reduction in subsequent risk compared with a low level of fitness. In this study, the combination of MHO and high fitness was considered a benign condition, as these participants had a better prognosis than those who did not have obesity but were unfit.

Evidence for the obesity paradox

An important aspect of this manuscript is to briefly review the controversies around the important and highly publicized concept of the 'obesity paradox'. Despite the adverse effects that overweight and obesity have that increase the incidence of cardiovascular risk factors and the prevalence of almost all cardiovascular diseases, numerous studies and meta-analyses over the past decade have clearly identified an obesity paradox. In these studies, patients with overweight and obesity who have established cardiovascular diseases have a considerably better prognosis than lean patients with the same

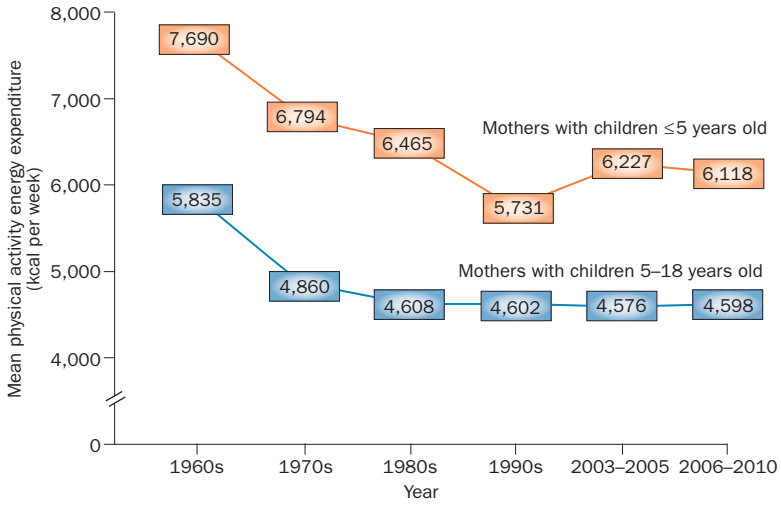

Figure 3 | Energy expenditure related to physical activity (mean kilocalories per week) in mothers in the USA, 1965–2010. For both groups of mothers, the overall decline in energy expenditure over the study period was statistically significant (P<0.001). For mothers with children <5 years old the change from the 1960s to the 1970s was significant (P<0.001), as was the change from the 1980s to the 1990s (P<0.05). For mothers with children 5–18 years old, the change from the 1960s to the 1970s was significant (P<0.001). Permission obtained from Elsevier © Archer, E. *et al. Mayo Clin. Proc.* **88**, 1368–1377 (2013).[16]

Box 1 | Potential reasons for the obesity paradox

- Unintentional weight loss
- Younger age at presentation*
- Lower prevalence of smoking*
- Greater metabolic reserve*
- Less cachexia*
- Lower levels of atrial natriuretic peptides*
- Attenuated response to hormones involved in the renin–angiotensin–aldosterone system
- Higher blood pressure, leading to use of more cardiac medications*
- Different aetiology, associated with a better prognosis
- Increased muscle mass and muscular strength*
- Implications regarding cardiorespiratory fitness
- Unmeasured confounding factors

*Patients with cardiovascular disease who are obese but metabolically healthy compared with patients with a normal weight. Permission obtained from Elsevier © Lavie, C. J. *et al. J. Am. Coll. Cardiol.* **63**, 1345–1354 (2014).[7]

cardiovascular diseases.[1,8,26,27] This obesity paradox has also been demonstrated in patients with hypertension, CHD, heart failure, atrial fibrillation and peripheral arterial disease, as well as in patients referred for exercise stress testing and/or echocardiography.[1] The obesity paradox also seems to occur in many other chronic conditions, such as chronic kidney disease, HIV, arthritis and several lung diseases.[1,28–30]

The obesity paradox has also been found in patients with heart failure or CHD when BMI and percentage body fat were used to assess obesity.[1,8,31–34] Although the data regarding the obesity paradox and waist circumference are controversial,[35–38] with some studies showing no obesity paradox with central obesity,[35,36] others have demonstrated an obesity paradox even in patients with central obesity and low fitness.[38] Interestingly, in patients with overweight or obesity and CHD, the obesity paradox has been noted despite the fact that patients with overweight and obesity have considerably worse CHD risk profiles than lean patients with CHD, including higher blood pressure and levels of glucose, increased incidence of T2DM, more dyslipidaemia and higher levels of inflammation (C-reactive protein).[32–34] Therefore, despite having a metabolically healthy profile, the lean patients with CHD still had a worse prognosis than patients with CHD and overweight or obesity.

Contribution of fitness

Potential mechanisms for the obesity paradox,[1,7,8] while not discussed in detail here, are summarized in Box 1. Of these mechanisms, we feel that fitness is particularly important in defining whether patients who are lean or have obesity are healthy or unhealthy. Major studies have demonstrated the importance of fitness for predicting the prognosis of patients with cardiovascular diseases as well as the risk of all-cause mortality.[39,40] Here, we briefly review the data on the fitness versus fatness debate, as well as whether the contribution of fitness could partly explain the obesity paradox in patients with cardiovascular diseases.

Fitness versus fatness

In trying to understand the contribution of fitness to the obesity paradox, it is first necessary to recognize the relative importance of fitness versus fatness to overall health. Clearly, excess body weight and low levels of fitness are both associated with a worse cardiovascular risk factor profile and an increased prevalence of cardiovascular diseases.[1,7,8,39,40] A major study demonstrated that for every one metabolic equivalent (which is the common way to express fitness and to judge exercise capacity on exercise stress tests) increase in level of fitness, the incidence of all-cause mortality was reduced by 13% and that of major cardiovascular events by 15%.[40] In a large study of >66,000 participants without cardiovascular disease, adding a single measure of fitness to a traditional cardiovascular risk factor model markedly improved the accuracy of both 10-year and 25-year predictions of major cardiovascular events compared with the traditional model.[41] The relative and combined importance of excess weight and levels of fitness in cardiovascular diseases remains somewhat controversial.[7] Nevertheless, many studies indicate that high levels of fitness markedly negate the adverse effects of excess fatness on prognosis, with data available for patients with hypertension, overweight or obesity, the metabolic syndrome and T2DM.[7,42–45] In many of these chronic diseases, patients who were fit had a better clinical prognosis than patients who were unfit regardless of BMI, which is an indication of the strength of fitness as a major cardiovascular risk factor.

A meta-analysis of 10 studies has quantified the joint association of fitness and weight status with mortality.[46] Unfit individuals have a twofold higher risk of mortality than fit normal-weight individuals, regardless of BMI. By contrast, individuals who are overweight or have obesity but who are fit have a risk of mortality similar to

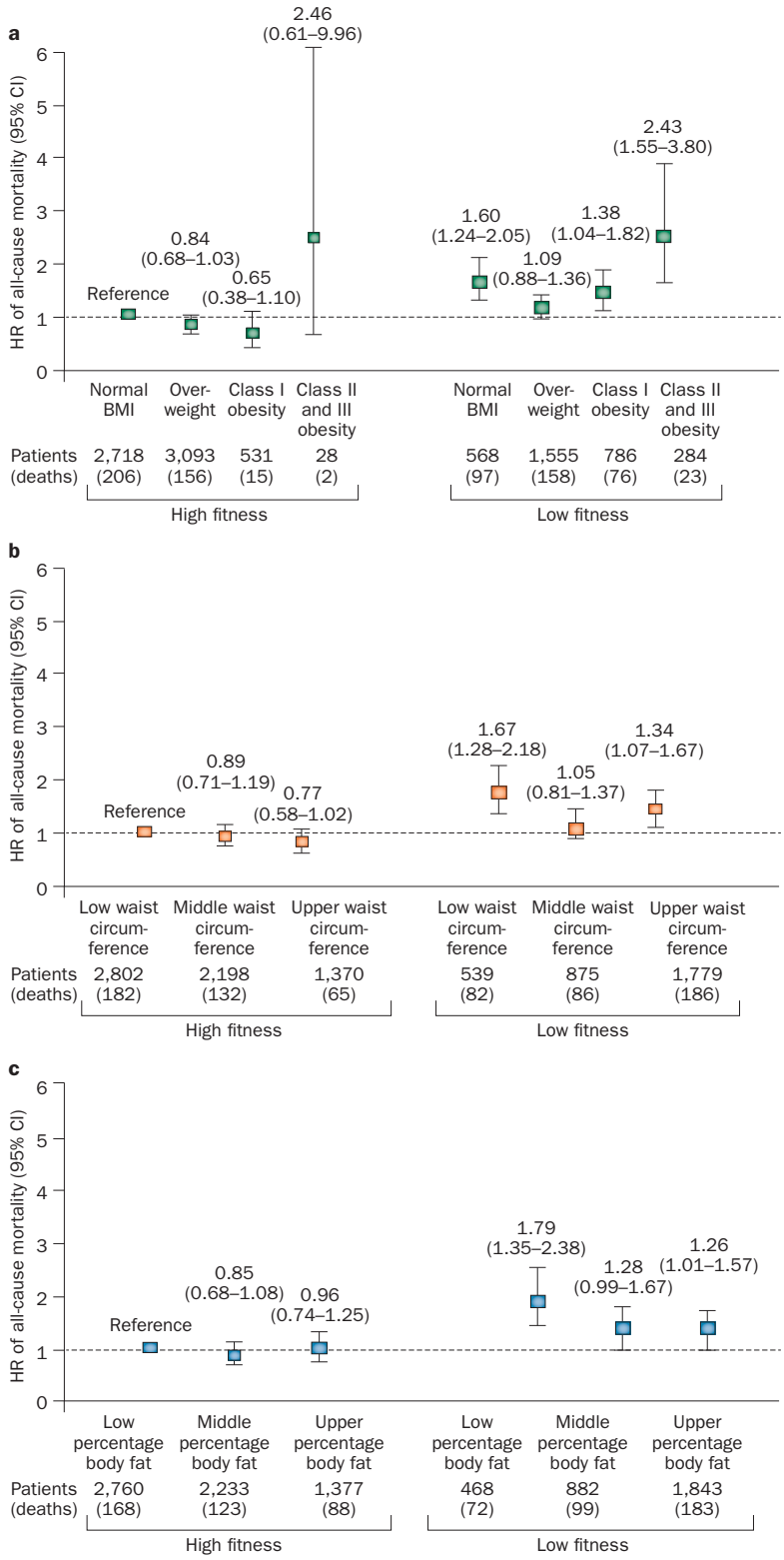

Figure 4 | The joint effects of different measures of obesity and cardiorespiratory fitness on all-cause mortality. **a** | BMI. **b** | Waist circumference. **c** | Percentage body fat. HR (boxes) and 95% CI (error bars represent values) were calculated after adjusting for age, baseline examination year, physical activity (active or inactive), smoking (current smoker or not), alcohol intake (>14 drinks per week or 0–14 drinks per week), hypercholesterolaemia, hypertension and diabetes mellitus (present or not for each), and family history of cardiovascular disease. Abbreviations: CI, confidence interval; HR, hazard ratio. Permission obtained from Elsevier © McAuley, P. A. *et al. Mayo Clin. Proc.* **87**, 443–451 (2012).[38]

that of fit normal-weight individuals. This investigation suggests that the obesity paradox might not influence fit individuals.

Over the past 5 years, studies have also assessed whether changes in fitness and fatness over time affect cardiovascular risk factors and mortality.[47,48] In a study of 3,148 healthy adults, changes in fatness (BMI and percentage body fat) and fitness predicted the development of hypertension, hypercholesterolaemia and the metabolic syndrome, but the effect of changes in fitness seemed to be a better predictor than changes in fatness.[48] In a study of 14,345 healthy men, a one metabolic equivalent increase in fitness on two maximal-fitness stress tests separated by an average of 6.3 years was associated with reductions in all-cause and cardiovascular mortality of 15% and 19%, respectively.[47] By contrast, changes in fatness were not associated with alterations in cardiovascular or all-cause mortality after adjustment for confounders and changes in fitness.[47] These data suggest that maintaining fitness is even more important than changes in weight for long-term health.

Fitness and the obesity paradox

Fitness might also be a critical component in understanding the obesity paradox. In addition to the study discussed in the previous section,[46] other studies have also addressed the contribution of fitness to the obesity paradox.[38,49–51,52] Furthermore, substantial evidence from patients with CHD and heart failure suggests that fitness has a marked effect on how adiposity influences the risk of subsequent major cardiovascular disease events.[38,49] In a study of 9,563 patients with known or suspected CHD, only those who were in the bottom one-third of age-related and sex-related fitness demonstrated a strong obesity paradox; the leanest patients (as measured by BMI, percentage body fat and waist circumference) had more cardiovascular events and mortality than the heaviest patients with CHD who were also unfit.[38] By contrast, the patients with CHD who had the highest levels of fitness had a better clinical prognosis than those with low levels of fitness, regardless of their levels of fatness, so no obesity paradox was noted (Figure 4).[38]

Similar findings were reported in a group of 2,066 patients with heart failure.[49] In this study, fitness was assessed by cardiopulmonary gas exchange fitness testing, and patients were divided into two groups using the classic cut-off point for heart failure (peak oxygen consumption [that is, VO_2 max] of 14 ml/kg per min).[49] Although a VO_2 max ≥14 ml/kg per min would not generally be considered a high level of fitness, patients with heart failure who had this level of fitness had a good prognosis regardless of their BMI status. By contrast, patients with heart failure who had low levels of fitness (VO_2 max <14 ml/kg per min) had a poor prognosis, particularly those who were lean; patients with overweight and obesity had lower mortality than lean patients, which indicates that an obesity paradox was present (Figure 5).[49] Therefore, these data support the idea that fitness has a strong effect on the relationship between adiposity and clinical prognosis in the obesity paradox. Of note,

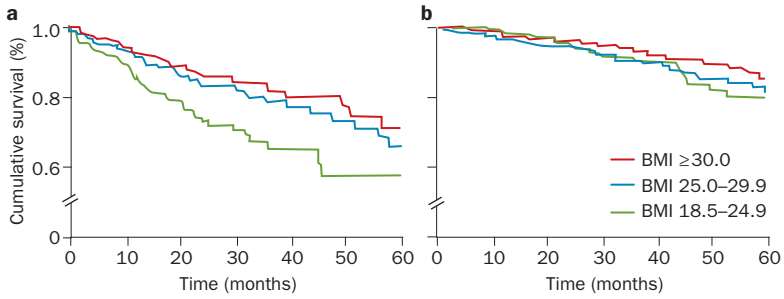

Figure 5 | Kaplan–Meier survival analyses according to BMI in a study of 2,066 patients with systolic heart failure. **a** | Low cardiorespiratory fitness group (VO_2 max <14 ml/kg per min, log rank 11.7, $P=0.003$). **b** | High cardiorespiratory fitness group (VO_2 max ≥14 ml/kg per min, log rank 1.72, $P=0.42$). Permission obtained from Elsevier © Lavie, C. J. *et al. Mayo Clin. Proc.* **88**, 251–258 (2013)[49] and from Elsevier © Lavie, C. J. *et al. Am. Heart J.* **166**, 1–3 (2013).[51]

however, this analysis included very few patients with class II obesity and none with class III obesity, so these data are applicable only to patients with heart failure who are overweight or have class I obesity.

Although we have focused on cardiorespiratory fitness in our discussion of fitness so far, it is important to emphasize that fitness also includes critical contributions of muscular fitness, or muscular stamina and strength. Muscular strength seems to influence the risk of developing cardiovascular disease and the overall prognosis of established cardiovascular disease.[53] In addition to having more fat mass, patients with MHO might also have higher quantities of nonfat mass, especially muscle mass, than lean patients.[54] In patients with CHD, those with a higher BMI had a better prognosis than patients with a normal BMI, which was particularly favourable in patients with CHD who had both high fat mass and high nonfat mass.[33,34] In fact, a low level of nonfat mass was a powerful independent predictor of subsequent mortality, increasing mortality risk by 3.1–3.9-fold, depending on exactly which factors were included in the multivariable analysis.[34]

Similarly, a high level of body fat was an independent predictor of increased muscular strength in patients with heart failure.[55] Muscle strength is an important contributor to the prognosis and survival of patients with heart failure, especially considering the adverse effects that frailty has on the prognosis of disease in these patients.[56] However, it should be noted that in the studies of CHD and heart failure,[31,33,34] body fat was assessed with the skinfold technique (the average of three skinfold measurements [thigh, chest and abdomen in men; thigh, triceps and suprailiac in women]), which measures subcutaneous fat. This type of fat could be associated with increased levels of 'good' hormones and cytokines (such as leptin and adiponectin) and enhanced insulin sensitivity, and might be cardioprotective; however, some studies suggest increased levels of visceral fat raise the risk of developing cardiovascular disease.[9] Therefore, the increased amounts of nonfat and muscle mass, which are important contributors to muscle strength and often accompany weight gain, might be an important concept in understanding the obesity paradox.

Lose weight, improve fitness or both?

Taking the obesity paradox into consideration, one can seriously question the relative benefits of efforts to reduce weight versus those to increase levels of physical activity and fitness. The effect of intentional weight reduction in the general population and in patients with cardiovascular diseases remains somewhat controversial.[1,7,8,10] Some long-term studies suggest that weight loss might worsen prognosis,[1,57] which has certainly been the case in many studies in patients with advanced heart failure and even in those with mild degrees of heart failure.[58–61] However, in the studies of patients with heart failure, weight loss was presumably not intentional; unintentional weight loss would be expected to have an adverse effect on prognosis in many patients with chronic diseases, including cardiovascular diseases and heart failure.[1,7,8,62]

In contrast to these results, many studies have found favourable affects with even modest degrees of purposeful weight reduction.[10] For example, in patients with impaired fasting glucose levels who are at high risk of developing T2DM, lifestyle modifications and small amounts of exercise training that resulted in only modest reductions in weight still led to nearly 60% reductions in the prevalence of T2DM.[63,64] Several studies in patients with hypertension have demonstrated considerable reductions in arterial blood pressure and improvements in left-ventricular geometry, similar to or greater than those noted with pharmacological agents.[1,10] Several studies in patients with CHD have demonstrated the safety of purposeful weight loss.[65–67] In addition, despite the obesity paradox, several studies have also found notable reductions in the incidence of cardiovascular events with purposeful weight reduction.[66,67] The effect of weight loss on cardiovascular structure and function, as well as the potential benefits of weight loss in patients with CHD, have been reviewed in detail.[10,65,68] In patients with heart failure, weight loss as a result of dietary therapy or bariatric surgery improved left-ventricular structure and systolic and diastolic function and reduced the severity of clinical symptoms.[1,7,8,10,69]

Despite these findings, a large-scale study published in 2013 (Look AHEAD; Action for Health in Diabetes) questioned the value of purposeful weight loss in patients with T2DM, at least with regard to all-cause mortality and major cardiovascular end points.[70] This randomized controlled trial compared an intensive lifestyle intervention of dietary weight loss counselling and moderate exercise to enhanced usual care of T2DM on cardiovascular end points in >5,000 patients with overweight and T2DM. Despite mild reductions in weight and small, but significant, improvements in fitness and control of T2DM, the intervention group did not show any statistically significant reduction in the incidence of cardiovascular events or mortality. Improved control of T2DM, however, might have been associated with reduced use of medications for diabetes mellitus, statins and other potential cardioprotective medications, such as angiotensin-converting-enzyme inhibitors. This change in medication use, which is known to be very cardioprotective and to reduce the incidence of major cardiovascular events, might have decreased the potential for the lifestyle interventions to

produce major reductions in the incidence of cardiovascular events; however, other important end points were improved, such as quality of life and functional capacity.[65,70] Nevertheless, the trial was terminated early after a mean follow-up of 9.6 years, as the therapy had no effect on the long-term incidence of cardiovascular events or mortality compared with the control approach.

However, the modest success (improved control of T2DM and benefits on cardiovascular risk factors and need for medications, but a lack of any benefit on hard cardiovascular end points or overall mortality) noted in Look AHEAD and the available literature suggest that unless the volume of aerobic exercise training is very high, clinically important weight loss and a reduction in the incidence of clinical events are unlikely to occur.[71–73] Nevertheless, physical activity and exercise training might be even more important for weight maintenance than for weight loss *per se*.[71] In addition, moderate and high levels of exercise training considerably increased fitness,[52,70–73] including both cardiorespiratory and muscular fitness, the importance of which was discussed in a previous section.

A detailed discussion of various weight-loss strategies, including new medications and bariatric surgery, is beyond the scope of this Review and has been reviewed elsewhere.[74] Bariatric surgery has been demonstrated to be more effective for patients with severe or morbid obesity complicated by comorbid conditions than for patients with moderate obesity.[74] In patients with overweight or class I obesity, increased physical activity and modest volumes of aerobic exercise training that increase fitness by ≥1 metabolic equivalent seem to offer the best protection against the occurrence of cardiovascular events.[40,41,71–73,75–77]

Conclusions

The ideal situation is for all individuals to maintain a lean, metabolically healthy profile, and to avoid low fitness throughout adult life.[17] However, substantial evidence suggests that patients with MHO have minimal to no increase in risk of CHD.[6,17,19] Furthermore, patients with overweight or obesity who are fit have a better prognosis than underweight or lean patients,[43,52] particularly those in the lower end of the normal BMI group (that is, BMI 18.5–22.0 kg/m^2) who are unfit.[43–46,52] In patients with cardiovascular diseases, a strong obesity paradox exists,[1,7,8] in that lean unfit patients with cardiovascular diseases have a poor prognosis in comparison with patients with cardiovascular diseases who are overweight or obese and are unfit. However, in fit patients with cardiovascular diseases (at least those with CHD and/or heart failure),[38,49,51] the prognosis is excellent and no obesity paradox exists. Greater efforts to improve physical activity, exercise training and overall fitness are needed in the primary and secondary prevention of cardiovascular diseases.[77]

Review criteria

We conducted a search of PubMed for articles published during the 16-year period from 1997 to 2013 using the following search terms (or combination of terms): “obesity”, “obesity paradox”, “metabolic syndrome”, “dyslipidaemia”, “hypertension”, “impaired glucose tolerance”, “type 2 diabetes mellitus”, “cardiovascular disease”, “coronary heart disease”, “stroke”, “myocardial infarction” and “mortality”. Only English-language articles were included. We also used additional articles that were identified from the bibliographies of the retrieved articles, as well as selected very recent references from 2014.

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Author contributions

C.J.L., A.D.S. and R.V.M. researched data for the article, contributed to discussion of the content and reviewed and/or edited the manuscript before submission. C.J.L. wrote the article.