Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications

Norbert Stefan, Hans-Ulrich Häring, Frank B Hu, Matthias B Schulze

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Department of Internal Medicine IV, University Hospital Tübingen, Tübingen, Germany (Prof N Stefan MD, Prof H-U Häring MD); **Institute of Diabetes Research and Metabolic Diseases, Tübingen, Germany** (N Stefan, H-U Häring); **German Center for Diabetes Research, Neuherberg, Germany** (N Stefan, H-U Häring, Prof M B Schulze DrPH); **Department of Nutrition, Harvard School of Public Health, Boston, MA, USA** (Prof F B Hu MD); **Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA** (F B Hu); **Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA** (F B Hu); **and Department of Molecular Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany** (M B Schulze)

Correspondence to: Prof Matthias B Schulze, German Institute of Human Nutrition Potsdam-Rehbruecke, Department of Molecular Epidemiology, 14558 Nuthetal, Germany
mschulze@dife.de

Obesity has become a worldwide epidemic that poses substantial health problems for both individuals and society. However, a proportion of obese individuals might not be at an increased risk for metabolic complications of obesity and, therefore, their phenotype can be referred to as metabolically healthy obesity. This novel concept of metabolically healthy obesity might become increasingly important to stratify individuals in the clinical treatment of obesity. However, no universally accepted criteria exist to define metabolically healthy obesity. Furthermore, many questions have been raised regarding the biological basis of this phenotype, the transitory nature of metabolically healthy obesity over time, and predictors of this phenotype. We describe the observational studies that gave rise to the idea of metabolically healthy obesity and the key parameters that can help to distinguish it from the general form of obesity. We also discuss potential biological mechanisms underlying metabolically healthy obesity and its public health and clinical implications.

Introduction

The health consequences of obesity are well documented. In particular, the worldwide increase in the incidence of type 2 diabetes, cardiovascular disease, and several types of cancer is thought to be largely attributed to the obesity epidemic.[1–4] Therefore, prevention and treatment of obesity to reduce risk of chronic diseases at the population and individual level is crucial. Although the deleterious metabolic effects of obesity are widely recognised at population level, individual differences exist in metabolic responses to obesity. Findings from many studies show that a subgroup of obese individuals might be protected from metabolic complications of obesity or might be at substantially lower risk than expected for their degree of obesity. This subgroup has been described as having metabolically healthy obesity.[5–9] Many questions have been raised regarding the biological basis, transitory nature, and predictors of metabolically healthy obesity.

Findings from epidemiologic studies have shown that increased waist circumference is associated with mortality and cardiovascular disease independent of overall adiposity.[4,10] Additionally, data from several small studies suggested that some obese people are not insulin resistant.[5,11–13] This finding was unexpected, because generally, a strong positive association exists between body-mass index (BMI) and insulin resistance. Insulin resistance is thought to represent one of the most important pathomechanisms of metabolic diseases and also of certain types of cancer.[14,15] In addition to body fat distribution and insulin resistance, other metabolic risk factors might also be useful in the characterisation of metabolically healthy obesity in view of their well-established association with risk, including lipid profiles, blood pressure, inflammation, or physical fitness.

In this Personal View we describe observational data that gave rise to the idea of metabolically healthy obesity. We then discuss the key parameters that might help to distinguish metabolically healthy obesity from the general form of obesity, such as smaller waist circumference, increased physical fitness, decreased insulin resistance, and low prevalence of metabolic risk factors despite a high BMI. We also discuss potential biological mechanisms underlying this phenotype and its clinical implications.

Observational data supporting the idea of metabolically healthy obesity

Individuals with metabolically healthy obesity are a subset of individuals who meet the standard BMI cutoff point for obesity (≥30 kg/m²), but are regarded as metabolically healthy because they do not have other major cardiovascular risk factors (figure 1). This subgroup is believed to be at much lower risk of cardiovascular morbidity and mortality

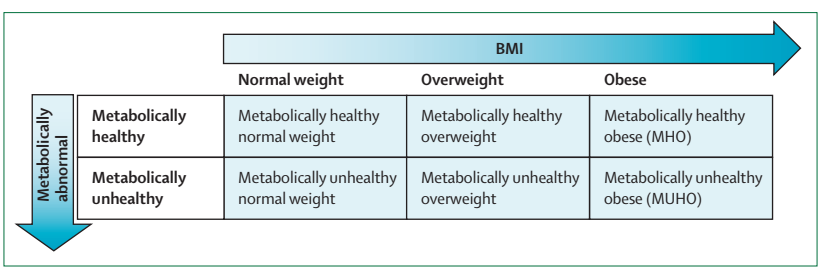

Figure 1: **Classification according to body fat on the basis of BMI and metabolic health**
Absence and presence of major cardiovascular risk factors allows stratification of normal weight, overweight, and obese individuals into metabolically healthy and metabolically unhealthy. Normal weight: BMI 18·5–24·9 kg m^{2}; overweight: BMI 25·0–29·9 kg/m^{2}; obese: BMI ≥30·0 kg/m^{2}. BMI=body-mass index.

Panel 1: **Criteria to define metabolically healthy obesity in epidemiological studies**

- Absence of abdominal obesity on the basis of waist circumference (men ≤102 cm, women ≤88 cm)
- Absence of metabolic syndrome components—eg, normal blood pressure, normal lipid values, normal fasting glucose concentrations (at times also including normal C-reactive protein concentrations)
- Insulin sensitive on the basis of the homoeostatic model assessment of insulin resistance (HOMA-IR)
- High level of cardiorespiratory fitness

compared with obese individuals with major cardiovascular risk factors, who can consequently be judged as being metabolically at risk or metabolically unhealthy obese. The term metabolically healthy obesity implies that individuals with this phenotype are not at higher risk of cardiovascular disease than non-obese individuals. While the classification of metabolically healthy obesity and metabolically unhealthy obesity both require determination of BMI and cardiovascular risk factors at the same time, prospective studies are needed to demonstrate that individuals classified as metabolically healthy obese are indeed protected against the cardiovascular complications of obesity. Substantial evidence has accumulated from prospective cohort studies in which sub-groups of obese individuals were compared with regard to their risk for cardiovascular disease or mortality, although how subgroups have been defined varies largely across studies (panel 1). Here we summarise the evidence from prospective studies on mortality.

Body fat distribution and mortality in obese individuals

An obvious approach to define metabolically healthy obesity is a more detailed anthropometric characterisation of obese individuals in addition to BMI. The measurement of waist circumferences allows better characterisation of body fat distribution than BMI, especially accumulation of body fat in the abdominal region. However, findings from large prospective cohort studies show that the association of risk of cardiovascular disease and death with increasing waist circumference is stronger in non-obese individuals compared with obese individuals.[4,10,16] Waist circumference measurement might therefore be more useful for the identification of high metabolic risk for normal weight and moderately obese patients than for severely obese patients. The strong association between BMI and waist circumference makes it unlikely that both provide different answers (figure 2). Measures that are less strongly related to BMI, but show metabolic risk, might be more informative for characterisation of metabolically healthy obesity. Figure 2 shows that although insulin resistance (assessed by the homoeostatic model assessment of insulin resistance [HOMA-IR]) is strongly associated with BMI, it has much larger variation compared with waist circumference at any given BMI among obese individuals. This results in a group of individuals with insulin resistance below the population average, even though they are morbidly obese. Although waist-to-hip ratio is less strongly associated with BMI than is waist circumference, this ratio is not more informative in quantifying cardiovascular risk among obese individuals than is waist circumference.[4,10] Thus, the use of waist

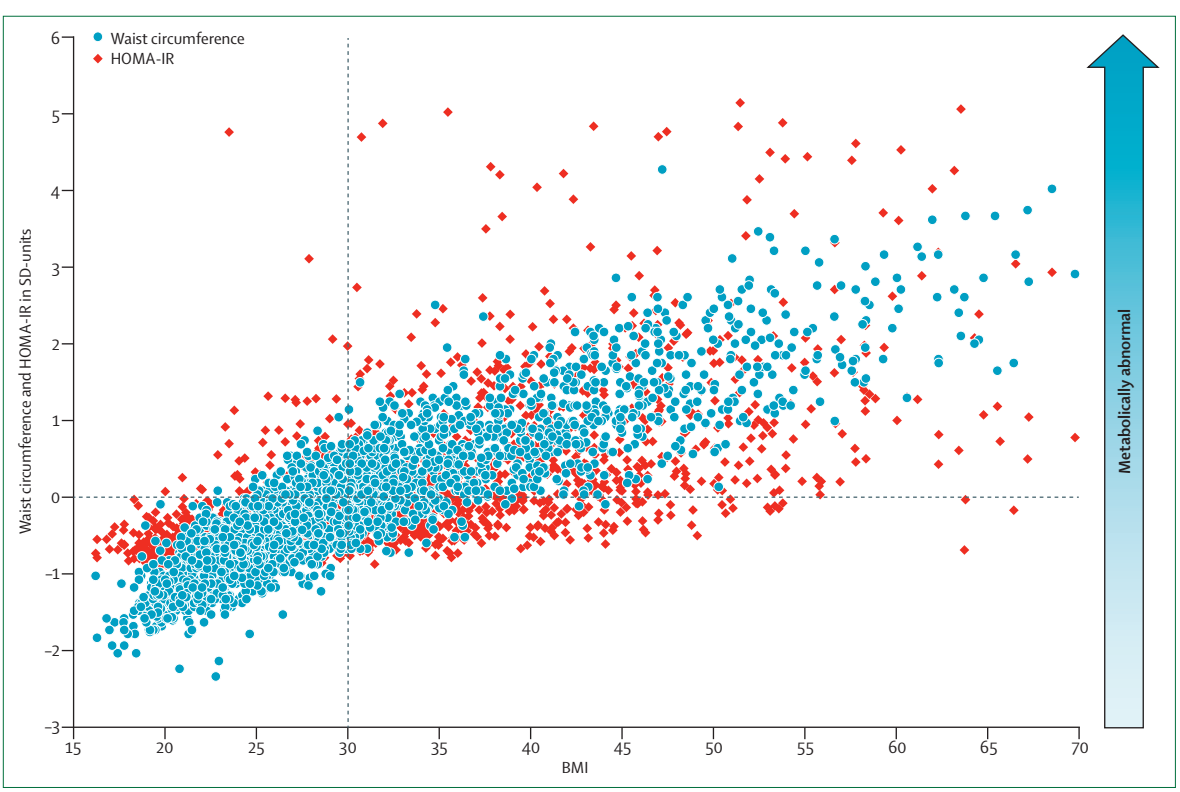

Figure 2: **Association between BMI, waist circumference, and insulin resistance in the Tübingen Family study and the Tübingen Lifestyle Intervention Program (n=2472)[8,17]**

Association between BMI and waist circumference is strong. By contrast, for insulin resistance—estimated from the homoeostatic model assessment—large variation is recorded for any given BMI among obese individuals. HOMA-IR=homoeostatic model assessment of insulin resistance.

circumference or waist to hip ratio alone is not sufficient to establish the metabolically healthy obesity phenotype.

Physical fitness, activity, and mortality among obese individuals

Besides components of metabolic syndrome and insulin resistance, physical fitness is an alternative means to define metabolically healthy obesity. Results from several prospective studies show that only obese, unfit individuals, but not obese, fit individuals, are at higher mortality risk than are normal weight fit individuals (table 1). Fitness is measured by a treadmill exercise test and categories of fit and unfit study participants are based on varying study-specific percentiles.[24–28] However, whether fitness is

	Study	Participants	Definition of unhealthy metabolic phenotype	Reference group	Outcome	Relative risk (95% CI) metabolically healthy obese	Relative risk (95% CI) metabolically unhealthy obese	Adjustment
Studies using insulin resistance to define metabolic health								
Kuk et al, 2009[18]	National Health and Nutrition Examination Survey III, USA	4602 men and women	HOMA-IR ≥2·5	Normal weight insulin sensitive	Total mortality	2·58 (1·0–6·7)	3·09 (1·6–6·2)	Age, sex, income, smoking status, ethnicity, and alcohol consumption
Arnlov et al, 2010[19]	Uppsala Longitudinal Study of Adult Men, Sweden	1758 men	HOMA-IR in top 25% of the distribution in participants without diabetes (>3·43)	Normal weight insulin sensitive	Total mortality Cardiovascular mortality	2·04 (1·25–3·32) 1·80 (0·79–4·08)	2·21 (1·64–2·99) 2·87 (1·87–4·42)	Age, smoking, and LDL cholesterol
Calori et al, 2011[20]	Cremona Study, Italy	2011 men and women	HOMA-IR ≥2·5	Nonobese insulin sensitive	Total mortality Cardiovascular mortality	0·99 (0·46–2·11) 0·73 (0·18–3·00)	1·40 (1·08–1·81) 1·61 (1·10–2·36)	Age and sex
Bo et al, 2012[21]	Asti (northwest Italy)	1658 men and women	HOMA-IR >2·5	Normal weight insulin sensitive	Total mortality Cardiovascular mortality	1·57 (0·93–2·21) 2·95 (1·03–3·98)	1·51 (1·04–1·98) 2·43 (1·57–3·29)	Age, sex and smoking
Durward et al, 2012[22]	National Health and Nutrition Examination Survey III, USA	4373 men and women	HOMA-IR ≥2·5	Normal weight insulin sensitive	Total mortality	1·42 (0·6–3·2)	2·07 (1·3–3·4)	Sex, age, income, education, race and ethnicity, smoking status, alcohol consumption, marital status, leisure time physical activity, and menopausal status in women
Hinnouho et al, 2013[23]	Whitehall II Study, UK	5269 men and women	HOMA-IR in top 25% of the distribution	Normal weight metabolic healthy	Total mortality Cardiovascular mortality	1·08 (0·67–1·74) 1·04 (0·41–2·66)	2·14 (1·56–2·94) 2·63 (1·51–4·60)	Age, sex, occupation, physical activity, smoking, alcohol, fruit and vegetable consumption, marital status, ethnicity
			Matsuda index in lower 75% of the distribution	Normal weight metabolic healthy	Total mortality Cardiovascular mortality	2·30 (1·13–4·70) 1·89 (0·43–8·33)	1·57 (1·08–2·28) 1·75 (0·89–3·41)	
Studies using cardiorespiratory fitness to define metabolic health								
Wei et al, 1999[24]	Aerobics Center Longitudinal Study, USA	25 714 men	Metabolic equivalents during maximum treadmill exercise test; value <age-specific cut points	Normal weight fit	Total mortality Cardiovascular mortality	1·1 (0·8–1·5) 1·6 (1·0–2·8)	3·1 (2·5-3·8) 5·0 (3·6–7·0)	Age and calendar year of baseline examination
Stevens et al, 2002[25]	Lipid Research Clinics Study, USA	2506 women and 2860 men	Duration of maximum treadmill exercise test; lowest 20%	Non-obese fit	Total mortality Cardiovascular mortality	Men: 1·25 (p<0·05) Women: 1·32 (p<0·05) Men: 1·39 (p<0·06) Women: 1·39 (p>0·05)	Men: 1·49 (p<0·05) Women: 1·57 (p<0·05) Men: 1·67 (p<0·05), Women: 1·95 (p<0·05)	Age, education, smoking, alcohol
Sui et al, 2007[26]	Aerobics Center Longitudinal Study, USA	2603 men and women	Duration of maximum treadmill exercise test; lowest 20%	Normal weight fit	Total mortality	BMI 30–34: 1·12 (0·76–1·66) BMI ≥35: 0·86 (0·21–3·50)	BMI 30–34: 1·68 (1·02–2·78) BMI ≥35: 3·35 (1·74–6·44)	Age, sex, examination year, smoking status, abnormal exercise electrocardiogram responses, baseline health conditions
Farrell et al, 2010[27]	Aerobics Center Longitudinal Study, USA	11 335 women	Duration of maximum treadmill exercise test; lowest 20%	Normal weight fit	Total mortality	0·5 (p>0·05)	2·5 (p<0·05)	Age and calendar year of baseline examination
McAuley et al, 2010[28]	Veterans Exercise Testing Study, USA	811 men	Metabolic equivalents of final treadmill speed and grade during maximal exercise test; lower third (<9 Metabolic Equivalent of Task)	Non-obese fit	Total mortality	1·03 (0·53–2·00)	2·13 (1·17–4·08)	Unadjusted (similar results in multivariate analyses)

HOMA-IR: homoeostatic model assessment-estimated insulin resistance.

Table 1: **Mortality in metabolically healthy obese individuals compared with metabolically unhealthy obese, using insulin resistance or physical fitness to define metabolic health**

independent of cardiovascular risk factors is not entirely clear from these studies. Physical activity is the main non-genetic determinant of fitness, and also has beneficial effects on body fat distribution, insulin sensitivity, and other characteristics of the metabolic syndrome. Therefore, fitness and metabolic risk factors are probably associated and thus fitness might only be a marker for a common lifestyle determinant of metabolically healthy obesity. Adjustment for fitness only partly explained the risk difference reported between metabolically healthy obesity and metabolically unhealthy obese subgroups, which were defined on the basis of the presence or absence of the metabolic syndrome in the Aerobics Center Longitudinal Study.[29] Consequently, physical fitness alone might not be regarded as a surrogate to identify metabolically healthy obese individuals who are otherwise identifiable by metabolic parameters.

Metabolic syndrome and insulin resistance and mortality in obese individuals

Investigators have frequently used either the absence of the metabolic syndrome or high insulin sensitivity (usually defined as a low HOMA-IR value) or a combination of both, to define metabolic health. Tables 1 and 2 summarise findings of such studies on mortality. Marked differences in total mortality between obesity subgroups when stratified by the metabolic syndrome were reported in several studies.[19,29–31] For example, Hamer and colleagues[31] found a higher mortality risk among obese participants in the Health Survey for England and the Scottish Health Survey, who had two or more cardiovascular risk factors (including large waist circumference, hypertension, diabetes, high C-reactive protein, and low HDL cholesterol) than in non-obese individuals who were metabolically healthy (relative risk [RR] 1·79, 95% CI 1·47–2·17). Obese participants without or with only one cardiovascular risk factor were not at increased risk of mortality compared with non-obese metabolically healthy individuals (RR 0·91, 95% CI 0·64–1·29). Similarly, data from several studies suggest that mortality risk is increased in metabolically unhealthy obese individuals, but not metabolically healthy obesity, compared with normal weight individuals, if metabolic health is defined by HOMA-IR.[20,22,23] However, findings from other studies showed similarly raised mortality risks in both metabolically healthy and metabolically unhealthy obese subgroups.[18,19,21,23,31,32]

Limitations in defining metabolically healthy obesity and conclusions from observational studies

What might explain these diverging results? Researchers have used different definitions of the metabolic syndrome and different components (eg, some exclude waist circumference as a criteria), which complicates the interpretation of the results.[19,33] Similarly, HOMA-IR has been used with varying cutoffs to define metabolic health. The use of a specific cutoff value for HOMA-IR is largely an arbitrary decision because the methods for insulin measurements are not standardised worldwide. Although physical fitness can be measured in epidemiological research and also in clinical practice, studies have used different measurement protocols and different cutoffs to discriminate fit from unfit participants. Even studies assessing waist circumference in obese patients have generally used study-specific percentiles to categorise risk groups.

Of note, different criteria defining metabolic health identify different subgroups of the obese population with little overlap. For example, according to data from NHANES III,[22] 20% of obese participants were classified as metabolically healthy according to a predefined HOMA-IR cutoff, whereas more than double (ie, 44%) were categorised as such on the basis of the absence of the metabolic syndrome according to the ATP-III definition. In view of the dependence of risk factors on age, prevalence estimates of metabolically healthy obesity can also be expected to be strongly dependent on the age distribution of populations.

Only a few studies compared different criteria to define metabolically healthy obesity, being largely restricted to comparisons of metabolic syndrome and definitions by HOMA-IR.[18,19,22,23] Thus, systematic assessments of different cardiovascular risk factors—in isolation or in combination—and the cutoffs that best discriminate subgroups among obese individuals with different cardiovascular risk are scarce. On the basis of results from observational studies, whether the absence of cardiovascular risk factors indeed eliminates the association between obesity and excess mortality is unclear. Most likely, metabolically healthy obesity shows an intermediate, rather than a permanent, low risk state. In support of this hypothesis, recent data from the North West Adelaide Health Study[34] suggest that metabolically healthy obese might be a transient phenotype for a proportion of individuals. Of all individuals classified as metabolically healthy obese at the beginning, a third changed to a high risk phenotype during the course of the study, but lower risk of type 2 diabetes and cardiovascular disease was restricted to the subgroup of metabolically healthy obese individuals who maintained this condition. Thus, the presence of metabolically healthy obesity during one clinical examination should not imply no metabolic risk; however, to keep the metabolically healthy obesity status might clearly be beneficial for metabolic health.

Potential mechanisms involved in the genesis of metabolically healthy obesity

Findings from animal studies

To identify mechanisms underlying adiposity-mediated metabolic diseases in human beings, data from animal studies need to be considered. In such studies, predominantly genetic modification of animals allows precise investigation of the interplay of metabolically relevant tissues and molecular signalling pathways.

	Study	Participants	Definition of metabolic syndrome	Reference group	Outcome	Relative risk (95% CI) metabolically healthy obese	Relative risk (95% CI) metabolically unhealthy obese	Adjustment
Kip et al, 2004[30]	Women's Ischemia Syndrome Evaluation study, USA	780 women	National Cholesterol Education Program Adult Treatment Panel III (without waist circumference); ≥three components	Normal weight metabolic healthy	Total mortality	0·66 (0·07–6·01)	2·08 (0·68–6·40)	Age, race, previous myocardial infarction, chronic obstructive pulmonary disease, and number of lesions with 50% stenosis
Kuk et al, 2009[18]	National Health and Nutrition Examination Survey III, USA	6011 men and women	Modified NCEP ATP III (without waist circumference); ≥ three components	Normal weight metabolic healthy	Total mortality	2·8 (1·2–6·7)	2·7 (1·5–5·2)	Age, sex, income, smoking status, ethnicity, and alcohol consumption
Arnlov et al, 2010[19]	Uppsala Longitudinal Study of Adult Men, Sweden	1758 men	Modified NCEP ATP III (without waist circumference); ≥ two components	Normal weight metabolic healthy	Total mortality Cardiovascular mortality	1·65 (1·03–2·66) 1·20 (0·49–2·93)	2·43 (1·81–3·27) 3·20 (2·12–4·82)	Age, smoking, and LDL cholesterol
Durward et al, 2012[22]	National Health and Nutrition Examination Survey III, USA	4373 men and women	NCEP ATP III (without waist circumference); ≥ three components	Normal weight metabolic healthy	Total mortality	1·54 (0·7–3·3)	1·98 (1·4–2·9)	Sex, age, income, education, race and ethnicity, smoking status, alcohol consumption, marital status, leisure time physical activity, and menopausal status in women
Hamer et al, 2012[31]	Health Survey for England and Scottish Health Survey, UK	25 608 men and women	≥ Two components: waist circumference >88 cm in women and >102 cm in men, blood pressure >130/85 mm Hg, hypertension diagnosis, use of antihypertensive drug, doctor-diagnosed diabetes, low-grade inflammation (C-reactive protein ≥3 mg/l), and HDL cholesterol <1·30 mmol/L in women and <1·03 men	Non-obese metabolic healthy	Total mortality Cardiovascular mortality	0·91 (0·64–1·29) 1·26 (0·74-2·13)	1·79 (1·47–2·17) 1·64 (1·17-2·30)	Age, sex, smoking, physical activity, socioeconomic group, and BMI
Choi et al, 2013[32]	Southwest Seoul Study, Korea	1737 men and women	Modified NCEP ATP III (without waist circumference); ≥ three components	Overweight metabolic healthy	Total mortality Cardiovascular mortality	1·2 (0·88–1·76) 1·9 (1·04–3·76)	1·4 (1·04–2·14) 1·6 (0·79–3·26)	Age, sex, and smoking
Hinnouho et al, 2013[23]	Whitehall II Study, UK	5269 men and women	Modified NCEP ATP III (without waist circumference) ≥ two components	Normal weight metabolic healthy	Total mortality Cardiovascular mortality	1·81 (1·16–2·84) 2·49 (1·05–5·91)	2·01 (1·43–2·83) 2·94 (1·56–5·56)	Age, sex, occupation, physical activity, smoking, alcohol, fruit and vegetable consumption, marital status, ethnicity
			≥ Two components: blood pressure ≥130/85 mm Hg, triglycerides ≥1·7 mmol/L, fasting glucose ≥5.6 mmol/L, HOMA >90th percentile, C-reactive protein >90th percentile, HDL cholesterol <1·3 mmol/L;	Normal weight metabolic healthy	Total mortality Cardiovascular mortality	2·11 (1·21–3·67) 2·05 (0·58–7·21)	2·23 (1·58–3·15) 2·24 (1·25–4·00)	
			Four of five criteria met: HOMA ≤2·7, triglycerides ≤1·7 mmol/L, HDL cholesterol ≥1·3 mmol/L, LDL-cholesterol ≤2·6 mmol/L, C-reactive protein ≤3·0 mg/L	Normal weight metabolic healthy	Total mortality Cardiovascular mortality	1·86 (1·02–3·41) 1·26 (0·29–5·56)	2·05 (1·44–2·92) 2·75 (1·44–5·28)	
Ortega et al 2013[29]	Aerobics Center Longitudinal Study, USA	43 265 men and women	International Diabetes Federation; ≥two components	..	Total mortality Cardiovascular mortality	1·0 (reference) 1·0 (reference)	1·61 (1·19–2·18) 1·77 (1·05–2·99)	Age, sex, examination year, smoking, alcohol consumption, fitness, and parental history of cardiovascular disease

NCEP ATP=National Cholesterol Education Program Adult Treatment Panel. HOMA=homoeostatic model assessment. LDL=low-density lipoprotein. HDL=low-density lipoprotein.

Table 2: **Mortality in metabolically healthy obese individuals compared with metabolically unhealthy obese, using metabolic syndrome to define metabolic health**

Three rodent models have provided important information about the protective effects of the expansion of adipose tissue on metabolism. The most compelling evidence that metabolically healthy obesity also exists in animals comes from a study by Philipp Scherer's research group in the adiponectin transgenic (AdTG) mouse. The AdTG leptin-deficient *ob/ob* mouse, which has higher circulating concentrations of adiponectin than its *ob/ob* littermate, was found to become morbidly obese, but remains insulin sensitive.[35] This phenotype is

accompanied by increased subcutaneous adipose tissue mass, and by a low fat content of the liver and the skeletal muscle.[35] Additionally, the AdTG *ob/ob* mouse shows an increased expression of peroxisome proliferator-activated receptor γ target genes, increased adipogenesis, a reduced infiltration of macrophages in adipose tissue, and low systemic inflammation compared with its *ob/ob* littermate.[35] Besides the direct protective effects of adiponectin on metabolism in this mouse model, the expansion of subcutaneous adipose tissue might provide a safe haven for the storage of lipids and, thereby, represent a mechanism to protect from lipotoxicity. The latter hypothesis is supported by many studies on lipodystrophy in which the absence of subcutaneous fat mass is thought to contribute largely to the impairment of metabolism in individuals with this disorder.[36]

More recently, another genetically modified mouse model of metabolically healthy obesity was described by the Scherer laboratory.[37] In an *ob/ob* mouse overexpressing the mitochondrial membrane protein mitoNEET, which inhibits mitochondrial iron transport into the mitochondrial matrix, a large expansion of predominantly subcutaneous adipose tissue is found; however, the mouse remains insulin sensitive compared with its non-transgenic *ob/ob* littermates. Increased amounts of adiponectin and decreased ectopic storage of liver and skeletal muscle lipids have been recorded in this animal model.[37]

The third animal model of metabolically healthy obesity was very recently published by the group of Barbara Kahn.[38] Their study showed that adipose carbohydrate responsive element binding protein β (ChREBPβ) protects from insulin resistance in mice with adipose-specific glucose transporter type 4 overexpression by increasing adipose tissue de novo lipogenesis, which results in expansion of subcutaneous adipose tissue.[38] Additionally, a positive association between subcutaneous adipose-ChREBPβ mRNA expression and insulin sensitivity, independent of BMI, was found in human beings.

Several other genetically modified murine models of obesity, with preserved insulin sensitivity, have been identified, and the respective mechanisms of action are under investigation.[39] A common feature of most of these models is that rodents displaying a metabolically healthy obesity-like phenotype have an increased mass of non-visceral adipose tissue, a metabolically beneficial adipokine pattern, and a low amount of lipid deposition in the liver. One hypothesis is that an increased lipid-storage capacity in subcutaneous adipose tissue or less inflammatory signalling in adipose tissue, or both, are important features of this phenotype in rodents (panel 2). Thus, many of these animal models already provide important information about pathways—eg, reduced iron transport into the mitochondrial matrix[37] and increased adipose tissue lipogenesis,[38] which might be of use in developing drugs that prevent metabolic diseases.

***Panel 2:* Mechanisms involved in the genesis of metabolically healthy obesity in animals**

- Increased adipogenesis in subcutaneous adipose tissue
- Increased de-novo lipogenesis in adipocytes from subcutaneous adipose tissue
- Decreased mitochondrial iron transport into the mitochondrial matrix
- Increased adiponectin and decreased inflammatory pathway signalling

Findings from human studies

Consistent with data from animal studies, obese individuals also have different fat distribution patterns that are related to distinct metabolic phenotypes.[8,40] Large differences can be seen in skeletal muscle and, predominantly, in liver fat content (figure 3).[8] Liver fat content is substantially associated with insulin sensitivity, and much more so than visceral fat mass.[8,41–44] Furthermore, liver fat content, but not visceral fat mass, was independent of atherosclerotic risk factors associated with coronary artery or abdominal aortic calcification in the Jackson Heart Study.[45] Additionally, in a large South Korean occupational cohort study,[46] high liver fat content was more strongly associated with incident type 2 diabetes than was being overweight and obesity. Findings from other studies also showed that a high liver fat content increases risk of type 2 diabetes, independent of established risk factors.[47–50] Thus, the absence of fatty liver might be especially useful to characterise a low-risk phenotype.[8,42]

Furthermore, besides the total amount of fat within the liver and the visceral cavity, the type of fat storage and the resulting inflammatory signalling also become relevant to metabolic health. In this respect, a metabolically benign and malignant fatty liver has been identified, the first of which is not associated with the commonly reported lipid-induced impairment of metabolism.[51] Here, the release of pro-inflammatory hepatokines,[52] including fetuin-A which mediates lipid-induced insulin resistance and sub-clinical inflammation in mice and human beings,[53,54] is low in benign fatty liver.[51]

Additionally, reduced infiltration of immune cells into adipose tissue and, consequently, a metabolically beneficial cytokine and adipokine secretion pattern, was found in morbidly obese but insulin-sensitive individuals.[40] In agreement with the data from animal studies, single nucleotide polymorphisms in the adiponectin receptor 1 gene[55] and hyperadiponectinaemia[40,56] are determinants of metabolically healthy obesity in human beings.

Strong support for the hypothesis that the expansion of subcutaneous adipose tissue and reduced storage of lipids in the liver, both of which are regulated by adiponectin, are crucial determinants of insulin sensitivity comes from pharmacological studies of peroxisome proliferator-activated receptor γ activation in

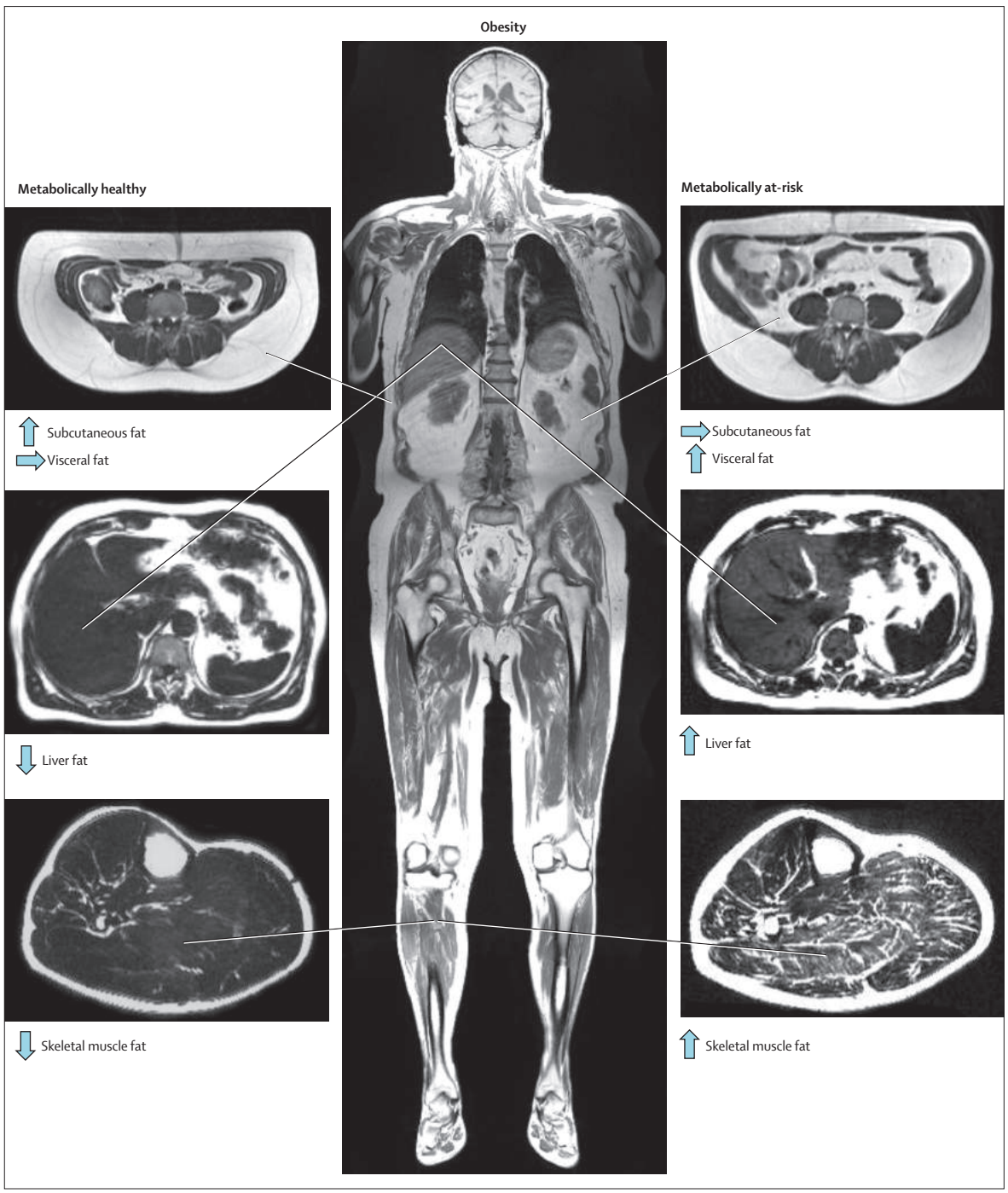

Figure 3: **Body fat distributions in metabolically healthy and metabolically at-risk obese individuals**
Individuals with metabolically healthy obesity have more subcutaneous, less visceral fat mass, and lower ectopic fat deposition in the liver and in the skeletal muscle than do metabolically at-risk obese individuals.

human beings. Thiazolidinedione treatment results in an increase in adiponectin concentrations, an expansion of subcutaneous adipose tissue, a decrease in liver fat content, and an increase in insulin sensitivity.[57] From this class of drugs, pioglitazone—although associated with an increased risk of bone fractures, body fluid retention, and possibly bladder cancer[57]—might be a promising treatment approach, especially for insulin-resistant individuals with non-alcoholic fatty liver disease or an increased risk of cardiovascular disease or both.[57,58] The

metabolically healthy obesity phenotype is also associated with increased cardiorespiratory fitness.[29] Whether the higher cardiorespiratory fitness level in metabolically healthy obese individuals in this study[29] was associated with a lower liver fat content, as was shown in a previous study,[17] could not be established.

Effectiveness of interventions in metabolically healthy obesity

In view of the magnitude of the obesity epidemic, stratification of obese individuals, in terms of their risk for obesity-related metabolic diseases, becomes more important for prevention and treatment purposes. Scarce resources can be more effectively used among those at risk; various prevention and treatment strategies can be very expensive and time consuming. Therefore, an important question is whether metabolically healthy obesity is indeed a concept allowing the discrimination of obese individuals who would not gain any metabolic benefit from lifestyle or clinical intervention.

Lifestyle intervention in metabolically healthy obesity

Lifestyle intervention is the firstline treatment in obese people to decrease bodyweight and to reduce the risk of metabolic and other adiposity-associated diseases. So far, three studies have investigated the effectiveness of lifestyle intervention in individuals with different risks for metabolic diseases. In a study by Karelis and colleagues,[59] 60 sedentary obese postmenopausal women, who were classified as having metabolically healthy obesity (upper quartile of insulin sensitivity) or as being obese and metabolically at risk, underwent a 6 month lifestyle intervention with modification of the diet and an increase in physical activity. Although an increase in insulin sensitivity was found in the at-risk group, a small decrease in insulin sensitivity was found in the women with metabolically healthy obesity. In a study by Kantartzis and coworkers,[60] a similar type of lifestyle intervention in 103 participants led to a decrease in visceral fat content in metabolically healthy obese men and women (upper quartile of insulin sensitivity), although insulin sensitivity did not change in this group. In the study by Janiszewski and colleagues,[61] insulin sensitivity and other parameters of cardiometabolic risk increased in the group with metabolically healthy obesity (defined in this study as the absence of abdominal obesity and no more than one component of the metabolic syndrome) and in the obese at-risk individuals undergoing a 3 to 6 month lifestyle intervention. However, in almost all of the at-risk individuals in these studies, insulin sensitivity did not reach the respective amounts that were found in the participants with metabolically healthy obesity.[59–61] Because these studies investigated short-term lifestyle interventions, the effects on hard endpoints (eg, incidence of type 2 diabetes, cardiovascular events, or death) could not be assessed. Nevertheless, because insulin resistance is predictive of mortality and coronary heart disease in non-diabetic individuals, and is predictive of coronary heart disease even in normoglycaemic individuals without impaired glucose tolerance,[62] one can assume that effects of a lifestyle intervention on insulin resistance are likely to be important for cardiovascular disease prevention.

Bariatric surgery

Bariatric surgery leads to a more substantial decrease in bodyweight than non-surgical procedures. A mean decrease of bodyweight of about 20% during several years of follow-up has been reported.[63–65] Favourable effects of weight loss achieved with bariatric surgery on various health outcomes have been recorded, including health-related quality of life, physical activity, joint pain, and dyspnoea.[66] Additionally, the metabolic benefits of bariatric surgery have been investigated extensively; however, little data is available on mortality and morbidity. Most of the data regarding these endpoints derive from the Swedish Obese Subjects (SOS) study.[65–68] Bariatric surgery is associated with a reduction of total mortality by 24%,[67] and of cardiovascular events by 53%.[65] Bariatric surgery is also associated with a reduction of the incidence of cancer in women by 42%, but not in

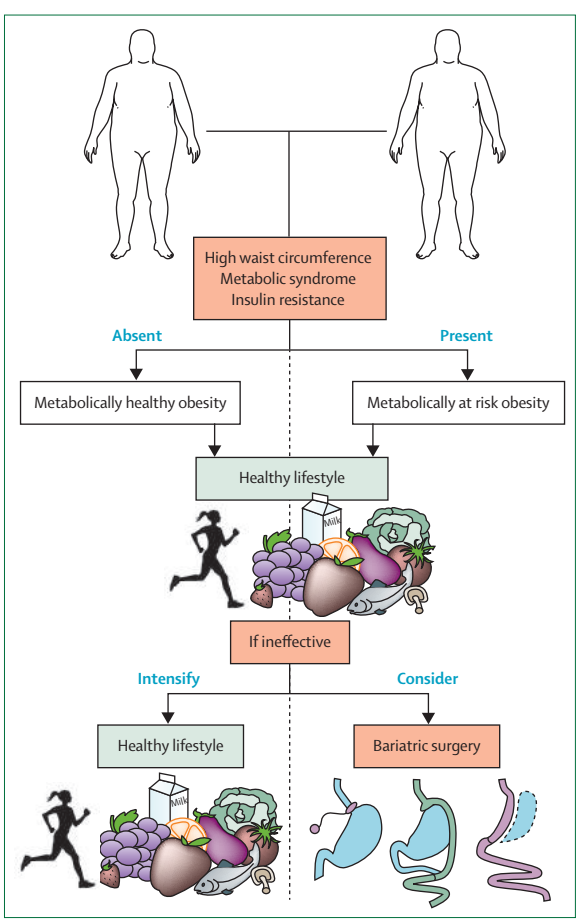

Figure 4: **Potential strategies to identify and treat metabolically healthy and metabolically at-risk obese individuals**

men.[68] These data support the hypothesis that bariatric surgery has a benefit in terms of mortality and metabolic health in both sexes, and cancer incidence in women.

However, Sjostrom and colleagues[65] reported a high number needed to treat (n=50) to prevent cardiovascular events. The authors also did a secondary subgroup analysis and studied whether the BMI, waist circumference, blood pressure, smoking, diabetes, the metabolic syndrome, or metabolic blood parameters obtained during fasting conditions at baseline predicted the effectiveness of bariatric surgery to prevent cardiovascular events. Only fasting insulin concentrations at baseline were substantially related to the effectiveness of the intervention. When the participants were separated by the median fasting insulin concentrations, a reduced cardiovascular risk with surgery compared with controls was reported among those with high insulin concentrations (RR 0·69, 95% CI 0·54–0·87), but not among those with low insulin concentrations (0·93; 0·67–1·28; $p_{interaction}$<0·01). The number needed to treat was also found to be largely reduced to a value of 21 for those with high insulin values (173 for those with lower concentrations). Fasting insulin also predicted the treatment effect with respect to mortality ($p_{interaction}$=0·013) and incidence of diabetes (p=0·007).[66] In this study, BMI at baseline was not predictive of the effectiveness of the intervention on mortality, cardiovascular disease, diabetes, or cancer incidence.[65,67,68] These results suggest that high fasting insulin concentrations might be a better selection criterion for bariatric surgery than BMI.[65] Other metabolic risk factors besides insulin concentrations seemed to modify the effectiveness of the intervention in the SOS trial. In view of the post-hoc exploratory nature of the subgroup analyses, replication of the findings in other populations and with other obesity surgery procedures is needed. Nonetheless, these data support the view that BMI should not be the only parameter to decide whether bariatric surgery should be offered to obese people when lifestyle change was not successful in decreasing bodyweight.[69] A-priori consideration of the risk status might help to select obese people who most probably benefit from this invasive intervention in respect to cardiovascular events, as is already recommended for individuals with a BMI between 35 and 40 kg/m² by the National Institutes of Health.[70]

***Panel 3*: Future needs in the specialty of metabolically healthy obesity**

- Establishment of a consensus definition of metabolically healthy obesity
- Systematic assessment of different cardiovascular risk factors and their cutoffs, which best discriminate subgroups among obese individuals with different cardiovascular risk both cross-sectionally and longitudinally
- Assessment of differences in metabolic health factors in the obese between men and women and between subgroups according to age, race, and ethnicity
- Initiation of randomised controlled intervention trials of lifestyle and drug interventions in patients with metabolically healthy obesity and metabolically unhealthy obesity
- Cost–benefit analyses for the targeted treatment of obesity on the basis of metabolically healthy obesity stratification
- Expansion of basic, animal, and human research to identify key mechanisms in the genesis of metabolically healthy obesity

Search strategy and selection criteria

We searched PubMed for full-text original studies and review articles written in English between Jan 1, 1990, and May 31, 2013, to identify reports on metabolic parameters and mortality in obese people. The search terms used were "metabolically healthy obesity", "metabolically benign obesity", "metabolic syndrome", "insulin sensitivity", "insulin resistance", "fitness", "bariatric surgery", and "lifestyle intervention" together with "mortality". The reference lists of the identified papers were also used to identify additional papers of interest. We also screened studies identified in a recent systematic review on obesity and mortality (Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body-mass index categories: a systematic review and meta-analysis. *JAMA* 2013; **309:** 71–82) for subgroup analysis by anthropometric characteristics, metabolic parameters, and physical fitness. The final reference list was selected on the basis of relevance to the subject of this Viewpoint. Studies on mortality were included if they were prospective observational cohort studies and provided estimates of risk associated with BMI for subgroups of obese individuals in comparison with non-obese individuals.

Clinical and public health implications

The lack of a standard definition of metabolically healthy obesity makes it unclear how the concept of metabolically healthy obesity can be incorporated into clinical practice. Nevertheless, clinicians need to carefully assess the metabolic status of obese people to devise strategies to reduce their risk of cardiovascular disease, mortality, and possibly cancer incidence. This reduction can be achieved with a measurement of the waist circumference, to provide an assessment of the body fat distribution beyond overall adiposity. Additionally, the determination of other parameters of the metabolic syndrome, especially blood pressure and lipid markers, are useful. A potentially effective way to differentiate individuals with metabolically healthy obesity from metabolically at-risk obese individuals is to assess insulin resistance. The fasting insulin value, which can be used together with the fasting glucose value to calculate the HOMA-IR, seems to be informative. However, because the methods used for insulin measurement are not standardised, a universal cutoff for insulin resistance cannot be defined. A lifestyle intervention (eg, a Mediterranean-type diet, which was found to be effective in the prevention of cardiovascular events in people with a BMI of 30 kg/m²)[71] and an increase in physical activity[72] are first-line interventions for all obese individuals. If this strategy does not decrease bodyweight and improve metabolic parameters, an intensified intervention should be applied. In the metabolically at-risk individuals, bariatric surgery should be considered according to the recommendations of the medical societies[73] (figure 4). In view of the uncertainties about the definition of metabolically healthy obesity and

its clinical applications, the public health relevance of the metabolically healthy obesity concept so far remains unclear. Consequently, several aspects need to be taken into account before the metabolically healthy obesity concept can be applied to clinical and public health practice (panel 3).

Conclusions

The idea of metabolically healthy obesity is not new, but the concept has only recently been widely recognised in the discipline. Insufficient standard criteria to define metabolically healthy obesity and the largely unknown biological mechanisms are barriers to the application of the metabolically healthy obesity phenotype to clinical practice. Nonetheless, this idea underscores the need to consider other metabolic and anthropometric parameters in addition to BMI. This concept might be used in future clinical practice to design intervention strategies (eg, lifestyle interventions *vs* bariatric surgery) tailored towards the metabolic profile of an individual. Whether such a targeted and individualised approach to obesity management and treatment is more effective than traditional approaches needs to be investigated in future studies. However, to only focus on treatment of cardiovascular risk factors among at-risk obese individuals is probably insufficient, and prevention of obesity through healthy diet and physical activity should be widely promoted.[74]

Conflicts of interest

We declare that we have no conflicts of interest.

Contributors

NS and MBS reviewed the published work and wrote the manuscript. H-UH and FBH reviewed the work and contributed to the discussion.

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References

1 Finucane MM, Stevens GA, Cowan MJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet* 2011; **377:** 557–67.

2 Hu FB, Willett WC, Li T, Stampfer MJ, Colditz GA, Manson JE. Adiposity as compared with physical activity in predicting mortality among women. *N Engl J Med* 2004; **351:** 2694–703.

3 Malik VS, Willett WC, Hu FB. Global obesity: trends, risk factors and policy implications. *Nat Rev Endocrinol* 2013; **9:** 13–27.

4 Pischon T, Boeing H, Hoffmann K, et al. General and abdominal adiposity and risk of death in Europe. *N Engl J Med* 2008; **359:** 2105–20.

5 McLaughlin T, Abbasi F, Lamendola C, Reaven G. Heterogeneity in the prevalence of risk factors for cardiovascular disease and type 2 diabetes mellitus in obese individuals: effect of differences in insulin sensitivity. *Arch Intern Med* 2007; **167:** 642–48.

6 Meigs JB, Wilson PW, Fox CS, et al. Body mass index, metabolic syndrome, and risk of type 2 diabetes or cardiovascular disease. *J Clin Endocrinol Metab* 2006; **91:** 2906–12.

7 Stefan N, Kantartzis K, Machann J, Schick F, Häring HU. Global trends in body-mass index. *Lancet* 2011; **377:** 1917.

8 Stefan N, Kantartzis K, Machann J, et al. Identification and characterization of metabolically benign obesity in humans. *Arch Intern Med* 2008; **168:** 1609–16.

9 Wildman RP, Muntner P, Reynolds K, et al. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004). *Arch Intern Med* 2008; **168:** 1617–24.

10 Wormser D, Kaptoge S, Di Angelantonio E, et al. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet* 2011; **377:** 1085–95.

11 Karelis AD, St-Pierre DH, Conus F, Rabasa-Lhoret R, Poehlman ET. Metabolic and body composition factors in subgroups of obesity: what do we know? *J Clin Endocrinol Metab* 2004; **89:** 2569–75.

12 Reaven G. All obese individuals are not created equal: insulin resistance is the major determinant of cardiovascular disease in overweight/obese individuals. *Diab Vasc Dis Res* 2005; **2:** 105–12.

13 Sims EA. Are there persons who are obese, but metabolically healthy? *Metabolism* 2001; **50:** 1499–504.

14 Odegaard JI, Chawla A. Pleiotropic actions of insulin resistance and inflammation in metabolic homeostasis. *Science* 2013; **339:** 172–77.

15 Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. *Nature* 2001; **414:** 799–806.

16 Leitzmann MF, Moore SC, Koster A, et al. Waist circumference as compared with body-mass index in predicting mortality from specific causes. *PLoS One* 2011; **6:** e18582.

17 Kantartzis K, Thamer C, Peter A, et al. High cardiorespiratory fitness is an independent predictor of the reduction in liver fat during a lifestyle intervention in non-alcoholic fatty liver disease. *Gut* 2009; **58:** 1281–88.

18 Kuk JL, Ardern CI. Are metabolically normal but obese individuals at lower risk for all-cause mortality? *Diabetes Care* 2009; **32:** 2297–99.

19 Arnlov J, Ingelsson E, Sundstrom J, Lind L. Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. *Circulation* 2010; **121:** 230–36.

20 Calori G, Lattuada G, Piemonti L, et al. Prevalence, metabolic features, and prognosis of metabolically healthy obese Italian individuals: the Cremona Study. *Diabetes Care* 2011; **34:** 210–15.

21 Bo S, Musso G, Gambino R, et al. Prognostic implications for insulin-sensitive and insulin-resistant normal-weight and obese individuals from a population-based cohort. *Am J Clin Nutr* 2012; **96:** 962–69.

22 Durward CM, Hartman TJ, Nickols-Richardson SM. All-cause mortality risk of metabolically healthy obese individuals in NHANES III. *J Obes* 2012; **2012:** 460321.

23 Hinnouho GM, Czernichow S, Dugravot A, Batty GD, Kivimaki M, Singh-Manoux A. Metabolically healthy obesity and risk of mortality: does the definition of metabolic health matter? *Diabetes Care* 2013; published online May 1. DOI:10.2337/dc12-1654.

24 Wei M, Kampert JB, Barlow CE, et al. Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight, and obese men. *JAMA* 1999; **282:** 1547–53.

25 Stevens J, Cai J, Evenson KR, Thomas R. Fitness and fatness as predictors of mortality from all causes and from cardiovascular disease in men and women in the lipid research clinics study. *Am J Epidemiol* 2002; **156:** 832–41.

26 Sui X, LaMonte MJ, Laditka JN, et al. Cardiorespiratory fitness and adiposity as mortality predictors in older adults. *JAMA* 2007; **298:** 2507–16.

27 Farrell SW, Fitzgerald SJ, McAuley PA, Barlow CE. Cardiorespiratory fitness, adiposity, and all-cause mortality in women. *Med Sci Sports Exerc* 2010; **42:** 2006–12.

28 McAuley PA, Kokkinos PF, Oliveira RB, Emerson BT, Myers JN. Obesity paradox and cardiorespiratory fitness in 12,417 male veterans aged 40 to 70 years. *Mayo Clin Proc* 2010; **85:** 115–21.

29 Ortega FB, Lee DC, Katzmarzyk PT, et al. The intriguing metabolically healthy but obese phenotype: cardiovascular prognosis and role of fitness. *Eur Heart J* 2013; **34:** 389–97.

30 Kip KE, Marroquin OC, Kelley DE, et al. Clinical importance of obesity versus the metabolic syndrome in cardiovascular risk in women: a report from the Women's Ischemia Syndrome Evaluation (WISE) study. *Circulation* 2004; **109:** 706–13.

31 Hamer M, Stamatakis E. Metabolically healthy obesity and risk of all-cause and cardiovascular disease mortality. *J Clin Endocrinol Metab* 2012; **97:** 2482–88.

32 Choi KM, Cho HJ, Choi HY, et al. Higher mortality in metabolically obese normal weight people than in metabolically healthy obese subjects in elderly Koreans. *Clin Endocrinol (Oxf)* 2013; published online Jan 18. DOI: 10.1111/cen.12154.

33 Stefan N, Fritsche A, Häring HU. Letter by Stefan et al regarding article, "Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men". *Circulation* 2010; **122:** e456.

34 Appleton SL, Seaborn CJ, Visvanathan R, et al. Diabetes and cardiovascular disease outcomes in the metabolically healthy obese phenotype: a cohort study. *Diabetes Care* 2013; published online Mar 14. DOI:10.2337/dc12-1971.

35 Kim JY, van de Wall E, Laplante M, et al. Obesity-associated improvements in metabolic profile through expansion of adipose tissue. *J Clin Invest* 2007; **117:** 2621–37.

36 Garg A. Lipodystrophies: genetic and acquired body fat disorders. *J Clin Endocrinol Metab* 2011; **96:** 3313–25.

37 Kusminski CM, Holland WL, Sun K, et al. MitoNEET-driven alterations in adipocyte mitochondrial activity reveal a crucial adaptive process that preserves insulin sensitivity in obesity. *Nat Med* 2012; **18:** 1539–49.

38 Herman MA, Peroni OD, Villoria J, et al. A novel ChREBP isoform in adipose tissue regulates systemic glucose metabolism. *Nature* 2012; **484:** 333–38.

39 Denis GV, Obin MS. 'Metabolically healthy obesity': origins and implications. *Mol Aspects Med* 2013; **34:** 59–70.

40 Kloting N, Fasshauer M, Dietrich A, et al. Insulin-sensitive obesity. *Am J Physiol Endocrinol Metab* 2010; **299:** E506–15.

41 Fabbrini E, Magkos F, Mohammed BS, et al. Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. *Proc Natl Acad Sci USA* 2009; **106:** 15430–35.

42 Kantartzis K, Machann J, Schick F, Fritsche A, Häring HU, Stefan N. The impact of liver fat vs visceral fat in determining categories of prediabetes. *Diabetologia* 2010; **53:** 882–89.

43 Tiikkainen M, Bergholm R, Vehkavaara S, et al. Effects of identical weight loss on body composition and features of insulin resistance in obese women with high and low liver fat content. *Diabetes* 2003; **52:** 701–07.

44 D'Adamo E, Cali AM, Weiss R, et al. Central role of fatty liver in the pathogenesis of insulin resistance in obese adolescents. *Diabetes Care* 2010; **33:** 1817–22.

45 Liu J, Musani SK, Bidulescu A, et al. Fatty liver, abdominal adipose tissue and atherosclerotic calcification in African Americans: the Jackson Heart Study. *Atherosclerosis* 2012; **224:** 521–25.

46 Sung KC, Jeong WS, Wild SH, Byrne CD. Combined influence of insulin resistance, overweight/obesity, and fatty liver as risk factors for type 2 diabetes. *Diabetes Care* 2012; **35:** 717–22.

47 Shibata M, Kihara Y, Taguchi M, Tashiro M, Otsuki M. Nonalcoholic fatty liver disease is a risk factor for type 2 diabetes in middle-aged Japanese men. *Diabetes Care* 2007; **30:** 2940–44.

48 Kim CH, Park JY, Lee KU, Kim JH, Kim HK. Fatty liver is an independent risk factor for the development of Type 2 diabetes in Korean adults. *Diabet Med* 2008; **25:** 476–81.

49 Bae JC, Rhee EJ, Lee WY, et al. Combined effect of nonalcoholic fatty liver disease and impaired fasting glucose on the development of type 2 diabetes: a 4-year retrospective longitudinal study. *Diabetes Care* 2011; **34:** 727–29.

50 Sung KC, Kim SH. Interrelationship between fatty liver and insulin resistance in the development of type 2 diabetes. *J Clin Endocrinol Metab* 2011; **96:** 1093–97.

51 Stefan N, Häring HU. The metabolically benign and malignant fatty liver. *Diabetes* 2011; **60:** 2011–17.

52 Stefan N, Häring HU. The role of hepatokines in metabolism. *Nat Rev Endocrinol* 2013; **9:** 144–52.

53 Pal D, Dasgupta S, Kundu R, et al. Fetuin-A acts as an endogenous ligand of TLR4 to promote lipid-induced insulin resistance. *Nat Med* 2012; published online July 29. DOI:10.1038/nm.2851.

54 Stefan N, Häring HU. Circulating fetuin-A and free fatty acids interact to predict insulin resistance in humans. *Nat Med* 2013; **19:** 394–95.

55 Stefan N, Machicao F, Staiger H, et al. Polymorphisms in the gene encoding adiponectin receptor 1 are associated with insulin resistance and high liver fat. *Diabetologia* 2005; **48:** 2282–91.

56 Doumatey AP, Bentley AR, Zhou J, Huang H, Adeyemo A, Rotimi CN. Paradoxical Hyperadiponectinemia is Associated With the Metabolically Healthy Obese (MHO) Phenotype in African Americans. *J Endocrinol Metab* 2012; **2:** 51–65.

57 Cariou B, Charbonnel B, Staels B. Thiazolidinediones and PPARgamma agonists: time for a reassessment. *Trends Endocrinol Metab* 2012; **23:** 205–15.

58 Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA* 2007; **298:** 1180–88.

59 Karelis AD, Messier V, Brochu M, Rabasa-Lhoret R. Metabolically healthy but obese women: effect of an energy-restricted diet. *Diabetologia* 2008; **51:** 1752–54.

60 Kantartzis K, Machann J, Schick F, et al. Effects of a lifestyle intervention in metabolically benign and malign obesity. *Diabetologia* 2011; **54:** 864–68.

61 Janiszewski PM, Ross R. Effects of weight loss among metabolically healthy obese men and women. *Diabetes Care* 2010; **33:** 1957–59.

62 Lempiainen P, Mykkanen L, Pyorala K, Laakso M, Kuusisto J. Insulin resistance syndrome predicts coronary heart disease events in elderly nondiabetic men. *Circulation* 1999; **100:** 123–28.

63 Adams TD, Davidson LE, Litwin SE, et al. Health benefits of gastric bypass surgery after 6 years. *JAMA* 2012; **308:** 1122–31.

64 Eckel RH. Clinical practice. Nonsurgical management of obesity in adults. *N Engl J Med* 2008; **358:** 1941–50.

65 Sjostrom L, Peltonen M, Jacobson P, et al. Bariatric surgery and long-term cardiovascular events. *JAMA* 2012; **307:** 56–65.

66 Sjostrom L. Review of the key results from the Swedish Obese Subjects (SOS) trial: a prospective controlled intervention study of bariatric surgery. *J Intern Med* 2013; **273:** 219–34.

67 Sjostrom L, Narbro K, Sjostrom CD, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med* 2007; **357:** 741–52.

68 Sjostrom L, Gummesson A, Sjostrom CD, et al. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. *Lancet Oncol* 2009; **10:** 653–62.

69 Livingston EH. Inadequacy of BMI as an indicator for bariatric surgery. *JAMA* 2012; **307:** 88–89.

70 NHLBI Obesity Education Initiative Expert Panel on the Identification, Evaluation, and Treatment of Obesity in Adults (US). Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. *Arch Intern Med* 1998; **158:** 1855–67.

71 Estruch R, Ros E, Salas-Salvado J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013; **368:** 1279–90.

72 Weintraub WS, Daniels SR, Burke LE, et al. Value of primordial and primary prevention for cardiovascular disease: a policy statement from the American Heart Association. *Circulation* 2011; **124:** 967–90.

73 Mechanick JI, Youdim A, Jones DB, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient–2013 update: Cosponsored by american association of clinical endocrinologists, The obesity society, and american society for metabolic & bariatric surgery. *Obesity (Silver Spring)* 2013; **21** (suppl 1)**:** S1–S27.

74 Despres JP. What is "metabolically healthy obesity"?: from epidemiology to pathophysiological insights. *J Clin Endocrinol Metab* 2012; **97:** 2283–85.