Check for updates

Received: 12 October 2022 | Revised: 23 July 2023 | Accepted: 11 August 2023

DOI: 10.1002/dmrr.3725

WILEY

REVIEW ARTICLE

Phenotyping obesity: A focus on metabolically healthy obesity and metabolically unhealthy normal weight

Rachel Agius[1,2] | Nikolai P. Pace[1] | Stephen Fava[1,2]

[1]University of Malta Medical School, Msida, Malta

[2]Mater Dei Hospital, Msida, Malta

Correspondence
Stephen Fava, University of Malta Medical School, Msida MSD2090, Malta.
Email: stephen.fava@um.edu.mt

Abstract

Over the past 4 decades, research has shown that having a normal body weight does not automatically imply preserved metabolic health and a considerable number of lean individuals harbour metabolic abnormalities typically associated with obesity. Conversely, excess adiposity does not always equate with an abnormal metabolic profile. In fact, evidence exists for the presence of a metabolically unhealthy normal weight (MUHNW) and a metabolically healthy obese (MHO) phenotype. It has become increasingly recognised that different fat depots exert different effects on the metabolic profile of each individual by virtue of their location, structure and function, giving rise to these different body composition phenotypes. Furthermore, other factors have been implicated in the aetiopathogenesis of the body composition phenotypes, including genetics, ethnicity, age and lifestyle/behavioural factors. Even though to date both MHO and MUHNW have been widely investigated and documented in the literature, studies report different outcomes on long-term cardiometabolic morbidity and mortality. Future large-scale, observational and population-based studies are required for better profiling of these phenotypes as well as to further elucidate the pathophysiological role of the adipocyte in the onset of metabolic disorders to allow for better risk stratification and a personalised treatment paradigm.

KEYWORDS
insulin resistance, metabolic syndrome, metabolically healthy obesity (MHO), metabolically unhealthy normal weight (MUHNW), obesity

1 | INTRODUCTION

Obesity is a chronic, complex relapsing disease whereby excessive or abnormal fat accumulation may impair health.[1] In 2017, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE), coined the phrase 'adiposity-based chronic disease (ABCD)' to be the new diagnostic term for obesity.[2] This term allows better characterisation of obesity by incorporating pathophysiology with disease chronicity and complexity.[3] Central obesity is a well-established causal factor in the development of insulin resistance (IR) and cardiometabolic risk factors (dysglycaemia, hypertension, and atherogenic dyslipidaemia), which predispose to adverse cardiovascular outcomes and to type 2 diabetes (T2 DM).[4,5]

A body mass index (BMI) cut-off value of ≥30 kg/m^2 is widely used to define obesity. This threshold stems from the dose-dependent relationship between increasing BMI and the risk of adverse cardiometabolic outcomes and mortality at the population level.[6] The BMI correlates with percentage body fat and is a practical clinical metric to gauge and assess obesity. Notwithstanding, at an individual-level, BMI does not sufficiently reflect total body adiposity. Specifically, it does not differentiate between three entities: body composition (fat mass vs. fat-free mass), body fat distribution (upper

 © 2023 John Wiley & Sons Ltd.

body [truncal] vs. lower body [gluteofemoral]; subcutaneous vs. visceral/ectopic fat) and adipocyte function. These three factors play a central role in the onset of adiposopathy, which, in turn, contributes to the development of cardiometabolic diseases.[7] Cardiometabolic risk varies across individuals with identical BMI since the pathogenic potential of excess adiposity is also driven by fat distribution and function, as reviewed by Pujia et al. and by Blüher.[8,9] This has led to the concept of different body composition phenotypes which incorporate both the BMI and metabolic health (MH).[10] The rationale for simultaneously considering MH with BMI stems from observations on a subset of obese individuals who present with a healthy metabolic profile, termed 'metabolically healthy obesity' (MHO).[9,11,12] Conversely, individuals with normal-range BMI who are hyperinsulinaemic and insulin resistant display a dysfunctional metabolic profile similar to that in obese individuals. This defines the 'metabolically unhealthy normal weight' (MUHNW) phenotype.[13–15] Thus, obesity is a metabolically heterogeneous disorder and different obesity-related phenotypes should be considered based on the inter-individual variability in body composition as well as in MH. However, it should be noted that various authors have reported that up to 50% of MHO individuals may transition to metabolically unhealthy obese (MUHO) within 10 years.[16–18] These phenotypes should therefore be regarded as dynamic states.

This review aims to evaluate the concept and aetiopathogenesis of both MHO and MUHNW through an assessment of their epidemiology, diagnostic criteria, and clinical and therapeutic relevance. A detailed appraisal of data from cross-sectional and prospective/longitudinal studies and consensuses obtained from systematic reviews and meta-analyses is included. A literature search using Pubmed/Medline and Google Scholar databases was carried out to identify original studies, systematic reviews and meta-analyses which looked at the characteristics, natural course, long-term outcomes and management of metabolically healthy obesity and metabolically unhealthy normal weight. The search was based on the following medical subject headings (MeSH): 'metabolically healthy obesity', 'MHO', 'metabolically unhealthy normal weight', 'MUHNW', 'obesity phenotype', 'body mass index', 'metabolic health', 'adipose tissue dysfunction', adiposopathy', in combination with 'cardiometabolic disease', 'type 2 diabetes', 'mortality', 'transition', 'dietary intervention', 'obesity management', 'exercise' and 'bariatric surgery'. Additionally, a manual search of the bibliographies of retrieved articles was carried out. Only articles written in the English language and published in peer-reviewed journals up to February 2023 were considered.

2 | DEFINITION AND PREVALENCE OF MHO AND MUHNW

Multiple criteria have been used to classify MH. Most epidemiological studies have defined MH based on the metabolic syndrome (Met S) criteria proposed by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III),[19] the International Diabetes Federation (IDF)[20] or the Joint Interim Statement ([JIS]).[21] Other studies use a combination of several cardiometabolic parameters and/or insulin resistance indices to define MH. The later include the hyperinsulinemic-euglycemic clamp, insulin sensitivity index (ISI) following an oral glucose tolerance test, the insulin suppression test, the Matsuda index, or the homoeostatic model assessment of insulin resistance (HOMA-IR). In addition, a combination of cardiorespiratory fitness and inflammatory, fibrinolytic, or immune function parameters have also been incorporated into MH definitions.[22–32] Alternatives to the BMI to assess adiposity include the waist circumference (with sex-specific cut-offs) and body fat percentage (BF%) assessed by a variety of methods such as dual energy absorptiometry (DXA), bioelectrical impedance, skin fold thickness, or hydrostatic weighing. These criteria lead to marked differences in both obesity and MHO/MUHNW prevalence within and between different populations.[33–36] Importantly, harmonisation criteria have been put forward by Lavie et al.,[5] and more recently Zembic et al. derived an empirical definition for MH based on data from the NHANES III and UK Biobank.[2,37]

Generally, MHO individuals exhibit a healthier metabolic and biochemical profile when compared to unhealthy obese individuals, including lower blood pressure and favourable lipid and glycaemic profiles; thus, several authors use these parameters to classify MHO.[22,31,38–41] In addition, studies also report improved renal function, lower levels of hepatic enzymes and a more favourable adipokine profile (high adiponectin and low leptin levels) in MHO individuals compared to MUHO.[24,29,41,42] Hormonal differences within the entero-insular axis following a glucose load (reduced glucose-dependent insulinotropic polypeptide [GIP] and glucagon levels and higher levels of glucagon-like peptide-1 [GLP-1]) in MHO individuals are also reported. These may, in part, contribute to the lower propensity for T2DM observed in MHO.[43] A summary of the various parameters used to define MH in most studies is represented in Supplementary Table S1.

The global prevalence estimates stand at 35% for MHO among obese individuals and 30% for MUHNW among normal weight subjects.[44,45] These statistics are partly definition-dependent and may merely reflect the *a priori* criteria used to define MH. Typically, the MHO phenotype is more prevalent in females and in non-Hispanic whites, whereas the prevalence of the MUHNW phenotype is higher in males and increases with age. Interestingly, when more stringent criteria (no cardiometabolic abnormalities) are used to define MH, only 16.6% of obese individuals are classified as MHO.[22] Conversely, using sex-specific waist circumference cut-offs to denote obesity, a higher percentage of non-abdominally obese individuals were metabolically unhealthy (28.3%), while 36.4% of subjects with abdominal obesity could be defined as metabolically healthy.[22] Liu et al. also corroborated these findings within a Chinese cohort and reported a 3-fold range in the prevalence of MHO when different definitions for MH were applied to the same population.[46] Evidence from systematic reviews shows that MHO prevalence ranges from 6% to 75% in global populations and identified 30 different definitions of MH.[47] These findings thus highlight that prevalence

15207560, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3725 by CAS - Wuhan Library of CAS, Wiley Online Library on [11/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

estimates for each body composition phenotype reported by various authors are definition-dependent. The use of consensus criteria should in future help to reduce such heterogeneity.

Multiple factors, including genetic, ethnic, and secular lifestyle changes, could also contribute to differences in the prevalence of body composition phenotypes reported in the literature. MHO prevalence is inversely correlated with age.[22,44,47] Increasing age is associated with sarcopenia, increased body fat and a predilection for visceral fat deposition.[48,49] Unexpectedly, a higher MHO prevalence was reported in Asians.[47] Individuals of Asian ethnicity have a tendency to accrue fat in visceral and ectopic areas and consequently have a lower degree of insulin sensitivity for a given BMI, thus rendering them at higher metabolic risk.[7,50] Sociocultural factors, including diet and lifestyle, can contribute to the observed ethnic variability in prevalence rates for the MHO.[44] Recently, Zembic et al. derived an empirical definition for MH based on anthropometric and metabolic factors known to be associated with increased cardiovascular and total mortality risk from the NHANES III and UK Biobank dataset.[37] Using this definition, MHO individuals were not at an increased risk of cardiovascular or all-cause mortality when compared to healthy normal weight individuals, while individuals who were classified as metabolically unhealthy (irrespective of their BMI) displayed increased risks.

Likewise, extensive variation (5%–45%) in the prevalence of MUHNW in the general population has been reported, with this also being dependent on the population and criteria used.[14,22,30,51,52] Again, the use of consensus criteria to define MH should help to remove definition-related variability. Gujral et al. reported that the prevalence of MUHNW was higher in all racial/ethnic minority groups compared with Whites, although conflicting findings have been published.[52] Some clinical biomarkers of MUHNW have been proposed, including the triglyceride-glucose index (TyG), serum ferritin and hepatic fat content.[53–55] Although the use of ultrasonography to quantify hepatic fat is impractical as a screening tool, calculated indices including Fibrosis-4 Index (FIB-4), the NAFLD fibrosis score (NFS) and the hepatic steatosis index (HSI) predict metabolic abnormalities, T2 DM, kidney disease, cancer and overall mortality. These scores use routinely available parameters, making them more accessible clinically.[56–58]

A different obesity phenotype, namely the normal weight obese individual (NWO) has also been proposed.[59] This is defined as the presence of a high total body fat content (>30%) and a lower amount of lean mass in normal weight individuals. NWO individuals have fasting hyperglycaemia, dyslipidaemia, insulin resistance, higher oxidative stress and a proinflammatory profile compared with healthy normal weight individuals. This increases cardiometabolic risk after adjusting for central obesity.[35,60,61]

A further phenotype is that of sarcopenic obesity, which is defined as an increased BMI or waist circumference and markers of low skeletal muscle mass and function.[62] It is thought that obesity-associated systemic inflammation accelerates muscle catabolism leading to sarcopenia.[63] The loss of muscle mass in turn exacerbates insulin resistance, since muscle is a major insulin-sensitive organ, resulting in a vicious cycle. The prevalence of sarcopenic obesity increases with increasing age[64] and is associated with diabetes, prediabetes, hepatic steatosis and cardiovascular disease.[64,65]

3 | PROPOSED AETIOPATHOLOGICAL MECHANISMS UNDERLYING THE MHO AND MUHNW PHENOTYPES: CHARACTERISTICS AND DETERMINANTS

3.1 | Adiposopathy: Adipose tissue biology and function

Several factors are implicated in the metabolic heterogeneity observed across BMI categories, including the dysregulation of adipose tissue function (adiposopathy). It is increasingly recognised that individuals with preserved MH have favourable adipocyte composition, distribution and functional patterns.[66,67] The primary features that characterise adiposopathy include reduced adipose tissue expandability and impaired adipogenesis, altered lipid metabolism as well as adipose tissue inflammation together with a proinflammatory adipokine profile[7,68,69] (Figure 1). There is evidence that obesity is associated with a reduction in adipose tissue glutamine levels as a result of altered expression of glutamine-metabolising genes and that this induces transcriptional activity of pro-inflammatory pathways.[70] Oral glutamine administration has been shown to reduce adiposity and improve insulin sensitivity in both high-fat fed Wistar rats and in humans.[71] It has also been recently reported that MHO adolescents have higher glutamine and glutamine/glutamate ratios compared to MUHO.[72]

There are important adipose site-specific effects on health outcomes. While the subcutaneous adipose tissue (SAT) compartment is the main fat storage depot, adipose tissue at other anatomic regions plays critical roles in the development of cardiometabolic disorders.[7,73,74] These regions include visceral adipose tissue (VAT) and adipose tissue in ectopic sites such as the liver, heart, pancreas, and skeletal muscle.[7,74] Advanced imaging techniques have enabled improved characterisation of these depots.[7,75] These depots differ in endocrine function and in adipocytokine secretion patterns that may partly underlie the varying metabolic abnormalities observed in obesity phenotypes.[69,76,77] As the primary triglyceride (TG) reservoir, subcutaneous adipocytes expand through hyperplasia in response to caloric excess, leading to an increase in small adipocytes with normal functionality and preserved insulin sensitivity. However, SAT has a finite expansion capacity, resulting in an overspill into the visceral and ectopic compartments. Visceral/ectopic adipocytes are more metabolically active and thus induce systemic inflammation, IR and hyperglycaemia.[78,79] The *adipose tissue expandability hypothesis* implies that during periods of sustained excess of calorie intake, the limited degree of SAT plasticity predisposes towards the accumulation of fat in visceral and ectopic sites, thereby leading to lipotoxicity and the subsequent development of metabolic disturbances.[80,81] Hyperinsulinemia can in turn lead to adipocyte senescence and cell

15207560, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3725 by CAS - Wuhan Library of CAS, Wiley Online Library on [11/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

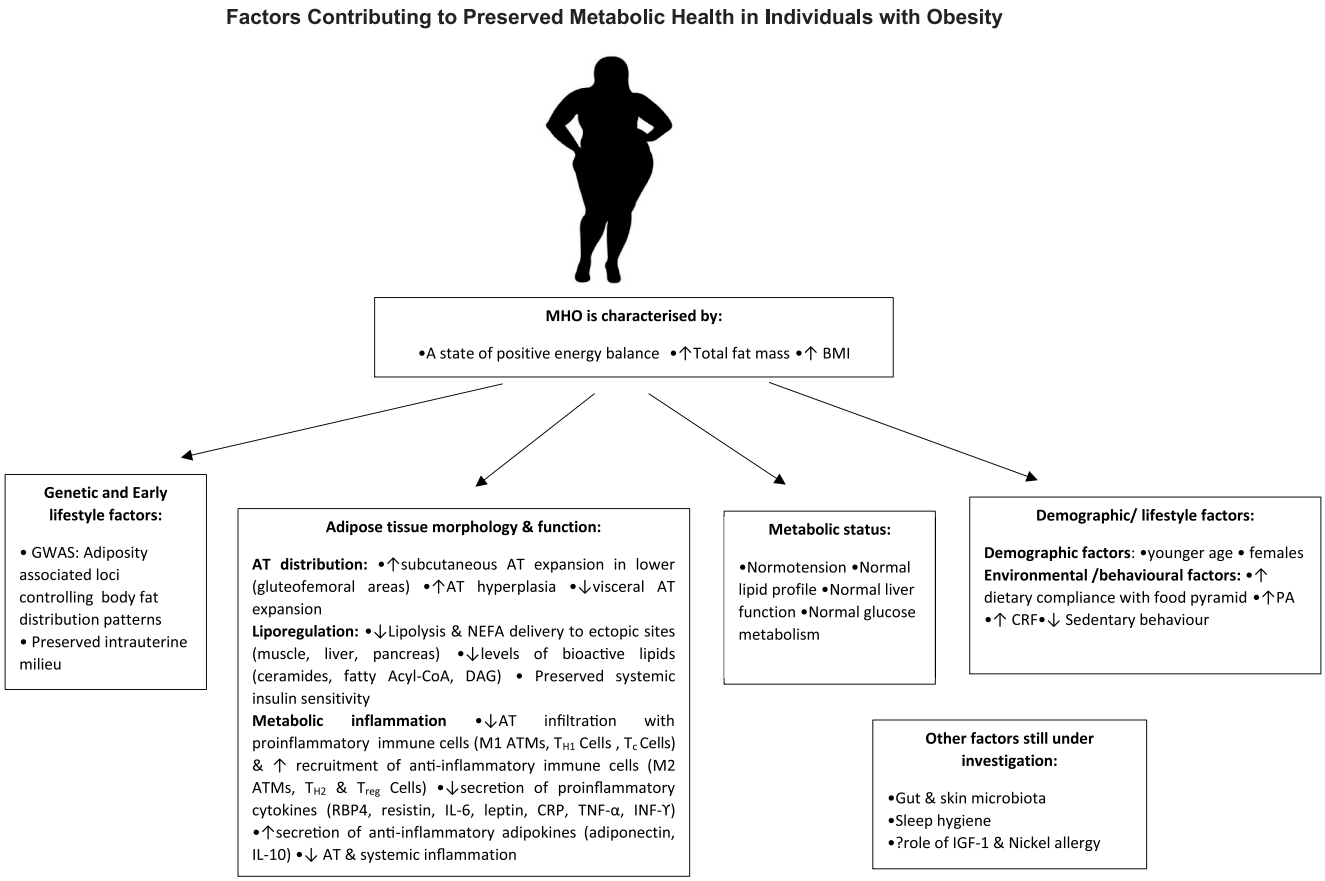

FIGURE 1 Proposed aetiopathological mechanisms differentiating the metabolically healthy obese from the metabolically unhealthy obese phenotype. Despite a state of positive energy balance and high total body fat and BMI, MHO is typically associated with genes relating to favourable body fat distribution patterns, preserved adipocyte morphology and function, a normal metabolic and insulin sensitivity status and certain demographic and lifestyle characteristics compared to MUHO. AT, adipose tissue; ATM, adipose tissue macrophages; BMI, body mass index; CRF, cardiorespiratory fitness; CRP- C-reactive protein; DAG, diacyl glycerol; GWAS, genome wide association studies; IGF-1, insulin-like growth factor-1; IL, interleukin; INF- ϒ, interferon- ϒ; MHO, metabolically healthy obesity; MUHO, metabolically unhealthy obesity; NEFA, non- esterified fatty acids; PA, physical activity; RBP4, retinol binding protein 4; T_H, helper T cells; T_c, cytotoxic T cells; T_{reg}, regulatory T cells; TNF-α, tumour necrosis factor- α.

cycle exit,[82] thereby resulting in a vicious cycle. Several lines of evidence support this hypothesis. In lean individuals, a lower proportion of subcutaneous gluteofemoral fat mass is the strongest predictor of the MUHNW. Furthermore, increased leg fat mass correlates with higher insulin sensitivity and a favourable metabolic profile.[15] The Women's Health Initiative Study demonstrated that reduced gluteofemoral fat mass is associated with a higher incidence of cardiometabolic diseases independently of truncal fat mass, further supporting the notion that adipose tissue within the peripheral gluteofemoral areas allows for the healthy storage of excess fat.[83] Similarly, despite a similar BMI, MHO individuals have a lower WC than MUHO individuals due to reduced VAT and hepatic fat. In response to weight gain, MHO individuals expand the SAT compartment, whereas MUHO individuals are more likely to gain fat in the visceral regions.[28,84–86] Although the exact mechanisms by which VAT/ectopic fat depots drive the dysmetabolic state are not fully elucidated, evidence supports VAT as a dysfunctional depot characterised by abnormal adipogenesis (hypertrophied adipocytes rather than hyperplasia) and inflammatory/immune dysregulation with resultant production of proinflammatory adipocytokines.[7,68] Furthermore, adipogenic progenitors have been reported to be more abundant in SAT than in VAT in mice fed a high-fat diet, and that a high-fat diet induces adipogenic progenitor proliferation in SAT but not in VAT.[87] The predilection for fat storage in subcutaneous versus visceral regions depends on multiple factors. Increasing age, male gender, senescence, smoking, physical inactivity and high fat or fructose diets favour an increase in VAT,[77, 84,88] possibly through epigenetic changes.[89]

The relationship between the expansion of VAT/ectopic fat depots and insulin resistance can be partially explained by the *lipotoxicity hypothesis*. Studies in support of this mechanism have shown that experimental delivery of non-esterified fatty acids (NEFA) into the circulation reduces β-cell insulin secretion and impairs hepatocyte/muscle insulin sensitivity, thereby reproducing the basic defects observed in T2DM.[7,77,90] Within skeletal muscle, increased intramyocellular lipid leads to insulin resistance, decreased glucose uptake

15207560, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3725 by CAS - Wuhan Library of CAS, Wiley Online Library on [11/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

and reduced glycogen synthesis. Increased NEFA delivery to pancreatic β-cells leads to impaired insulin secretion, which exacerbates lipolysis and further propagates the influx of NEFA within the circulation.[77,91,92] Delivery of NEFA to the liver (from both VAT and SAT depots) leads to hepatic IR, lipogenesis, and gluconeogenesis. These factors contribute to the observed relationship between abdominal adiposity, IR and dyslipidaemia.[7,93–95] Moreover, NEFAs are pro-inflammatory, leading to reactive oxygen species (ROS) generation, endothelial cell damage and the formation of a proatherogenic vascular milieu that exacerbates cardiovascular risk.[96] A large body of evidence also demonstrates that visceral fat exhibits distinct morphological and functional features from subcutaneous fat. VAT expansion through hypertrophy generates larger dysmorphic adipocytes and inefficient remodelling of the extracellular matrix with impaired vascularisation. This process results in hypoxia and adipose tissue inflammation. The *inflammation hypothesis* centres around the pro-inflammatory response induced by dysmorphic adipose tissue, infiltrated by pro-inflammatory M1 macrophages, leading to the generation of multiple inflammatory adipocytokines (such as tumour necrosis factor [TNF]-α, interleukin [IL]-6, resistin, retinol binding protein [RBP]-4, leptin and angiotensin II), which drive insulin resistance and metabolic abnormalities.[69,77,97,98] MHO is characterised by a favourable inflammatory profile including a decrease in the production of pro-inflammatory adipokines outlined above and, conversely, increased anti-inflammatory adipokine production (including adiponectin, IL-4, IL-10, IL-13).[28,92,99–101]

Likewise, the MUHNW phenotype also presents with abnormal body composition and body fat distribution patterns, including higher VAT, liver and muscle fat content and reduced skeletal muscle mass, leading to the metabolic derangement typical of obesity.[86,102] Despite a normal-range BMI, MUHNW individuals exhibit a proinflammatory adipocytokine profile and increased cardiovascular risk.[15,86,97] In MUHNW, a greater proportion of body fat has been documented, with the risk of metabolic abnormality correlating with body fat percentage in both males and females.[103] In young lean subjects, the percentage body fat represents the single strongest predictor of low insulin sensitivity.[86] However, some investigators have failed to identify differences in percent body fat between healthy and unhealthy normal weight subjects.[104,105] Furthermore, in the NHANES III cohort, normal weight subjects with central obesity (as determined by a raised WHR) had the worst long-term survival outcome compared to all other body composition phenotypes.[106] Such findings reinforce increased visceral fat, fatty liver, and lower body fat mass as important cardiometabolic risk components. A recent epidemiologic analysis in a subset of normal weight women from the Women's Health Initiative reported inverse correlations between leg fat mass and CVD risk, and positive correlations between truncal fat and CVD risk.[83] These findings are consistent with evidence from adipose tissue biopsy studies in humans whereby inadequate expansion of lower body adipocytes and impaired adipogenesis results in 'adipose overflow' with resultant ectopic deposition of lipids in the visceral areas giving rise to lipotoxicity and increased cardiometabolic risk.[29,107]

Recent investigations sought to further explore the pathophysiological continuum between the MUHNW phenotype and unhealthy obesity.[15,108] Within the general population, some lean individuals exhibit features akin to the lipodystrophy syndromes (paucity of subcutaneous fat, hepatic steatosis, and severe IR) which drive cardiometabolic risk. In individuals with a lipodystrophy-like phenotype, a lower percentage of subcutaneous leg fat mass and relative insulin deficiency are the major drivers of metabolic ill-health.[15]

3.2 | Genetic contribution to MHO and MUHNW

Obesity is a polygenic trait, regulated by complex gene-environment interactions and transgenerational epigenetic mechanisms. Although multiple pathways are implicated in the development of obesity and alternate fat distribution patterns, the exact genetic mechanisms causing MHO are undetermined.[109]

Genome-wide association studies (GWAS) have identified several loci associated with body fat distribution patterns and the development of metabolic abnormalities independently of BMI. GWAS have also enabled the construction of polygenic risk scores characterising different obesity phenotypes.[110,111] Typically, GWAS-identified variants exert small effect sizes on BMI when considered in isolation and explain a minimal proportion of the phenotypic variance in BMI.[112] Conversely, the consideration of polygenic risk scores that aggregate the effect of multiple variants as a single polygenic predictor has been shown to robustly stratify the risk of severe obesity and cardiometabolic disease in adults.[113]

Adiposity related traits, such as the WHR, have high heritability estimates (60%) and polymorphisms in several loci (including *TBX15*, *RSP03*, *HOXC13*) are related to body fat distribution.[114] The MHO phenotype is associated with variants related to a lower risk of cardiometabolic abnormalities despite a higher BMI. This reinforces the notion of a distinct genetic component driving different adipose distribution patterns.[110,111] A recent GWAS meta-analysis suggests that the heritability of fat distribution is stronger in females than in males, and that approximately one-third of all signals are sexually dimorphic.[115]

Functionally, adiposity-related signals identified by GWAS are enriched for genes involved in adipocyte differentiation, adipogenesis, and transcriptional regulation of insulin signalling and lipolysis.[116] There is also evidence that genes linked to adipogenesis are differentially methylated in obesity.[117] Furthermore, distinct adipocyte gene expression patterns distinguish MHO from MUHO.[118] Importantly, differentially expressed transcripts are linked to cardiovascular disease, inflammatory pathways and branched chain amino acid catabolism.[95,102]

Genetic factors also impact on the various ways by which adipose fat depots store energy. The *adipose tissue expandability hypothesis* outlined earlier relates to the transition of normal adipose tissue to one which leads to metabolic derangement characterised by adipocyte hypertrophy. Strong support for this hypothesis comes from pharmacological studies of peroxisome proliferator-activated

15207560, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3725 by CAS - Wuhan Library of CAS, Wiley Online Library on [11/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

receptor- γ (PPARγ) activation in both murine and human studies.[12,116,119] Knock-out studies with PPARγ lipodystrophy murine models identified altered adipokine secretion patterns following saturation of adipose tissue. Treatment with thiazolidinediones (PPARγ agonists) results in an increase in adiponectin concentrations, expansion of subcutaneous adipose tissue, a decrease in liver fat content, and an increase in insulin sensitivity. Thus, thiazolidinediones might be a promising treatment approach in insulin-resistant individuals with non-alcoholic fatty liver disease or an increased risk of CVD.[120,121] The genetics of obesity extends beyond adipocyte biology to loci involved in satiety and appetite regulation. Recently, 27 variants previously associated with obesity have also been implicated in the regulation of food intake, energy expenditure, as well as food reward pathways.[122]

Additional molecular mechanisms are implicated in MHO. The systemic proinflammatory state and oxidative stress accompanying obesity and MetS have been associated with telomere attrition. Moreover, dynamic changes in adiposity lead to changes in telomere length (TL) such that weight loss leads to an increase in telomere length, whereas weight gain accelerates telomere attrition.[123] Limited data exist on telomere length in MHO versus MUHO, although MHO has been associated with higher TL.[124]

Mitochondrial bioenergetics and body composition are also interrelated. A reduction in the mtDNA copy number is generally associated with poor health through detrimental effects on ATP production, changes in mitochondrial gene-expression, or an altered oxidative stress response. Reduced skeletal muscle mtDNA content in T2DM patients has been described.[125–128] Additionally, a reduction in leucocyte mtDNA copy number is associated with obesity, IR, and Met-S.[129–132] Other studies further support mtDNA as a potential biomarker of metabolic disease and obesity, with mtDNA copy number independently associated with visceral fat accumulation in healthy young adults.[133,134] Bordoni et al. reported an association between lower buccal mtDNA copy number and an unfavourable body composition profile.[135] Further investigations are warranted in order to fully evaluate the role of mtDNA as a Met-S risk biomarker in obesity.

Much of the molecular evidence supporting MUHNW comes from studies which address a lipodystrophy-like phenotype in the general population. Seminal work by Yaghootkar et al. identified common alleles at loci (such as *IRS1*, *GRB14* and *PPARG*, *ARL15*), which demonstrate a genetic basis for the metabolically abnormal normal weight individual. A 'polygenic lipodystrophy' score composed of 11 common genetic variants shows associations with adverse metabolic traits, including an increased risk of hypertension, T2 DM, and coronary artery disease despite a lower BMI.[110,136] Recently, Lotta et al. also reported several loci which are associated with metabolic risk and coronary heart disease in individuals with lower percentage body fat, BMI, and lower gynoid and leg fat mass, thus providing additional evidence of the genetic contribution towards a 'lipodystrophy-like' phenotype in the general population.[137]

Accumulating evidence also reinforces the shared contribution of early life environmental and genetic factors. An adverse intrauterine milieu of either under- and over-nutrition has been linked to the 'thrifty phenotype', which predisposes to adult obesity and Met-S. In the early 90s, Hales and Barker postulated that poor foetal and early post-natal nutrition 'impose mechanisms of nutritional thrift on the growing individual' leading to impaired development of the endocrine pancreas and increased susceptibility to T2DM. Furthermore, they also suggested that infants whose 'birth weights were at the lower end of the normal range, who were thin or short at birth, or who were small in relation to placental size have increased rates of coronary heart disease'.[138,139] These factors act through complex epigenetic modifications.[140] More recent work suggests that there is a U-shaped relationship between birth weight and risk of cardiometabolic abnormalities, such that extremes of birth weight are both associated with obesity and Met-S in adolescence and adulthood.[141,142] However, conflicting findings have been reported. Some studies have shown that higher birth weight and early postnatal weight gain was associated with higher insulin sensitivity and lower hepatic insulin resistance reminiscent of the MHO phenotype, although the mechanisms around this relationship are unascertained.[143] More studies are required in this area to further identify modifiable risk factors for the MUHO phenotype. Another hypothesis is the 'thrifty genotype' hypothesis. This postulates that evolutionary selection of genes originally beneficial for energy storage during times of starvation could partly explain the current obesity and T2DM epidemics in the Westernised world, where caloric excess and sedentary behaviour predominate.[144]

3.3 | Lifestyle and behavioural factors

A growing body of research sheds light on the role of environmental/lifestyle factors as determinants of both MH and obesity. Most studies focus on the role of diet, physical fitness, age, smoking and alcohol intake as being a few of the potential contributors towards obesity and MH.[12,122,145,146] Changes in dietary intake and physical activity have both contributed to the obesity epidemic and may partly explain the metabolic heterogeneity in lean and obese individuals. The overconsumption of calorie dense food, in tandem with the global increase in urbanisation and sedentary behaviours, results in a state of positive energy imbalance leading to increased accumulation of adipose tissue and progression to overt obesity.[145,147]

Matheson et al. showed that adoption of four healthy lifestyle habits (modest alcohol intake, non-smoking, 30 min of exercise daily and eating five portions of fruit/vegetables daily) results in identical mortality risk in obese and lean individuals.[148] However, the precise contribution of each of these lifestyle factors to MHO is still unclear. Most studies did not report any differences in total energy intake, dietary macronutrient composition and quality between MHO and MUHO subjects. However, better compliance with the food pyramid recommendations increased the likelihood of a MHO phenotype.[122]

The beneficial effects of physical activity on the incidence of T2DM, CVD, obesity, cancer and all-cause mortality as well as the adverse effects of a sedentary lifestyle on metabolic outcomes are

15207560, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3725 by CAS - Wuhan Library of CAS, Wiley Online Library on [11/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

well-documented.[149–151] Physical activity and cardiorespiratory fitness characterises and maintains MH in individuals with obesity.[152,153] Physical activity is associated with increased fatty acid oxidation, leading to lower accumulation in the liver and visceral compartments.[154]

Smoking and alcohol consumption are widely studied modifiable lifestyle factors that impact MH. Wildman et al. and others showed that modest alcohol intake was associated with the MHO. This association is however disputed as conflicting findings showing no differences in alcohol and smoking habits between MHO and MUHO individuals have been published.[155] The effects of modest alcohol intake on both glucose and HDL-C levels are also well-documented; however, the adverse effects of excessive alcohol consumption include increased TG levels and increased abdominal obesity. Therefore, the link between alcohol consumption and MH may thus be bimodal.[156]

3.4 | Emerging endocrine disruptors and additional factors

Obesity, particularly visceral adiposity, is associated with lower serum IGF-1 levels and a blunted growth hormone (GH) response on dynamic testing.[157] IGF-1 is a liver-derived peptide with mitogenic and anabolic effects that mediates the actions of GH. It holds promise as a potential biomarker of MH, with MHO individuals having higher values for IGF-1 compared to MUHO. Incorporating IGF-1 levels into a machine learning model increased the accuracy for predicting the MHO and MUHO phenotypes.[158] Recently, pre-clinical studies have also implicated Nickel (Ni) as an endocrine disruptor. This is associated with the dysregulation of glucose metabolism as well as disruption of the GH-IGF-1 axis in human subjects. Nickel allergy has been observed to occur more frequently among Italian subjects with obesity. Furthermore, subjects with morbid obesity and nickel allergy exhibited a worse overall metabolic and body composition profile and an impaired GH response on dynamic testing.[159] Such findings implicate Ni exposure in the pathogenesis of obesity and hormonal dysregulation. There is also evidence that resistance to the effects of fibroblast growth factor 21 (FGF21) contributes to a metabolically unhealthy phenotype.[160] FGF21 is secreted mainly by the liver but also by other organs, such as adipose tissue and the pancreas.[161] It improves lipid and glucose parameters.[161] For this reason, it is also emerging as a marker for NAFLD,[162] fatty pancreas,[163] dysglycaemia,[164] cardiovascular disease[165] and mortality.[165,166] It also predicts the incidence of coronary artery disease, the metabolic syndrome, diabetes mellitus, renal progression in diabetes as well as all-cause and cardiovascular mortality.[167]

Metabolic and lifestyle factors are also relevant to MUHNW.[168] Eckel et al. observed that the traditional T2DM risk factors in obesity are also contributors to T2DM in lean subjects.[169] Furthermore, MUHNW females were more likely to have a higher intake of saturated fats and a lower polyunsaturated/saturated fatty acids ratio accompanied by lower dietary fibre intake than healthy normal weight females.[104] The effect of diet on the gut microbiome is discussed below. Most studies identify smoking status, alcohol consumption and lower education levels to be potential contributors to the MUHNW phenotype.[23,51,170] These findings were also supported in the meta-analysis by Wang et al.[44] Smoking is associated with decreased insulin sensitivity through multiple mechanisms, including sarcopenia.[171,172]

Sleep habits, including sleep quality and quantity, are associated with obesity, IR and Met-S,[173] with most studies reporting that short sleep duration is associated with adverse metabolic traits.[174–176] A single night of sleep deprivation was observed to decrease insulin sensitivity and increase NEFA levels in MHNW adults.[177] The pathophysiological mechanisms linking sleep deprivation with metabolic dysfunction involve complex central endocrine changes, such as lower levels of leptin, higher levels of ghrelin, loss of diurnal variation in cortisol secretion, as well as increased catecholamine production.[178,179] Sleep restriction also results in the loss of the beneficial effects of GH on muscle mass and fat distribution.[180] Sleep debt is also associated with an increased prediction towards the consumption of high-fat or carbohydrate-rich foods as well as reduced physical activity,[181] as a result of the aforementioned endocrine changes[181] and enhanced activation of brain reward and food-sensitive centres in response to unhealthy food.[182]

3.5 | Role of gut and skin microbiota

The gastrointestinal tract (GIT) modulates energy homoeostasis through its microbiome, which includes Gram-negative Bacteroidete and Probacteria and the Gram-positive Acenetobactieria and Firmicutes.[183,184] Typically, these microbes act in a symbiotic fashion with the human host by maintaining mucosal immunity, aiding the breakdown of complex non-absorbable plant-derived polysaccharides and maintaining energy homoeostasis. Alteration in the gut microbiome is associated with an increased risk of obesity. Reduction of *Bacteroidetes* species and a higher proportion of *Firmicutes* in obese versus lean states have been reported.[185,186] Furthermore, transfer of caecal bacteria from obese to germ-free (GF) lean mice induces an increase in adiposity.[187] The proposed mechanisms linking microbiomes to obesity and to a metabolically unhealthy phenotype include increased absorption of calories from the gut even in the absence of excess food intake.[188] It has been postulated that high-fat diets lead to microbial imbalances, which consequently cause an increase in the intestinal permeability and translocation of bacterial products (endotoxin lipopolysaccharide [LPS]) to the circulation. This incites hypertrophy of the mesenteric adipocytes and activation of proinflammatory pathways.[88,189] This relationship has been replicated in both human and animal studies, with positive correlations between intestinal permeability markers and anthropometric adiposity indices as well as the degree of liver and visceral fat and IR.[190,191] Importantly, significant differences in the microbial diversity and composition of gut microbiota between the MHO and MUHO phenotypes have been reported. Bacterial

15207560, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3725 by CAS - Wuhan Library of CAS, Wiley Online Library on [11/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

metabolites may also mediate the relationship between the microbiome and MH.[192] For example, metagenomics analysis in a large European population with severe obesity found altered bacterial biotin status to be associated with an inflammatory phenotype and altered metabolic profile. Depletion of gut microbiota by antibiotics in mice confirms the microbial contribution to host biotin levels.[192] Furthermore, oral biotin improved glycaemia in high-fat diet-fed mice.[193] Dietary fibre-induced changes in the gut microbiome can also significantly increase short-chain fatty acids production and decrease metabolically detrimental compounds such as indole and hydrogen sulphide thereby improving the metabolic profile.[194,195]

4 | NATURAL COURSE AND CLINICAL IMPLICATIONS OF MHO AND MUHNW

Another area which has been intensively investigated and widely debated relates to the long-term trajectories of MHO and MUHNW, particularly their natural course and clinical implications on cardiometabolic diseases and mortality. Prospective studies in several ethnicities show that MHO is a dynamic state that progressively degenerates into MUHO,[40] with up to 50% of MHO subjects transitioning to MUHO within 10 years.[16–18] Recently, machine-learning technology has been found to accurately predict the risk of developing MUHO at 5 or 10 years in a population of Italian patients with obesity.[158]

The preservation of MH is also transient among lean individuals, with only 30% of MHNW individuals remaining metabolically healthy after 20 years of follow up.[16] Most studies focus on a single transition (metabolic deterioration), yet it is possible for individuals to experience bidirectional transitions in both metabolic and weight status. Zhang et al. reported the highest transitions from MUHNW to MHNW and from MHO to MUHO over a follow-up time of approximately 1 year, reinforcing obesity phenotypes as unstable and dynamic traits.[196]

The major determinants of metabolic deterioration include visceral adiposity, IR, dyslipidaemia, NAFLD and inflammation.[18,197–200] The Multi-Ethnic Study of Atherosclerosis (MESA) study showed that both obesity duration and severity were strongly associated with the progression of MHO to incident Met-S.[201] Additionally, sociodemographic and dietary factors are implicated as predictors of metabolic transition.[202] Emotional stress is also associated with a metabolically unhealthy phenotype.[203] This may be mediated through increased cortisol secretion during stress,[204] which can cause deterioration in metabolic health through its metabolic effects[205,206] as well as through the increased preference of unhealthy food choices.[207] Age-related decline in testosterone in males and menopause-related decline in oestrogen in females may also contribute to the transition to an unhealthy phenotype in view of the known beneficial metabolic effects of these sex hormones.[208–210]

Meta-analyses of longitudinal studies across different ethnicities show that the MHO phenotype has an intermediate cardiometabolic risk between that of MHNW and MUHO, independent of its definition.[16,211–214] However, when utilising a harmonised definition of MH, Al-Khalidi et al. recently reported that MHO was not associated with an increased risk of all-cause or cardiometabolic mortality.[215] The ATTICA study found excess cardiovascular risk only in those who progressed to MUHO.[17] Other authors suggest that the accumulation of cardiometabolic risk factors, rather than BMI, confers the greatest risk.[31,216–220] Furthermore, despite a generally more favourable metabolic profile observed in MHO, subtle differences in cardiometabolic risk parameters relative to MHNW have also been described.[23,201,221,222] These differences extend to subclinical CVD risk as assessed by increased carotid intima media thickness (cIMT) and coronary artery calcification.[223–225] However, Lin et al. showed that the increased risk of subclinical atherosclerosis only occurred in MHO individuals who transitioned to MUHO.[226] Furthermore, metabolic abnormalities are associated with a dose-dependent increase in risk of cardiovascular disease, even when MHO is defined by the absence of metabolic abnormalities.[217]

There is some evidence that protection from CVD risk in MHO subjects stems from the preservation of cardiorespiratory fitness (CRF). Ortega et al. observed that certain MHO individuals, despite a high percentage of body fat, had a favourable CRF with a lower risk for cardiovascular outcomes compared to MUHO, and a similar risk compared to healthy normal-fat participants.[34] Additionally, a recent meta-analysis by the same authors confirmed that MHO individuals who engaged in more physical activity, had higher levels of CRF and spent less time in sedentary behaviour compared to MUHO. Notably, risk of all-cause and cardiovascular mortality and morbidity became insignificant after adjusting for physical activity.[153]

Studies evaluating T2DM risk in MHO identified an approximate 4-fold increased risk compared with MHNW.[179,180,197,212,213,227] Subjects who progressed to MUHO were at higher risk for developing T2DM compared to those who retained the MHO status, yet this risk was lower when compared to those with stable MUHO.[228] On the other hand, Wang et al. reported that individuals with persistent MHO were not at increased risk compared with stable MHNW after 6 years of follow-up[229] but with very wide 95% confidence intervals in the odds ratio (0.20–1.40). Others also noted that the risk of T2DM in MHO varied according to the degree of subclinical chronic systemic inflammation (meta-inflammation), IR and β-cell function as well as the presence of liver and visceral abdominal fat.[18,230–233]

Few studies assessing long-term cardiometabolic trajectories in MUHNW are available. As outlined earlier, the presence of unhealthy metabolic status is associated with a dose-dependent increase in cardiometabolic and mortality risk compared with MHNW.[216,217,229] One meta-analysis showed that metabolically unhealthy subjects carried a significantly higher risk of incident T2M compared with metabolically healthy subjects across all BMI categories, particularly in East Asians.[234] Additionally, some researchers found the MUHNW phenotype to carry a risk similar to MUHO for adverse long-term outcomes, while others found it to present a worse cardiometabolic prognosis when compared to MHO.[211,216,235] Data from the UK Biobank recently observed that subjects with overweight/obesity and

15207560, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3725 by CAS - Wuhan Library of CAS, Wiley Online Library on [11/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

T2DM had a lower risk for all-cause mortality than those in a similar BMI category but without T2DM.[236] Furthermore, the presence of overweight or class I obesity in subjects with diabetes was associated with a lower risk for all-cause mortality compared with individuals with a normal BMI.[236] Conversely, Carnethon et al. showed that normal weight individuals with T2DM had higher odds for all-cause mortality compared with subjects with a BMI ≥25 kg/m^2.[237] The finding that a higher BMI (even in those classified as having severe obesity) was protective against all-cause mortality in patients with T2DM has also been replicated across different ethnicities.[238] Interestingly, individuals within the underweight or near-normal BMI categories were observed to have the highest risk compared with all other BMI categories.[238] These data support the obesity paradox (i.e. the reduced mortality risk observed in people with obesity as compared to normal weight) at least within subjects with diabetes.[239] Moreover, it also emphasises the different underlying pathophysiology for 'lean diabetes' whereby β-cell failure, rather than insulin resistance, predominates, leading to more severe levels of hyperglycaemia and therefore a higher risk for microvascular complications compared to subjects with insulin-resistance diabetes and obesity.[240,241]

With respect to incident CVD risk, Fauchier et al. showed that lean subjects with just one metabolic abnormality carried an elevated risk of CV events, compared to normal weight individuals with no metabolic abnormalities. Furthermore, this risk was higher than that observed in obese participants with no metabolic abnormalities.[242]

The worse cardiovascular outcomes observed in both MUHNW and MUHO individuals are partly attributable to subclinical cardiac systolic and diastolic dysfunction.[243] Additionally, MUHNW individuals have a higher prevalence and severity of angiographic coronary artery disease even after controlling for potential confounding factors.[225] Studies have also shown that MUHNW is associated with an increased risk of heart failure.[244] These associations reinforce that MHO and MUHNW are not benign conditions; rather they are dynamic states that represent a spectrum of adverse cardiometabolic disease risk, with the risk of MHO being intermediate to that of MHNW and MUHNW.

Transition between BMI categories can also occur, as shown in the Santiago Longitudinal Study.[245] This study also found that insulin resistance and non-alcoholic liver disease were more common in 23-year-old individuals who had long-standing or recent-onset obesity compared with individuals who were never obese or who had transitioned from obesity to non-obesity.

4.1 | Therapeutic interventions

Current obesity management guidelines do not distinguish between the management of different subclasses of obesity. In particular, there is no mention of the assessment of body fat distribution or visceral adiposity in the work-up towards risk stratification and targeted treatment strategies for individuals with obesity.[246] Most scientific organisations and regulatory bodies advocate weight loss of around 5%–10% from baseline body weight (using a combination of lifestyle interventions, pharmacotherapy or bariatric procedures) for all obese subjects since it is associated with improvements in several cardiometabolic risk factors.[247,248]

To date, there is no strong evidence to suggest whether individuals with MHO stand to gain any metabolic benefit from lifestyle interventions.[249] For example, one meta-analysis found that caloric restriction results in reductions in BMI, systolic and diastolic blood pressure, and triglycerides, but not in glucose, insulin resistance, or CRP.[250] Another meta-analysis reported that calorie restriction, with or without exercise, reduces only diastolic blood pressure.[45]

A variety of dietary approaches consisting of different macronutrient compositions have been used to induce clinically significant weight loss and improve cardiometabolic risk. Such diets include low and very low carbohydrate (ketogenic) diets, low-fat/high-fat or high protein diets, meal replacements and diets which regulate the timing of caloric intake (intermittent fasting).[251–253] So far, there are plausible data, which show that all dietary interventions, irrespective of their macronutrient content, exert beneficial effects on body weight and metabolic parameters, with no one diet being superior to the other. Rather, adherence to the diet was observed to be the key factor in the success of long-term weight loss and weight loss maintenance. Adherence to a Mediterranean-Style diet (characterised by an abundant consumption of monounsaturated fat in the form of olive oil and nuts), has been consistently associated with a lower incidence of CVD, T2DM, all-cause mortality and cancer mortality, even in the absence of significant weight loss.[254–256] Interestingly, in the study by Park et al., MHO individuals who complied with the Mediterranean diet had a lower all-cause mortality risk over a median follow-up of 18.5 years. However, such findings were not observed among MUHO individuals, suggesting that the MUHO phenotype may require alternative therapeutic strategies to reduce mortality risk.[257] Recently, a randomised controlled study by Lean et al. showed that the use of a low calorie diet (by way of a low energy formula replacement diet) within a primary care setting was associated with remission of T2DM in overweight and obese individuals.[258] However, achieving and maintaining weight loss can be challenging for many patients.[259] Another plausible treatment approach would be one which focusses on improving cardiometabolic health. Given the aforementioned findings, incorporating a Mediterranean style diet (which consists of qualitative rather than quantitative changes to the macronutrient component) can be a more acceptable treatment option for patients and may also motivate adherence to lifestyle changes.[260] With regard to physical activity, a growing body of evidence is demonstrating that incorporation of aerobic exercise even without a hypocaloric diet in viscerally obese patients is associated with improvements in plasma glucose-insulin homoeostasis as well as in other markers of cardiometabolic risk and with decreased CVD events. This occurs as a consequence of preferential visceral adipose tissue loss even in the absence of overt weight loss,[261] with one meta-analysis showing that while dietary interventions lead to higher total body weight loss, this may not necessarily be reflected in improved VAT and may be a poor marker

15207560, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3725 by CAS - Wuhan Library of CAS, Wiley Online Library on [11/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

for evaluation of cardiometabolic health.[262] Exercise also results in reductions in hepatic, heart and pancreatic fat depots.[261,262] Another meta-analysis found that lifestyle interventions (diet or exercise) can reduce ectopic fat accumulation in the internal organs of overweight and obese adults, with a dose-response relationship between BMI reduction and decreased hepatic adiposity.[263]

Over the past decade the US Food and Drug administration (FDA) has approved a handful of pharmaceutical agents as part of the treatment armamentarium for the chronic management of obesity in conjunction with lifestyle modification. Recently, the GLP-1 receptor analogue (GLP-1 RA) semaglutide was observed to induce a mean weight loss of approximately 15% as well as improvements in a number of cardiometabolic endpoints in the phase 3 Semaglutide Treatment Effect in People with Obesity (STEP) clinical programme.[264] Furthermore, studies have shown that GLP-1 analogues also exert positive effects on the cardiovascular system through weight-independent mechanisms, including improved vascular endothelial function, ischaemic conditioning and reduction in systemic inflammation.[265–267] Furthermore, they have a positive impact on body composition through significant improvements in VAT, fat mass index (FMI), epicardial fat and hepatic steatosis, thus making them an appealing drug in the management of different obesity phenotypes.[268–270] FGF21 is also being proposed as a potential novel therapeutic modality, especially with regard to improving hepatic steatosis.[271,272]

Bariatric surgery to date is still the most effective strategy for weight loss and weight loss maintenance.[273] It has also been associated with improvements in cardiometabolic risk factors, improvement or remission of T2 DM, reduction in CVD events, total mortality, and cancer incidence.[274,275] Both sleeve gastrectomy and gastric bypass are associated with significant reductions in visceral fat depot sizes and in adipose tissue inflammation leading to favourable effects on glucose metabolism in insulin sensitive tissues.[276] Genua et al., noted that the MHO phenotype was associated with a higher percentage of total weight loss when compared with MUHO and this was independent of the baseline BMI and type of surgery performed.[277] On the other hand, Goday et al.[278] assessed the metabolic benefits of bariatric surgery in metabolically healthy but morbidly obese subjects. They observed significant improvements in blood pressure, lipid profiles, plasma glucose and HOMA-IR values 1 year after bariatric surgery, despite them having lost a comparable amount of weight to their unhealthy counterparts.

The management of MUHNW may prove to be more challenging in clinical practice.[279] Studies which evaluated dietary interventions have demonstrated that it is the quality rather than the quantity of calories consumed to be a key factor in reducing CVD risk and mortality.[280] Analogous to individuals with acquired or inherited lipodystrophies, management of patients with MUHNW would involve some form of treatment which would promote adipocyte differentiation and insulin sensitivity to restore MH. Such individuals have low percentage leg fat mass, implying impaired subcutaneous adipose tissue expansion. Stefan et al. suggested the use of PPAR-γ agonists such as pioglitazone since these drugs have insulin-sensitising effects as well as improved adipocyte differentiation. Moreover, these individuals are characterised by increased intra-abdominal adiposity and higher waist circumference than their healthy counterparts and thus targeting this body compartment (as happens with use of TZDs) will also aid in improving metabolic dysfunction.[15,68]

Thus, the general approach for the management of MHO and MUHNW would be one which incorporates a healthy lifestyle through a healthy diet and physical activity, with improvements in cardiometabolic parameters and cardiorespiratory fitness. Hopefully, in the near future novel pharmacological agents modulating different fat depots may prove to be a promising treatment option both for subjects with metabolically unhealthy normal weight but also in those suffering from overweight or obesity.

5 | CONCLUSION

Obesity has now reached pandemic proportions. The presence of excess adiposity (irrespective of metabolic status) not only contributes towards increased risk of cardiometabolic diseases but is also associated with several other debilitating health conditions (such as osteoarthritis and sleep apnoea) which also decrease the quality of life. This calls for timely diagnosis and institution of treatment as well as for the implementation of more effective preventive strategies from a public health point of view. On the other hand, amelioration, or preservation of MH irrespective of the individuals' BMI (sometimes even with modest or negligible weight loss) is still associated with clinical benefits and may be a more prudent treatment target than the amount of weight loss and more tangible to achieve in such individuals. Further research involving both basic science and clinical studies is required for a better understanding of the pathophysiological, molecular and biological mechanisms which underlie the various body composition phenotypes, with a specific focus on adipocyte biology and function. Furthermore, the future availability of novel devices would make for faster, easier, and cheaper assessment of the different fat depots in clinical practice. This would allow for better characterisation and risk stratification of the different obesity phenotypes with the ultimate goal being to provide customised preventive strategies as well as targeted and more cost-effective treatment paradigms.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the literature review and writing the manuscript.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

15207560, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3725 by CAS - Wuhan Library of CAS, Wiley Online Library on [11/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

ETHICS STATEMENT

Not applicable since this is a review article.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

ORCID

Nikolai P. Pace https://orcid.org/0000-0002-7332-874X
Stephen Fava https://orcid.org/0000-0002-2372-7101

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/dmrr.3725.

REFERENCES

1. Bray GA, Kim KK, Wilding JPH, World Obesity Federation. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. *Obes Rev Off J Int Assoc Study Obes*. 2017;18(7):715-723. https://doi.org/10.1111/obr.12551
2. Mechanick JI, Hurley DL, Garvey WT. Adiposity-based chronic disease as a new diagnostic term: the American Association of Clinical Endocrinologists and American College ofndocrinology position statement. *Endocr Pract Off J Am Coll Endocrinol Am Assoc Clin Endocrinol*. 2017;23(3):372-378. https://doi.org/10.4158/ep161688.ps
3. Frühbeck G, Busetto L, Dicker D, et al. The ABCD of obesity: an EASO position statement on a diagnostic term with clinical and scientific implications. *Obes Facts*. 2019;12(2):131-136. https://doi.org/10.1159/000497124
4. Lyall DM, Celis-Morales C, Ward J, et al. Association of body mass index with cardiometabolic disease in the UK Biobank: a Mendelian randomization study. *JAMA Cardiol*. 2017;2(8):882-889. https://doi.org/10.1001/jamacardio.2016.5804
5. Lavie CJ, Laddu D, Arena R, Ortega FB, Alpert MA, Kushner RF. Healthy weight and obesity prevention: JACC health promotion series. *J Am Coll Cardiol*. 2018;72(13):1506-1531. https://doi.org/10.1016/j.jacc.2018.08.1037
6. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC Publ Health*. 2009;9(1):88. https://doi.org/10.1186/1471-2458-9-88
7. Neeland IJ, Ross R, Després JP, et al. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. *Lancet Diabetes Endocrinol*. 2019;7(9):715-725. https://doi.org/10.1016/s2213-8587(19)30084-1
8. Pujia R, Tarsitano MG, Arturi F, et al. Advances in phenotyping obesity and in its dietary and pharmacological treatment: a narrative review. *Front Nutr*. 2022;9:804719. https://doi.org/10.3389/fnut.2022.804719
9. Blüher M. Metabolically healthy obesity. *Endocr Rev*. 2020;41(3):bnaa004. https://doi.org/10.1210/endrev/bnaa004
10. Blundell JE, Dulloo AG, Salvador J, Frühbeck G, on behalf of the EASO SAB Working Group on BMI G. Beyond BMI--phenotyping the obesities. *Obes Facts*. 2014;7(5):322-328. https://doi.org/10.1159/000368783
11. Sims EA. Are there persons who are obese, but metabolically healthy? *Metabolism*. 2001;50(12):1499-1504. https://doi.org/10.1053/meta.2001.27213
12. Stefan N, Häring HU, Hu FB, Schulze MB. Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. *Lancet Diabetes Endocrinol*. 2013;1(2):152-162. https://doi.org/10.1016/s2213-8587(13)70062-7
13. Ruderman NB, Schneider SH, Berchtold P. The 'metabolically-obese,' normal-weight individual. *Am J Clin Nutr*. 1981;34(8):1617-1621. https://doi.org/10.1093/ajcn/34.8.1617
14. Dvorak RV, DeNino WF, Ades PA, Poehlman ET. Phenotypic characteristics associated with insulin resistance in metabolically obese but normal-weight young women. *Diabetes*. 1999;48(11):2210-2214. https://doi.org/10.2337/diabetes.48.11.2210
15. Stefan N, Schick F, Häring HU. Causes, characteristics, and consequences of metabolically unhealthy normal weight in humans. *Cell Metab*. 2017;26(2):292-300. https://doi.org/10.1016/j.cmet.2017.07.008
16. Eckel N, Li Y, Kuxhaus O, Stefan N, Hu FB, Schulze MB. Transition from metabolic healthy to unhealthy phenotypes and association with cardiovascular disease risk across BMI categories in 90 257 women (the Nurses' Health Study): 30 year follow-up from a prospective cohort study. *Lancet Diabetes Endocrinol*. 2018;6(9):714-724. https://doi.org/10.1016/s2213-8587(18)30137-2
17. Kouvari M, Panagiotakos DB, Yannakoulia M, et al. Transition from metabolically benign to metabolically unhealthy obesity and 10-year cardiovascular disease incidence: the ATTICA cohort study. *Metabolism*. 2019;93:18-24. https://doi.org/10.1016/j.metabol.2019.01.003
18. Hwang YC, Hayashi T, Fujimoto WY, et al. Visceral abdominal fat accumulation predicts the conversion of metabolically healthy obese subjects to an unhealthy phenotype. *Int J Obes*. 2015;39(9):1365-1370. https://doi.org/10.1038/ijo.2015.75
19. National Cholesterol Education Program (NCEP). Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report. *Circulation*. 2002;106:3143-3421.
20. Alberti KGMM, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A consensus statement from the International Diabetes Federation. *Diabet Med J Br Diabet Assoc*. 2006;23(5):469-480. https://doi.org/10.1111/j.1464-5491.2006.01858.x
21. Alberti KGMM, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120(16):1640-1645. https://doi.org/10.1161/circulationaha.109.192644
22. 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(15):1617-1624. https://doi.org/10.1001/archinte.168.15.1617
23. Agius R, Pace NP, Fava S. Characterisation of body size phenotypes in a middle-aged Maltese population. *J Nutr Sci*. 2021;10:e81. https://doi.org/10.1017/jns.2021.74
24. Sesti G, Succurro E, Arturi F, et al. IGF-1 levels link estimated glomerular filtration rate to insulin resistance in obesity: a study in obese, but metabolically healthy, subjects and obese, insulin-resistant subjects. *Nutr Metab Cardiovasc Dis NMCD*. 2011;21(12):933-940. https://doi.org/10.1016/j.numecd.2010.02.008
25. 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(7):642-648. https://doi.org/10.1001/archinte.167.7.642

15207560, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3725 by CAS - Wuhan Library of CAS, Wiley Online Library on [11/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

26. Klöting N, Fasshauer M, Dietrich A, et al. Insulin-sensitive obesity. *Am J Physiol Endocrinol Metab*. 2010;299(3):E506-E515. https://doi.org/10.1152/ajpendo.00586.2009
27. Iacobellis G, Ribaudo MC, Zappaterreno A, Iannucci CV, Leonetti F. Prevalence of uncomplicated obesity in an Italian obese population. *Obes Res*. 2005;13(6):1116-1122. https://doi.org/10.1038/oby.2005.130
28. Stefan N, Kantartzis K, Machann J, et al. Identification and characterization of metabolically benign obesity in humans. *Arch Intern Med*. 2008;168(15):1609-1616. https://doi.org/10.1001/archinte.168.15.1609
29. Messier V, Karelis AD, Prud'homme D, Primeau V, Brochu M, Rabasa-Lhoret R. Identifying metabolically healthy but obese individuals in sedentary postmenopausal women. *Obes Silver Spring Md*. 2010;18(5):911-917. https://doi.org/10.1038/oby.2009.364
30. 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(1):210-215. https://doi.org/10.2337/dc10-0665
31. 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;36(8):2388-2394. https://doi.org/10.2337/dc12-1971
32. Wang W, He J, Hu Y, et al. Comparison of the incidence of cardiovascular diseases in weight groups with healthy and unhealthy metabolism. *Diabetes Metab Syndr Obes Targets Ther*. 2021;14:4155-4163. https://doi.org/10.2147/dmso.s330212
33. Shea JL, Randell EW, Sun G. The prevalence of metabolically healthy obese subjects defined by BMI and dual-energy X-ray absorptiometry. *Obes Silver Spring Md*. 2011;19(3):624-630. https://doi.org/10.1038/oby.2010.174
34. 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(5):389-397. https://doi.org/10.1093/eurheartj/ehs174
35. De Lorenzo A, Del Gobbo V, Premrov MG, Bigioni M, Galvano F, Di Renzo L. Normal-weight obese syndrome: early inflammation? *Am J Clin Nutr*. 2007;85(1):40-45. https://doi.org/10.1093/ajcn/85.1.40
36. Romero-Corral A, Somers VK, Sierra-Johnson J, et al. Normal weight obesity: a risk factor for cardiometabolic dysregulation and cardiovascular mortality. *Eur Heart J*. 2010;31(6):737-746. https://doi.org/10.1093/eurheartj/ehp487
37. Zembic A, Eckel N, Stefan N, Baudry J, Schulze MB. An empirically derived definition of metabolically healthy obesity based on risk of cardiovascular and total mortality. *JAMA Netw Open*. 2021;4(5):e218505. https://doi.org/10.1001/jamanetworkopen.2021.8505
38. Meigs JB, Wilson PWF, Fox CS, et al. Body mass index, metabolic syndrome, and risk of type 2 diabetes or cardiovascular disease. *J Clin Endocrinol Metab*. 2006;91(8):2906-2912. https://doi.org/10.1210/jc.2006-0594
39. Durward CM, Hartman TJ, Nickols-Richardson SM. All-cause mortality risk of metabolically healthy obese individuals in NHANES III. *J Obes*. 2012;2012:460321-460412. https://doi.org/10.1155/2012/460321
40. Soriguer F, Gutiérrez-Repiso C, Rubio-Martín E, et al. Metabolically healthy but obese, a matter of time? Findings from the prospective Pizarra study. *J Clin Endocrinol Metab*. 2013;98(6):2318-2325. https://doi.org/10.1210/jc.2012-4253
41. Aguilar-Salinas CA, García EG, Robles L, et al. High adiponectin concentrations are associated with the metabolically healthy obese phenotype. *J Clin Endocrinol Metab*. 2008;93(10):4075-4079. https://doi.org/10.1210/jc.2007-2724
42. Mauriège P, Karelis AD, Taleb N, Clément AA, Joanisse DR. Comparing an adiposopathy approach with four popular classifications schemes to categorize the metabolic profile of postmenopausal women. *J Physiol Biochem*. 2020;76(4):609-622. https://doi.org/10.1007/s13105-020-00766-w
43. Calanna S, Piro S, Di Pino A, et al. Beta and alpha cell function in metabolically healthy but obese subjects: relationship with enteroinsular axis. *Obes Silver Spring Md*. 2013;21(2):320-325. https://doi.org/10.1002/oby.20017
44. Wang B, Zhuang R, Luo X, et al. Prevalence of metabolically healthy obese and metabolically obese but normal weight in adults worldwide: a meta-analysis. *Horm Metab Res Horm Stoffwechselforschung Horm Metab*. 2015;47(11):839-845. https://doi.org/10.1055/s-0035-1559767
45. Lin H, Zhang L, Zheng R, Zheng Y. The prevalence, metabolic risk and effects of lifestyle intervention for metabolically healthy obesity: a systematic review and meta-analysis: a PRISMA-compliant article. *Medicine (Baltim)*. 2017;96(47):e8838. https://doi.org/10.1097/md.0000000000008838
46. Liu C, Wang C, Guan S, et al. The prevalence of metabolically healthy and unhealthy obesity according to different criteria. *Obes Facts*. 2019;12(1):78-90. https://doi.org/10.1159/000495852
47. Rey-López JP, de Rezende LF, Pastor-Valero M, Tess BH. The prevalence of metabolically healthy obesity: a systematic review and critical evaluation of the definitions used. *Obes Rev Off J Int Assoc Study Obes*. 2014;15(10):781-790. https://doi.org/10.1111/obr.12198
48. Gallagher D, Visser M, Sepúlveda D, Pierson RN, Harris T, Heymsfield SB. How useful is body mass index for comparison of body fatness across age, sex, and ethnic groups? *Am J Epidemiol*. 1996;143(3):228-239. https://doi.org/10.1093/oxfordjournals.aje.a008733
49. Kuk JL, Saunders TJ, Davidson LE, Ross R. Age-related changes in total and regional fat distribution. *Ageing Res Rev*. 2009;8(4):339-348. https://doi.org/10.1016/j.arr.2009.06.001
50. Iliodromiti S, McLaren J, Ghouri N, et al. Liver, visceral and subcutaneous fat in men and women of South Asian and white European descent: a systematic review and meta-analysis of new and published data. *Diabetologia*. 2023;66(1):44-56. https://doi.org/10.1007/s00125-022-05803-5
51. Lee K. Metabolically obese but normal weight (MONW) and metabolically healthy but obese (MHO) phenotypes in Koreans: characteristics and health behaviors. *Asia Pac J Clin Nutr*. 2009;18:280-284.
52. Gujral UP, Vittinghoff E, Mongraw-Chaffin M, et al. Cardiometabolic abnormalities among normal-weight persons from five racial/ethnic groups in the United States: a cross-sectional analysis of two cohort studies. *Ann Intern Med*. 2017;166(9):628-636. https://doi.org/10.7326/m16-1895
53. Lee SH, Han K, Yang HK, et al. A novel criterion for identifying metabolically obese but normal weight individuals using the product of triglycerides and glucose. *Nutr Diabetes*. 2015;5(4):e149. https://doi.org/10.1038/nutd.2014.46
54. Urata N, Kawanaka M, Nishino K, et al. Fatty liver, and not visceral fat, is more associated with liver fibrosis and diabetes in non-obese Japanese individuals: a cross-sectional study. *Life Basel Switz*. 2020;10(9):175. https://doi.org/10.3390/life10090175
55. Ren Z, Cao X, Li C, et al. Ferritin, transferrin, and transferrin receptor in relation to metabolic obesity phenotypes: findings from the China Health and Nutrition Survey. *Front Public Health*. 2022;10:922863. https://doi.org/10.3389/fpubh.2022.922863
56. Taylor A, Siddiqui MK, Ambery P, et al. Metabolic dysfunction-related liver disease as a risk factor for cancer. *BMJ Open Gastroenterol*. 2022;9(1):e000817. https://doi.org/10.1136/bmjgast-2021-000817
57. Önnerhag K, Hartman H, Nilsson PM, Lindgren S. Non-invasive fibrosis scoring systems can predict future metabolic complications and overall mortality in non-alcoholic fatty liver disease

15207560, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3725 by CAS - Wuhan Library of CAS, Wiley Online Library on [11/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

(NAFLD). *Scand J Gastroenterol*. 2019;54(3):328-334. https://doi.org/10.1080/00365521.2019.1583366

58. Lee JH, Kim D, Kim HJ, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. *Dig Liver Dis*. 2010;42(7):503-508. https://doi.org/10.1016/j.dld.2009.08.002
59. De Lorenzo A, Martinoli R, Vaia F, Di Renzo L. Normal weight obese (NWO) women: an evaluation of a candidate new syndrome. *Nutr Metab Cardiovasc Dis NMCD*. 2006;16(8):513-523. https://doi.org/10.1016/j.numecd.2005.10.010
60. Madeira FB, Silva AA, Veloso HF, et al. Normal weight obesity is associated with metabolic syndrome and insulin resistance in young adults from a middle-income country. *PloS One*. 2013;8(3):e60673. https://doi.org/10.1371/journal.pone.0060673
61. Kim JY, Han SH, Yang BM. Implication of high-body-fat percentage on cardiometabolic risk in middle-aged, healthy, normal-weight adults. *Obes Silver Spring Md*. 2013;21(8):1571-1577. https://doi.org/10.1002/oby.20020
62. Donini LM, Busetto L, Bischoff SC, et al. Definition and diagnostic criteria for sarcopenic obesity: ESPEN and EASO consensus statement. *Obes Facts*. 2022;15(3):321-335. https://doi.org/10.1159/000521241
63. Schrager MA, Metter EJ, Simonsick E, et al. Sarcopenic obesity and inflammation in the InCHIANTI study. *J Appl Physiol*. 2007;102(3):919-925. https://doi.org/10.1152/japplphysiol.00627.2006
64. Murdock DJ, Wu N, Grimsby JS, et al. The prevalence of low muscle mass associated with obesity in the USA. *Skelet Muscle*. 2022;12(1):26. https://doi.org/10.1186/s13395-022-00309-5
65. Chung GE, Park HE, Lee H, et al. Sarcopenic obesity is significantly associated with coronary artery calcification. *Front Med*. 2021;8:651961. https://doi.org/10.3389/fmed.2021.651961
66. Goossens GH. The metabolic phenotype in obesity: fat mass, body fat distribution, and adipose tissue function. *Obes Facts*. 2017;10(3):207-215. https://doi.org/10.1159/000471488
67. Bays H. Central obesity as a clinical marker of adiposopathy; increased visceral adiposity as a surrogate marker for global fat dysfunction. *Curr Opin Endocrinol Diabetes Obes*. 2014;21(5):345-351. https://doi.org/10.1097/med.0000000000000093
68. Stefan N. Causes, consequences, and treatment of metabolically unhealthy fat distribution. *Lancet Diabetes Endocrinol*. 2020;8(7):616-627. https://doi.org/10.1016/s2213-8587(20)30110-8
69. Blüher M. Adipose tissue dysfunction contributes to obesity related metabolic diseases. *Best Pract Res Clin Endocrinol Metab*. 2013;27(2):163-177. https://doi.org/10.1016/j.beem.2013.02.005
70. Petrus P, Lecoutre S, Dollet L, et al. Glutamine links obesity to inflammation in human white adipose tissue. *Cell Metab*. 2020;31(2):375-390.e11. https://doi.org/10.1016/j.cmet.2019.11.019
71. Abboud KY, Reis SK, Martelli ME, et al. Oral glutamine supplementation reduces obesity, pro-inflammatory markers, and improves insulin sensitivity in DIO wistar rats and reduces waist circumference in overweight and obese humans. *Nutrients*. 2019;11(3):536. https://doi.org/10.3390/nu11030536
72. Jeong S, Jang HB, Kim HJ, Lee HJ. Identification of biomarkers related to metabolically unhealthy obesity in Korean obese adolescents: a cross-sectional study. *Children*. 2023;10(2):322. https://doi.org/10.3390/children10020322
73. Piché ME, Poirier P, Lemieux I, Després JP. Overview of epidemiology and contribution of obesity and body fat distribution to cardiovascular disease: an update. *Prog Cardiovasc Dis*. 2018;61(2):103-113. https://doi.org/10.1016/j.pcad.2018.06.004
74. Shulman GI. Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. *N Engl J Med*. 2014;371(12):1131-1141. https://doi.org/10.1056/nejmra1011035
75. Cornier MA, Després JP, Davis N, et al. Assessing adiposity: a scientific statement from the American Heart Association. *Circulation*. 2011;124(18):1996-2019. https://doi.org/10.1161/cir.0b013e318233bc6a
76. Bays HE, González-Campoy JM, Bray GA, et al. Pathogenic potential of adipose tissue and metabolic consequences of adipocyte hypertrophy and increased visceral adiposity. *Expert Rev Cardiovasc Ther*. 2008;6(3):343-368. https://doi.org/10.1586/14779072.6.3.343
77. Teixeira TFS, Alves RDM, Moreira APB, Peluzio MdoCG. Main characteristics of metabolically obese normal weight and metabolically healthy obese phenotypes. *Nutr Rev*. 2015;73(3):175-190. https://doi.org/10.1093/nutrit/nuu007
78. Mathieu P, Poirier P, Pibarot P, Lemieux I, Després JP. Visceral obesity: the link among inflammation, hypertension, and cardiovascular disease. *Hypertens Dallas Tex*. 2009;53(4):577-584. https://doi.org/10.1161/hypertensionaha.108.110320
79. Tchernof A, Després JP. Pathophysiology of human visceral obesity: an update. *Physiol Rev*. 2013;93(1):359-404. https://doi.org/10.1152/physrev.00033.2011
80. Carobbio S, Pellegrinelli V, Vidal-Puig A. Adipose tissue function and expandability as determinants of lipotoxicity and the metabolic syndrome. *Adv Exp Med Biol*. 2017;960:161-196.
81. Carobbio S, Rodriguez-Cuenca S, Vidal-Puig A. Origins of metabolic complications in obesity: ectopic fat accumulation. The importance of the qualitative aspect of lipotoxicity. *Curr Opin Clin Nutr Metab Care*. 2011;14(6):520-526. https://doi.org/10.1097/mco.0b013e32834ad966
82. Li Q, Hagberg CE, Silva Cascales H, et al. Obesity and hyperinsulinemia drive adipocytes to activate a cell cycle program and senesce. *Nat Med*. 2021;27(11):1941-1953. https://doi.org/10.1038/s41591-021-01501-8
83. Chen GC, Arthur R, Iyengar NM, et al. Association between regional body fat and cardiovascular disease risk among postmenopausal women with normal body mass index. *Eur Heart J*. 2019;40(34):2849-2855. https://doi.org/10.1093/eurheartj/ehz391
84. Stefan N. Metabolically healthy and unhealthy normal weight and obesity. *Endocrinol Metab Seoul Korea*. 2020;35(3):487-493. https://doi.org/10.3803/enm.2020.301
85. Brochu M, Tchernof A, Dionne IJ, et al. What are the physical characteristics associated with a normal metabolic profile despite a high level of obesity in postmenopausal women? *J Clin Endocrinol Metab*. 2001;86(3):1020-1025. https://doi.org/10.1210/jc.86.3.1020
86. 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(6):2569-2575. https://doi.org/10.1210/jc.2004-0165
87. Joe AW, Yi L, Even Y, Vogl AW, Rossi FM. Depot-specific differences in adipogenic progenitor abundance and proliferative response to high-fat diet. *Stem Cells*. 2009;27(10):2563-2570. https://doi.org/10.1002/stem.190
88. Brandão I, Martins MJ, Monteiro R. Metabolically healthy obesity-heterogeneity in definitions and unconventional factors. *Metabolites*. 2020;10(2):48. https://doi.org/10.3390/metabo10020048
89. Arner P, Sinha I, Thorell A, Rydén M, Dahlman-Wright K, Dahlman I. The epigenetic signature of subcutaneous fat cells is linked to altered expression of genes implicated in lipid metabolism in obese women. *Clin Epigenetics*. 2015;7(1):93. https://doi.org/10.1186/s13148-015-0126-9
90. Boden G. Role of fatty acids in the pathogenesis of insulin resistance and NIDDM. *Diabetes*. 1997;46(1):3-10. https://doi.org/10.2337/diabetes.46.1.3
91. Succurro E, Marini MA, Frontoni S, et al. Insulin secretion in metabolically obese, but normal weight, and in metabolically healthy but obese individuals. *Obes Silver Spring Md*. 2008;16(8):1881-1886. https://doi.org/10.1038/oby.2008.308
92. Samocha-Bonet D, Chisholm DJ, Tonks K, Campbell LV, Greenfield JR. Insulin-sensitive obesity in humans - a 'favorable fat' phenotype?

15207560, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3725 by CAS - Wuhan Library of CAS, Wiley Online Library on [11/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Trends Endocrinol Metab TEM. 2012;23(3):116-124. https://doi.org/10.1016/j.tem.2011.12.005
93. Klein S. The case of visceral fat: argument for the defense. *J Clin Invest*. 2004;113(11):1530-1532. https://doi.org/10.1172/jci200422028
94. Karpe F, Dickmann JR, Frayn KN. Fatty acids, obesity, and insulin resistance: time for a reevaluation. *Diabetes*. 2011;60(10):2441-2449. https://doi.org/10.2337/db11-0425
95. Leavens KF, Birnbaum MJ. Insulin signaling to hepatic lipid metabolism in health and disease. *Crit Rev Biochem Mol Biol*. 2011;46(3):200-215. https://doi.org/10.3109/10409238.2011.562481
96. Wang L, Gill R, Pedersen TL, Higgins LJ, Newman JW, Rutledge JC. Triglyceride-rich lipoprotein lipolysis releases neutral and oxidized FFAs that induce endothelial cell inflammation. *J Lipid Res*. 2009;50(2):204-213. https://doi.org/10.1194/jlr.m700505-jlr200
97. Cembrowska P, Stefańska A, Odrowąż-Sypniewska G. Obesity phenotypes: normal-weight individuals with metabolic disorders versus metabolically healthy obese. *Med Res J*. 2017;1(3):95-99. https://doi.org/10.5603/mrj.2016.0016
98. Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. *Diabetes*. 2007;56(4):1010-1013. https://doi.org/10.2337/db06-1656
99. 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(2):51-65.
100. Karelis AD, Faraj M, Bastard JP, et al. The metabolically healthy but obese individual presents a favorable inflammation profile. *J Clin Endocrinol Metab*. 2005;90(7):4145-4150. https://doi.org/10.1210/jc.2005-0482
101. Primeau V, Coderre L, Karelis AD, et al. Characterizing the profile of obese patients who are metabolically healthy. *Int J Obes*. 2011;35(7):971-981. https://doi.org/10.1038/ijo.2010.216
102. Klitgaard HB, Kilbak JH, Nozawa EA, Seidel AV, Magkos F. Physiological and lifestyle traits of metabolic dysfunction in the absence of obesity. *Curr Diab Rep*. 2020;20(6):17. https://doi.org/10.1007/s11892-020-01302-2
103. Shea JL, King MTC, Yi Y, Gulliver W, Sun G. Body fat percentage is associated with cardiometabolic dysregulation in BMI-defined normal weight subjects. *Nutr Metab Cardiovasc Dis NMCD*. 2012;22(9):741-747. https://doi.org/10.1016/j.numecd.2010.11.009
104. Hyun YJ, Koh SJ, Chae JS, et al. Atherogenecity of LDL and unfavorable adipokine profile in metabolically obese, normal-weight woman. *Obes Silver Spring Md*. 2008;16(4):784-789. https://doi.org/10.1038/oby.2007.127
105. Ding C, Chan Z, Chooi YC, et al. Regulation of glucose metabolism in nondiabetic, metabolically obese normal-weight Asians. *Am J Physiol Endocrinol Metab*. 2018;314(5):E494-E502. https://doi.org/10.1152/ajpendo.00382.2017
106. Sahakyan KR, Somers VK, Rodriguez-Escudero JP, et al. Normal-weight central obesity: implications for total and cardiovascular mortality. *Ann Intern Med*. 2015;163(11):827-835. https://doi.org/10.7326/m14-2525
107. Stefan N, Fritsche A, Schick F, Häring HU. Phenotypes of prediabetes and stratification of cardiometabolic risk. *Lancet Diabetes Endocrinol*. 2016;4(9):789-798. https://doi.org/10.1016/s2213-8587(16)00082-6
108. Tchkonia T, Thomou T, Zhu Y, et al. Mechanisms and metabolic implications of regional differences among fat depots. *Cell Metab*. 2013;17(5):644-656. https://doi.org/10.1016/j.cmet.2013.03.008
109. Speakman JR, Levitsky DA, Allison DB, et al. Set points, settling points and some alternative models: theoretical options to understand how genes and environments combine to regulate body adiposity. *Dis Model Mech*. 2011;4(6):733-745. https://doi.org/10.1242/dmm.008698
110. Yaghootkar H, Lotta LA, Tyrrell J, et al. Genetic evidence for a link between favorable adiposity and lower risk of type 2 diabetes, hypertension, and heart disease. *Diabetes*. 2016;65(8):2448-2460. https://doi.org/10.2337/db15-1671
111. Scott RA, Fall T, Pasko D, et al. Common genetic variants highlight the role of insulin resistance and body fat distribution in type 2 diabetes, independent of obesity. *Diabetes*. 2014;63(12):4378-4387. https://doi.org/10.2337/db14-0319
112. Yengo L, Sidorenko J, Kemper KE, et al. Meta-analysis of genome-wide association studies for height and body mass index in ~700000 individuals of European ancestry. *Hum Mol Genet*. 2018;27(20):3641-3649. https://doi.org/10.1093/hmg/ddy271
113. Khera AV, Chaffin M, Wade KH, et al. Polygenic prediction of weight and obesity trajectories from birth to adulthood. *Cell*. 2019;177(3):587-596.e9. https://doi.org/10.1016/j.cell.2019.03.028
114. Rask-Andersen M, Karlsson T, Ek WE, Johansson Å. Genome-wide association study of body fat distribution identifies adiposity loci and sex-specific genetic effects. *Nat Commun*. 2019;10(1):339. https://doi.org/10.1038/s41467-018-08000-4
115. Pulit SL, Stoneman C, Morris AP, et al. Meta-analysis of genome-wide association studies for body fat distribution in 694 649 individuals of European ancestry. *Hum Mol Genet*. 2019;28(1):166-174. https://doi.org/10.1093/hmg/ddy327
116. Iacobini C, Pugliese G, Blasetti Fantauzzi C, Federici M, Menini S. Metabolically healthy versus metabolically unhealthy obesity. *Metabolism*. 2019;92:51-60. https://doi.org/10.1016/j.metabol.2018.11.009
117. Dahlman I, Sinha I, Gao H, et al. The fat cell epigenetic signature in post-obese women is characterized by global hypomethylation and differential DNA methylation of adipogenesis genes. *Int J Obes*. 2015;39(6):910-919. https://doi.org/10.1038/ijo.2015.31
118. Das SK, Ma L, Sharma NK. Adipose tissue gene expression and metabolic health of obese adults. *Int J Obes*. 2015;39(5):869-873. https://doi.org/10.1038/ijo.2014.210
119. Mathew H, Farr OM, Mantzoros CS. Metabolic health and weight: understanding metabolically unhealthy normal weight or metabolically healthy obese patients. *Metabolism*. 2016;65(1):73-80. https://doi.org/10.1016/j.metabol.2015.10.019
120. Tan CY, Vidal-Puig A. Adipose tissue expandability: the metabolic problems of obesity may arise from the inability to become more obese. *Biochem Soc Trans*. 2008;36(Pt 5):935-940. https://doi.org/10.1042/bst0360935
121. 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(10):1180-1188. https://doi.org/10.1001/jama.298.10.1180
122. Phillips CM. Metabolically healthy obesity across the life course: epidemiology, determinants, and implications. *Ann N Y Acad Sci*. 2017;1391(1):85-100. https://doi.org/10.1111/nyas.13230
123. García-Calzón S, Gea A, Razquin C, et al. Longitudinal association of telomere length and obesity indices in an intervention study with a Mediterranean diet: the PREDIMED-NAVARRA trial. *Int J Obes*. 2014;38(2):177-182. https://doi.org/10.1038/ijo.2013.68
124. Lejawa M, Osadnik K, Osadnik T, Pawlas N. Association of metabolically healthy and unhealthy obesity phenotypes with oxidative stress parameters and telomere length in healthy young adult men. Analysis of the MAGNETIC study. *Antioxid Basel Switz*. 2021;10(1):93. https://doi.org/10.3390/antiox10010093
125. Xu FX, Zhou X, Shen F, Pang R, Liu SM. Decreased peripheral blood mitochondrial DNA content is related to HbA1c, fasting plasma glucose level and age of onset in type 2 diabetes mellitus. *Diabet Med J Br Diabet Assoc*. 2012;29(7):e47-e54. https://doi.org/10.1111/j.1464-5491.2011.03565.x
126. Lee HK, Song JH, Shin CS, et al. Decreased mitochondrial DNA content in peripheral blood precedes the development of

15207560, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3725 by CAS - Wuhan Library of CAS, Wiley Online Library on [11/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

non-insulin-dependent diabetes mellitus. *Diabetes Res Clin Pract*. 1998;42(3):161-167. https://doi.org/10.1016/s0168-8227(98)00110-7

127. Silva JP, Köhler M, Graff C, et al. Impaired insulin secretion and beta-cell loss in tissue-specific knockout mice with mitochondrial diabetes. *Nat Genet*. 2000;26(3):336-340. https://doi.org/10.1038/81649
128. Antonetti DA, Reynet C, Kahn CR. Increased expression of mitochondrial-encoded genes in skeletal muscle of humans with diabetes mellitus. *J Clin Invest*. 1995;95(3):1383-1388. https://doi.org/10.1172/jci117790
129. Meng S, Wu S, Liang L, et al. Leukocyte mitochondrial DNA copy number, anthropometric indices, and weight change in US women. *Oncotarget*. 2016;7(37):60676-60686. https://doi.org/10.18632/oncotarget.10325
130. Skuratovskaia DA, Sofronova JK, Zatolokin PA, et al. Additional evidence of the link between mtDNA copy number and the body mass index. *Mitochondrial DNA Part DNA Mapp Seq Anal*. 2018;29(8):1240-1244. https://doi.org/10.1080/24701394.2018.1436170
131. Zheng LD, Linarelli LE, Liu L, et al. Insulin resistance is associated with epigenetic and genetic regulation of mitochondrial DNA in obese humans. *Clin Epigenetics*. 2015;7(1):60. https://doi.org/10.1186/s13148-015-0093-1
132. Agius R, Pace NP, Fava S. Reduced leukocyte mitochondrial copy number in metabolic syndrome and metabolically healthy obesity. *Front Endocrinol*. 2022;13. https://doi.org/10.3389/fendo.2022.886957
133. Skuratovskaia D, Zatolokin P, Vulf M, Mazunin I, Litvinova L. Interrelation of chemerin and TNF-α with mtDNA copy number in adipose tissues and blood cells in obese patients with and without type 2 diabetes. *BMC Med Genomics*. 2019;12(Suppl 2):40. https://doi.org/10.1186/s12920-019-0485-8
134. Lee JY, Lee DC, Im JA, Lee JW. Mitochondrial DNA copy number in peripheral blood is independently associated with visceral fat accumulation in healthy young adults. *Int J Endocrinol*. 2014;2014:586017. https://doi.org/10.1155/2014/586017
135. Bordoni L, Smerilli V, Nasuti C, Gabbianelli R. Mitochondrial DNA methylation and copy number predict body composition in a young female population. *J Transl Med*. 2019;17(1):399. https://doi.org/10.1186/s12967-019-02150-9
136. Yaghootkar H, Scott RA, White CC, et al. Genetic evidence for a normal-weight 'metabolically obese' phenotype linking insulin resistance, hypertension, coronary artery disease, and type 2 diabetes. *Diabetes*. 2014;63(12):4369-4377. https://doi.org/10.2337/db14-0318
137. Lotta LA, Gulati P, Day FR, et al. Integrative genomic analysis implicates limited peripheral adipose storage capacity in the pathogenesis of human insulin resistance. *Nat Genet*. 2017;49(1):17-26. https://doi.org/10.1038/ng.3714
138. Hales CN. Fetal and infant growth and impaired glucose tolerance in adulthood: the 'thrifty phenotype' hypothesis revisited. *Acta Paediatr Oslo Nor*. 19921997;422(S422):73-77. https://doi.org/10.1111/j.1651-2227.1997.tb18350.x
139. Barker DJ. The fetal and infant origins of adult disease. *BMJ*. 1990;301(6761):1111. https://doi.org/10.1136/bmj.301.6761.1111
140. Heijmans BT, Tobi EW, Stein AD, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proc Natl Acad Sci U S A*. 2008;105(44):17046-17049. https://doi.org/10.1073/pnas.0806560105
141. Agius R, Savona-Ventura C, Vassallo J. Transgenerational metabolic determinants of fetal birth weight. *Exp Clin Endocrinol Diabetes Off J Ger Soc Endocrinol Ger Diabetes Assoc*. 2013;121(07):431-435. https://doi.org/10.1055/s-0033-1345121
142. Tam CHT, Wang Y, Luan J, et al. Non-linear relationship between birthweight and cardiometabolic risk factors in Chinese adolescents and adults. *Diabet Med J Br Diabet Assoc*. 2015;32(2):220-225. https://doi.org/10.1111/dme.12630
143. Bouhours-Nouet N, Dufresne S, de Casson FB, et al. High birth weight and early postnatal weight gain protect obese children and adolescents from truncal adiposity and insulin resistance: metabolically healthy but obese subjects? *Diabetes Care*. 2008;31(5):1031-1036. https://doi.org/10.2337/dc07-1647
144. Neel JV. Diabetes mellitus: a 'thrifty' genotype rendered detrimental by 'progress'. *Am J Hum Genet*. 1962;14:353-362.
145. Camhi SM, Whitney Evans E, Hayman LL, Lichtenstein AH, Must A. Healthy eating index and metabolically healthy obesity in U.S. adolescents and adults. *Prev Med*. 2015;77:23-27. https://doi.org/10.1016/j.ypmed.2015.04.023
146. Lopez-Garcia E, Guallar-Castillon P, Leon-Muñoz L, Rodriguez-Artalejo F. Prevalence and determinants of metabolically healthy obesity in Spain. *Atherosclerosis*. 2013;231(1):152-157. https://doi.org/10.1016/j.atherosclerosis.2013.09.003
147. Camhi SM, Waring ME, Sisson SB, Hayman LL, Must A. Physical activity and screen time in metabolically healthy obese phenotypes in adolescents and adults. *J Obes*. 2013;2013:984613-984710. https://doi.org/10.1155/2013/984613
148. Matheson EM, King DE, Everett CJ. Healthy lifestyle habits and mortality in overweight and obese individuals. *J Am Board Fam Med JABFM*. 2012;25(1):9-15. https://doi.org/10.3122/jabfm.2012.01.110164
149. Phillips CM. Metabolically healthy obesity: definitions, determinants and clinical implications. *Rev Endocr Metab Disord*. 2013;14(3):219-227. https://doi.org/10.1007/s11154-013-9252-x
150. Lee IM, Shiroma EJ, Lobelo F, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet Lond Engl*. 2012;380(9838):219-229. https://doi.org/10.1016/s0140-6736(12)61031-9
151. Sattelmair J, Pertman J, Ding EL, Kohl HW, Haskell W, Lee IM. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. *Circulation*. 2011;124(7):789-795. https://doi.org/10.1161/circulationaha.110.010710
152. Prince RL, Kuk JL, Ambler KA, Dhaliwal J, Ball GDC. Predictors of metabolically healthy obesity in children. *Diabetes Care*. 2014;37(5):1462-1468. https://doi.org/10.2337/dc13-1697
153. Ortega FB, Cadenas-Sanchez C, Migueles JH, et al. Role of physical activity and fitness in the characterization and prognosis of the metabolically healthy obesity phenotype: a systematic review and meta-analysis. *Prog Cardiovasc Dis*. 2018;61(2):190-205. https://doi.org/10.1016/j.pcad.2018.07.008
154. Pujia A, Gazzaruso C, Ferro Y, et al. Individuals with metabolically healthy overweight/obesity have higher fat utilization than metabolically unhealthy individuals. *Nutrients*. 2016;8(1):2. https://doi.org/10.3390/nu8010002
155. Martínez-Larrad MT, Corbatón Anchuelo A, Del Prado N, Ibarra Rueda JM, Gabriel R, Serrano-Ríos M. Profile of individuals who are metabolically healthy obese using different definition criteria. A population-based analysis in the Spanish population. *PloS One*. 2014;9:e106641. https://doi.org/10.1371/journal.pone.0106641
156. Kroenke CH, Chu NF, Rifai N, et al. A cross-sectional study of alcohol consumption patterns and biologic markers of glycemic control among 459 women. *Diabetes Care*. 2003;26(7):1971-1978. https://doi.org/10.2337/diacare.26.7.1971
157. Miller KK, Biller BMK, Lipman JG, Bradwin G, Rifai N, Klibanski A. Truncal adiposity, relative growth hormone deficiency, and cardiovascular risk. *J. Clin. Endocrinol. Metab*. 2005;90(2):768-774. https://doi.org/10.1210/jc.2004-0894
158. Masi D, Risi R, Biagi F, et al. Application of a machine learning technology in the definition of metabolically healthy and unhealthy status: a retrospective study of 2567 subjects suffering from

15207560, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3725 by CAS - Wuhan Library of CAS, Wiley Online Library on [11/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

obesity with or without metabolic syndrome. *Nutrients*. 2022;14(2):373. https://doi.org/10.3390/nu14020373
159. Watanabe M, Masieri S, Costantini D, et al. Overweight and obese patients with nickel allergy have a worse metabolic profile compared to weight matched non-allergic individuals. *PloS One*. 2018;13(8):e0202683. https://doi.org/10.1371/journal.pone.0202683
160. Zhang X, Yeung DC, Karpisek M, et al. Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans. *Diabetes*. 2008;57(5):1246-1253. https://doi.org/10.2337/db07-1476
161. Tezze C, Romanello V, Sandri M. FGF21 as modulator of metabolism in health and disease. *Front Physiol*. 2019;10:419. https://doi.org/10.3389/fphys.2019.00419
162. Tucker B, McClelland RL, Allison MA, et al. Relationship of fibroblast growth factor 21 levels with inflammation, lipoproteins and non-alcoholic fatty liver disease. *Atherosclerosis*. 2020;299:38-44. https://doi.org/10.1016/j.atherosclerosis.2020.03.009
163. Han F, Yin L, Yu X, et al. High circulating fibroblast growth factor-21 levels as a screening marker in fatty pancreas patients. *PeerJ*. 2023;11:e15176. https://doi.org/10.7717/peerj.15176
164. Karamfilova V, Assyov Y, Nedeva I, et al. Fibroblast growth factor 21 as a marker of prediabetes in patients with non-alcoholic fatty liver disease. *Turk J Gastroenterol*. 2022;33(3):233-239. https://doi.org/10.5152/tjg.2021.201165
165. Lenart-Lipinska M, Matyjaszek-Matuszek B, Gernand W, Nowakowski A, Solski J. Serum fibroblast growth factor 21 is predictive of combined cardiovascular morbidity and mortality in patients with type 2 diabetes at a relatively short-term follow-up. *Diabetes Res Clin Pract*. 2013;101:194-200. https://doi.org/10.1016/j.diabres.2013.04.010
166. Li Q, Zhang Y, Ding D, et al. Association between serum fibroblast growth factor 21 and mortality among patients with coronary artery disease. *J Clin Endocrinol Metab*. 2016;101(12):4886-4894. https://doi.org/10.1210/jc.2016-2308
167. Lakhani I, Gong M, Wong WT, et al. International Health Informatics Study (IHIS) Network. Fibroblast growth factor 21 in cardiometabolic disorders: a systematic review and meta-analysis. *Metabolism*. 2018;83:11-17. https://doi.org/10.1016/j.metabol.2018.01.017
168. Conus F, Allison DB, Rabasa-Lhoret R, et al. Metabolic and behavioral characteristics of metabolically obese but normal-weight women. *J Clin Endocrinol Metab*. 2004;89(10):5013-5020. https://doi.org/10.1210/jc.2004-0265
169. Eckel N, Mühlenbruch K, Meidtner K, Boeing H, Stefan N, Schulze MB. Characterization of metabolically unhealthy normal-weight individuals: risk factors and their associations with type 2 diabetes. *Metabolism*. 2015;64(8):862-871. https://doi.org/10.1016/j.metabol.2015.03.009
170. Hajian-Tilaki K, Heidari B. Metabolically healthy obese and unhealthy normal weight in Iranian adult population: prevalence and the associated factors. *Diabetes Metab Syndr*. 2018;12(2):129-134. https://doi.org/10.1016/j.dsx.2017.11.005
171. Attvall S, Fowelin J, Lager I, Von Schenck H, Smith U. Smoking induces insulin resistance--a potential link with the insulin resistance syndrome. *J Intern Med*. 1993;233(4):327-332. https://doi.org/10.1111/j.1365-2796.1993.tb00680.x
172. Petersen AMW, Magkos F, Atherton P, et al. Smoking impairs muscle protein synthesis and increases the expression of myostatin and MAFbx in muscle. *Am J Physiol Endocrinol Metab*. 2007;293(3):E843-E848. https://doi.org/10.1152/ajpendo.00301.2007
173. Koren D, Taveras EM. Association of sleep disturbances with obesity, insulin resistance and the metabolic syndrome. *Metabolism*. 2018;84:67-75. https://doi.org/10.1016/j.metabol.2018.04.001
174. Spaeth AM, Dinges DF, Goel N. Effects of experimental sleep restriction on weight gain, caloric intake, and meal timing in healthy adults. *Sleep*. 2013;36(7):981-990. https://doi.org/10.5665/sleep.2792
175. Gangwisch JE, Malaspina D, Boden-Albala B, Heymsfield SB. Inadequate sleep as a risk factor for obesity: analyses of the NHANES I. *Sleep*. 2005;28(10):1289-1296. https://doi.org/10.1093/sleep/28.10.1289
176. Choi KM, Lee JS, Park HS, Baik SH, Choi DS, Kim SM. Relationship between sleep duration and the metabolic syndrome: Korean National Health and Nutrition Survey 2001. *Int J Obes*. 2008;32:1091-1097. https://doi.org/10.1038/ijo.2008.62
177. Donga E, van Dijk M, van Dijk JG, et al. A single night of partial sleep deprivation induces insulin resistance in multiple metabolic pathways in healthy subjects. *J Clin Endocrinol Metab*. 2010;95(6):2963-2968. https://doi.org/10.1210/jc.2009-2430
178. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet Lond Engl*. 1999;354(9188):1435-1439. https://doi.org/10.1016/s0140-6736(99)01376-8
179. Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *PLoS Med*. 2004;1(3):e62. https://doi.org/10.1371/journal.pmed.0010062
180. Stich FM, Huwiler S, D'Hulst G, Lustenberger C. The potential role of sleep in promoting a healthy body composition: underlying mechanisms determining muscle, fat, and bone mass and their association with sleep. *Neuroendocrinology*. 2022;112(7):673-701. https://doi.org/10.1159/000518691
181. Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med*. 2004;141(11):846-850. https://doi.org/10.7326/0003-4819-141-11-200412070-00008
182. St-Onge MP, Wolfe S, Sy M, Shechter A, Hirsch J. Sleep restriction increases the neuronal response to unhealthy food in normal-weight individuals. *Int J Obes*. 2014;38(3):411-416. https://doi.org/10.1038/ijo.2013.114
183. Dabke K, Hendrick G, Devkota S. The gut microbiome and metabolic syndrome. *J Clin Invest*. 2019;129(10):4050-4057. https://doi.org/10.1172/jci129194
184. Nam YD, Jung MJ, Roh SW, Kim MS, Bae JW. Comparative analysis of Korean human gut microbiota by barcoded pyrosequencing. *PloS One*. 2011;6(7):e22109. https://doi.org/10.1371/journal.pone.0022109
185. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. *Nature*. 2006;444(7122):1022-1023. https://doi.org/10.1038/4441022a
186. Bäckhed F, Ding H, Wang T, et al. The gut microbiota as an environmental factor that regulates fat storage. *Proc Natl Acad Sci U S A*. 2004;101(44):15718-15723. https://doi.org/10.1073/pnas.0407076101
187. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature*. 2006;444(7122):1027-1031. https://doi.org/10.1038/nature05414
188. Ley RE, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. *Proc Natl Acad Sci U S A*. 2005;102(31):11070-11075. https://doi.org/10.1073/pnas.0504978102
189. Erridge C, Attina T, Spickett CM, Webb DJ. A high-fat meal induces low-grade endotoxemia: evidence of a novel mechanism of postprandial inflammation. *Am J Clin Nutr*. 2007;86(5):1286-1292. https://doi.org/10.1093/ajcn/86.5.1286
190. Cani PD, Amar J, Iglesias MA, et al. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes*. 2007;56(7):1761-1772. https://doi.org/10.2337/db06-1491

15207560, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3725 by CAS - Wuhan Library of CAS, Wiley Online Library on [11/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

191. Lam YY, Ha CWY, Campbell CR, et al. Increased gut permeability and microbiota change associate with mesenteric fat inflammation and metabolic dysfunction in diet-induced obese mice. *PloS One*. 2012;7(3):e34233. https://doi.org/10.1371/journal.pone.0034233
192. Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. *Nat Rev Microbiol*. 2021;19(1):55-71. https://doi.org/10.1038/s41579-020-0433-9
193. Belda E, Voland L, Tremaroli V, et al. Impairment of gut microbial biotin metabolism and host biotin status in severe obesity: effect of biotin and prebiotic supplementation on improved metabolism. *Gut*. 2022;71(12):2463-2480. https://doi.org/10.1136/gutjnl-2021-325753
194. Zhao L, Zhang F, Ding X, et al. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. *Science*. 2018;359(6380):1151-1156. https://doi.org/10.1126/science.aao5774
195. Ojo O, Feng QQ, Ojo OO, Wang XH. The role of dietary fibre in modulating gut microbiota dysbiosis in patients with type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials. *Nutrients*. 2020;12(11):3239. https://doi.org/10.3390/nu12113239
196. Zhang H, Tang X, Hu D, Li G, Song G. Transition patterns of metabolism-weight phenotypes over time: a longitudinal study using the multistate Markov model in China. *Front Public Health*. 2022;10:1026751. https://doi.org/10.3389/fpubh.2022.1026751
197. Hamer M, Bell JA, Sabia S, Batty GD, Kivimäki M. Stability of metabolically healthy obesity over 8 years: the English longitudinal study of ageing. *Eur J Endocrinol*. 2015;173(5):703-708. https://doi.org/10.1530/eje-15-0449
198. Kouvari M, Chrysohoou C, Skoumas J, et al. The presence of NAFLD influences the transition of metabolically healthy to metabolically unhealthy obesity and the ten-year cardiovascular disease risk: a population-based cohort study. *Metabolism*. 2022;128:154893. https://doi.org/10.1016/j.metabol.2021.154893
199. Schröder H, Ramos R, Baena-Díez JM, et al. Determinants of the transition from a cardiometabolic normal to abnormal overweight/obese phenotype in a Spanish population. *Eur J Nutr*. 2014;53(6):1345-1353. https://doi.org/10.1007/s00394-013-0635-2
200. Eshtiaghi R, Keihani S, Hosseinpanah F, Barzin M, Azizi F. Natural course of metabolically healthy abdominal obese adults after 10 years of follow-up: the Tehran Lipid and Glucose Study. *Int J Obes*. 2015;39(3):514-519. https://doi.org/10.1038/ijo.2014.176
201. Mongraw-Chaffin M, Foster MC, Kalyani RR, et al. Obesity severity and duration are associated with incident metabolic syndrome: evidence against metabolically healthy obesity from the multi-ethnic study of atherosclerosis. *J Clin Endocrinol Metab*. 2016;101(11):4117-4124. https://doi.org/10.1210/jc.2016-2460
202. Elías-López D, Vargas-Vázquez A, Mehta R, et al. Natural course of metabolically healthy phenotype and risk of developing Cardiometabolic diseases: a three years follow-up study. *BMC Endocr Disord*. 2021;21(1):85. https://doi.org/10.1186/s12902-021-00754-1
203. Vilela DLS, Fonseca PG, Pinto SL, Bressan J. Influence of dietary patterns on the metabolically healthy obesity phenotype: a systematic review. *Nutr Metab Cardiovasc Dis*. 2021;31(10):2779-2791. https://doi.org/10.1016/j.numecd.2021.05.007
204. Mehrabi F, Amiri P, Cheraghi L, Kheradmand A, Hosseinpanah F, Azizi F. Emotional states of different obesity phenotypes: a sex-specific study in a west-Asian population. *BMC Psychiatr*. 2021;21(1):124. https://doi.org/10.1186/s12888-021-03131-3
205. Michels N, Sioen I, Huybrechts I, et al. Negative life events, emotions and psychological difficulties as determinants of salivary cortisol in Belgian primary school children. *Psychoneuroendocrinology*. 2012;37(9):1506-1515. https://doi.org/10.1016/j.psyneuen.2012.02.004
206. Toledo-Corral CM, Ding L, Morales JC, Chapman TM, Romero MB, Weigensberg MJ. Morning serum cortisol is uniquely associated with cardiometabolic risk independent of body composition in Latino adolescents. *Metab Syndr Relat Disord*. 2023;21(4):214-221. https://doi.org/10.1089/met.2022.0091
207. Michels N, Sioen I, Braet C, et al. Relation between salivary cortisol as stress biomarker and dietary pattern in children. *Psychoneuroendocrinology*. 2013;38(9):1512-1520. https://doi.org/10.1016/j.psyneuen.2012.12.020
208. Kuryłowicz A. Estrogens in adipose tissue physiology and obesity-related dysfunction. *Biomedicines*. 2023;11(3):690. https://doi.org/10.3390/biomedicines11030690
209. Kalyani RR, Dobs AS. Androgen deficiency, diabetes, and the metabolic syndrome in men. *Curr Opin Endocrinol Diabetes Obes*. 2007;14(3):226-234. https://doi.org/10.1097/MED.0b013e32814db856
210. Kelly DM, Jones TH. Testosterone: a metabolic hormone in health and disease. *J Endocrinol*. 2013;217(3):R25-R45. https://doi.org/10.1530/JOE-12-0455
211. Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions? A systematic review and meta-analysis. *Ann Intern Med*. 2013;159(11):758-769. https://doi.org/10.7326/0003-4819-159-11-201312030-00008
212. Bell JA, Kivimaki M, Hamer M. Metabolically healthy obesity and risk of incident type 2 diabetes: a meta-analysis of prospective cohort studies. *Obes Rev Off J Int Assoc Study Obes*. 2014;15(6):504-515. https://doi.org/10.1111/obr.12157
213. Jung CH, Lee MJ, Kang YM, et al. The risk of incident type 2 diabetes in a Korean metabolically healthy obese population: the role of systemic inflammation. *J Clin Endocrinol Metab*. 2015;100(3):934-941. https://doi.org/10.1210/jc.2014-3885
214. Eckel N, Meidtner K, Kalle-Uhlmann T, Stefan N, Schulze MB. Metabolically healthy obesity and cardiovascular events: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2016;23(9):956-966. https://doi.org/10.1177/2047487315623884
215. Al-Khalidi B, Kimball SM, Kuk JL, Ardern CI. Metabolically healthy obesity, vitamin D, and all-cause and cardiometabolic mortality risk in NHANES III. *Clin Nutr*. 2019;38(2):820-828. https://doi.org/10.1016/j.clnu.2018.02.025
216. Guo F, Garvey WT. Cardiometabolic disease risk in metabolically healthy and unhealthy obesity: stability of metabolic health status in adults. *Obes Silver Spring Md*. 2016;24(2):516-525. https://doi.org/10.1002/oby.21344
217. Caleyachetty R, Thomas GN, Toulis KA, et al. Metabolically healthy obese and incident cardiovascular disease events among 3.5 million men and women. *J Am Coll Cardiol*. 2017;70(12):1429-1437. https://doi.org/10.1016/j.jacc.2017.07.763
218. Dhana K, Koolhaas CM, van Rossum EFC, et al. Metabolically healthy obesity and the risk of cardiovascular disease in the elderly population. *PloS One*. 2016;11(4):e0154273. https://doi.org/10.1371/journal.pone.0154273
219. 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(6):706-713. https://doi.org/10.1161/01.cir.0000115514.44135.a8
220. Wildman RP, McGinn AP, Lin J, et al. Cardiovascular disease risk of abdominal obesity vs. metabolic abnormalities. *Obes Silver Spring Md*. 2011;19(4):853-860. https://doi.org/10.1038/oby.2010.168
221. Bell JA, Hamer M. Healthy obesity as an intermediate state of risk: a critical review. *Expert Rev Endocrinol Metab*. 2016;11(5):403-413. https://doi.org/10.1080/17446651.2016.1220298
222. Marini MA, Succurro E, Frontoni S, et al. Metabolically healthy but obese women have an intermediate cardiovascular risk profile between healthy nonobese women and obese insulin-resistant

15207560, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3725 by CAS - Wuhan Library of CAS, Wiley Online Library on [11/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

women. *Diabetes Care*. 2007;30(8):2145-2147. https://doi.org/10.2337/dc07-0419
223. Chang Y, Kim BK, Yun KE, et al. Metabolically-healthy obesity and coronary artery calcification. *J Am Coll Cardiol*. 2014;63(24):2679-2686. https://doi.org/10.1016/j.jacc.2014.03.042
224. Sinn DH, Kang D, Cho SJ, et al. Weight change and development of subclinical carotid atherosclerosis among metabolically healthy adults: a cohort study. *J Clin Endocrinol Metab*. 2020;105(3):dgz040-e416. https://doi.org/10.1210/clinem/dgz040
225. Kwon BJ, Kim DW, Her SH, et al. Metabolically obese status with normal weight is associated with both the prevalence and severity of angiographic coronary artery disease. *Metabolism*. 2013;62(7):952-960. https://doi.org/10.1016/j.metabol.2013.01.006
226. Lin L, Zhang J, Jiang L, et al. Transition of metabolic phenotypes and risk of subclinical atherosclerosis according to BMI: a prospective study. *Diabetologia*. 2020;63(7):1312-1323. https://doi.org/10.1007/s00125-020-05116-5
227. Twig G, Afek A, Derazne E, et al. Diabetes risk among overweight and obese metabolically healthy young adults. *Diabetes Care*. 2014;37(11):2989-2995. https://doi.org/10.2337/dc14-0869
228. Song Z, Gao M, Lv J, et al. Metabolically healthy obesity, transition to unhealthy phenotypes, and type 2 diabetes in 0.5 million Chinese adults: the China Kadoorie Biobank. *Eur J Endocrinol*. 2022;186(2):233-244. https://doi.org/10.1530/eje-21-0743
229. Wang B, Zhang M, Wang S, et al. Dynamic status of metabolically healthy overweight/obesity and metabolically unhealthy and normal weight and the risk of type 2 diabetes mellitus: a cohort study of a rural adult Chinese population. *Obes Res Clin Pract*. 2018;12(1):61-71. https://doi.org/10.1016/j.orcp.2017.10.005
230. Rydén M, Petrus P, Andersson DP, et al. Insulin action is severely impaired in adipocytes of apparently healthy overweight and obese subjects. *J Intern Med*. 2019;285(5):578-588. https://doi.org/10.1111/joim.12887
231. Ampuero J, Aller R, Gallego-Durán R, et al. Significant fibrosis predicts new-onset diabetes mellitus and arterial hypertension in patients with NASH. *J Hepatol*. 2020;73(1):17-25. https://doi.org/10.1016/j.jhep.2020.02.028
232. Sung KC, Wild SH, Kwag HJ, Byrne CD. Fatty liver, insulin resistance, and features of metabolic syndrome: relationships with coronary artery calcium in 10,153 people. *Diabetes Care*. 2012;35(11):2359-2364. https://doi.org/10.2337/dc12-0515
233. Hjelmgren O, Gummesson A, Bergström G, Schmidt C. Beta-cell function, self-rated health, and lifestyle habits in 64-year-old Swedish women with metabolically healthy obesity phenotype. *J Obes Metab Syndr*. 2020;29(1):39-46. https://doi.org/10.7570/jomes19078
234. Lotta LA, Abbasi A, Sharp SJ, et al. Definitions of metabolic health and risk of future type 2 diabetes in BMI categories: a systematic review and network meta-analysis. *Diabetes Care*. 2015;38(11):2177-2187. https://doi.org/10.2337/dc15-1218
235. 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*. 2013;79(3):364-370. https://doi.org/10.1111/cen.12154
236. Dhalwani NN, Zaccardi F, Davies MJ, Khunti K. Body mass index and mortality in people with and without diabetes: a UK Biobank study. *Nutr Metab Cardiovasc Dis NMCD*. 2018;28(12):1208-1216. https://doi.org/10.1016/j.numecd.2018.07.007
237. Carnethon MR, De Chavez PJD, Biggs ML, et al. Association of weight status with mortality in adults with incident diabetes. *JAMA*. 2012;308(6):581-590. https://doi.org/10.1001/jama.2012.9282
238. Akirov A, Shochat T, Masri-Iraqi H, Dicker D, Diker-Cohen T, Shimon I. Body mass index and mortality in patients with and without diabetes mellitus. *Diabetes Metab Res Rev*. 2018;34(4):e2979. https://doi.org/10.1002/dmrr.2979
239. Lavie CJ, De Schutter A, Milani RV. Healthy obese versus unhealthy lean: the obesity paradox. *Nat Rev Endocrinol*. 2015;11(1):55-62. https://doi.org/10.1038/nrendo.2014.165
240. Lontchi-Yimagou E, Dasgupta R, Anoop S, et al. An atypical form of diabetes among individuals with low BMI. *Diabetes Care*. 2022;45(6):1428-1437. https://doi.org/10.2337/dc21-1957
241. Mohan V, Vijayaprabha R, Rema M, et al. Clinical profile of lean NIDDM in South India. *Diabetes Res Clin Pract*. 1997;38(2):101-108. https://doi.org/10.1016/s0168-8227(97)00088-0
242. Fauchier G, Bisson A, Bodin A, et al. Metabolically healthy obesity and cardiovascular events: a nationwide cohort study. *Diabetes Obes Metab*. 2021;23(11):2492-2501. https://doi.org/10.1111/dom.14492
243. Dobson R, Burgess MI, Sprung VS, et al. Metabolically healthy and unhealthy obesity: differential effects on myocardial function according to metabolic syndrome, rather than obesity. *Int J Obes*. 2016;40(1):153-161. https://doi.org/10.1038/ijo.2015.151
244. Voulgari C, Tentolouris N, Dilaveris P, Tousoulis D, Katsilambros N, Stefanadis C. Increased heart failure risk in normal-weight people with metabolic syndrome compared with metabolically healthy obese individuals. *J Am Coll Cardiol*. 2011;58(13):1343-1350. https://doi.org/10.1016/j.jacc.2011.04.047
245. Burrows R, Correa-Burrows P, Bunout D, et al. Obesity and impairment of pancreatic β-cell function in early adulthood, independent of obesity age of onset: the Santiago Longitudinal Study. *Diabetes Metab Res Rev*. 2021;37(2):e3371. https://doi.org/10.1002/dmrr.3371
246. Garvey WT, Mechanick JI, Brett EM, et al. American association of clinical endocrinologists and american college of endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocr Pract Off J Am Coll Endocrinol Am Assoc Clin Endocrinol*. 2016;22(Suppl 3):1-203. https://doi.org/10.4158/ep161356.esgl
247. Williamson DA, Bray GA, Ryan DH. Is 5% weight loss a satisfactory criterion to define clinically significant weight loss? *Obes Silver Spring Md*. 2015;23(12):2319-2320. https://doi.org/10.1002/oby.21358
248. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation*. 2014;129(25 Suppl 2):S102-S138. https://doi.org/10.1161/01.cir.0000437739.71477.ee
249. Perseghin G. Is a nutritional therapeutic approach unsuitable for metabolically healthy but obese women? *Diabetologia*. 2008;51:1567-1569. https://doi.org/10.1007/s00125-008-1077-x
250. Stelmach-Mardas M, Walkowiak J. Dietary Interventions and changes in cardio-metabolic parameters in metabolically healthy obese subjects: a systematic review with meta-analysis. *Nutrients*. 2016;8:455. https://doi.org/10.3390/nu8080455
251. Freire R. Scientific evidence of diets for weight loss: different macronutrient composition, intermittent fasting, and popular diets. *Nutr Burbank Los Angel Cty Calif*. 2020;69:110549. https://doi.org/10.1016/j.nut.2019.07.001
252. Tay J, Thompson CH, Luscombe-Marsh ND, et al. Effects of an energy-restricted low-carbohydrate, high unsaturated fat/low saturated fat diet versus a high-carbohydrate, low-fat diet in type 2 diabetes: a 2-year randomized clinical trial. *Diabetes Obes Metab*. 2018;20(4):858-871. https://doi.org/10.1111/dom.13164
253. Kirkpatrick CF, Bolick JP, Kris-Etherton PM, et al. Review of current evidence and clinical recommendations on the effects of low-carbohydrate and very-low-carbohydrate (including ketogenic) diets for the management of body weight and other cardiometabolic risk factors: a scientific statement from the National Lipid Association Nutrition and Lifestyle Task Force. *J*

15207560, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3725 by CAS - Wuhan Library of CAS, Wiley Online Library on [11/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Clin Lipidol. 2019;13(5):689-711.e1. https://doi.org/10.1016/j.jacl.2019.08.003
254. Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med*. 2018;378(25):e34. https://doi.org/10.1056/nejmoa1800389
255. Salas-Salvadó J, Bulló M, Estruch R, et al. Prevention of diabetes with Mediterranean diets: a subgroup analysis of a randomized trial. *Ann Intern Med*. 2014;160:1-10. https://doi.org/10.7326/m13-1725
256. Di Daniele N, Noce A, Vidiri MF, et al. Impact of Mediterranean diet on metabolic syndrome, cancer and longevity. *Oncotarget*. 2017;8(5):8947-8979. https://doi.org/10.18632/oncotarget.13553
257. Park YM, Steck SE, Fung TT, et al. Mediterranean diet and mortality risk in metabolically healthy obese and metabolically unhealthy obese phenotypes. *Int J Obes*. 2016;40(10):1541-1549. https://doi.org/10.1038/ijo.2016.114
258. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet Lond Engl*. 2018;391(10120):541-551. https://doi.org/10.1016/s0140-6736(17)33102-1
259. Hall KD, Kahan S. Maintenance of lost weight and long-term management of obesity. *Med Clin North Am*. 2018;102(1):183-197. https://doi.org/10.1016/j.mcna.2017.08.012
260. Gaesser GA, Angadi SS, Sawyer BJ. Exercise and diet, independent of weight loss, improve cardiometabolic risk profile in overweight and obese individuals. *Phys Sportsmed*. 2011;39(2):87-97. https://doi.org/10.3810/psm.2011.05.1898
261. Borel AL, Nazare JA, Baillot A, et al. Cardiometabolic risk improvement in response to a 3-yr lifestyle modification program in men: contribution of improved cardiorespiratory fitness vs. weight loss. *Am J Physiol Endocrinol Metab*. 2017;312(4):E273-E281. https://doi.org/10.1152/ajpendo.00278.2016
262. Vissers D, Hens W, Taeymans J, Baeyens JP, Poortmans J, Van Gaal L. The effect of exercise on visceral adipose tissue in overweight adults: a systematic review and meta-analysis. *PloS One*. 2013;8(2):e56415. https://doi.org/10.1371/journal.pone.0056415
263. Hens W, Taeyman J, Cornelis J, Gielen J, Van Gaal L, Vissers D. The effect of lifestyle interventions on excess ectopic fat deposition measured by noninvasive techniques in overweight and obese adults: a systematic review and meta-analysis. *J Phys Act Health*. 2016;13(6):671-694. https://doi.org/10.1123/jpah.2015-0560
264. Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384(11):989-1002. https://doi.org/10.1056/nejmoa2032183
265. Dai Y, Mehta JL, Chen M. Glucagon-like peptide-1 receptor agonist liraglutide inhibits endothelin-1 in endothelial cell by repressing nuclear factor-kappa B activation. *Cardiovasc Drugs Ther*. 2013;27(5):371-380. https://doi.org/10.1007/s10557-013-6463-z
266. Zhao X, Wang M, Wen Z, et al. GLP-1 receptor agonists: beyond their pancreatic effects. *Front Endocrinol*. 2021;12:721135. https://doi.org/10.3389/fendo.2021.721135
267. Zhao T, Parikh P, Bhashyam S, et al. Direct effects of glucagon-like peptide-1 on myocardial contractility and glucose uptake in normal and postischemic isolated rat hearts. *J Pharmacol Exp Ther*. 2006;317(3):1106-1113. https://doi.org/10.1124/jpet.106.100982
268. Volpe S, Lisco G, Racaniello D, et al. Once-weekly semaglutide induces an early improvement in body composition in patients with type 2 diabetes: a 26-Week Prospective Real-Life Study. *Nutrients*. 2022;14(12):2414. https://doi.org/10.3390/nu14122414
269. Wilding JPH, Batterham RL, Calanna S, et al. Impact of semaglutide on body composition in adults with overweight or obesity: exploratory analysis of the STEP 1 Study. *J Endocr Soc*. 2021;5(Suppl_1):A16-A17. https://doi.org/10.1210/jendso/bvab048.030
270. Volpe S, Lisco G, Fanelli M, et al. Once-weekly subcutaneous semaglutide improves fatty liver disease in patients with type 2 diabetes: a 52-week prospective real-life study. *Nutrients*. 2022;14(21):4673. https://doi.org/10.3390/nu14214673
271. Raptis DD, Mantzoros CS, Polyzos SA. Fibroblast Growth Factor-21 as a potential therapeutic target of nonalcoholic fatty liver disease. *Ther Clin Risk Manag*. 2023;19:77-96. https://doi.org/10.2147/TCRM.S352008
272. Nielsen MH, Gillum MP, Vrang N, et al. Hepatoprotective effects of the long-acting fibroblast growth factor 21 analog PF-05231023 in the GAN diet-induced obese and biopsy-confirmed mouse model of nonalcoholic steatohepatitis. *Am J Physiol Gastrointest Liver Physiol*. 2023;324(5):G378-G388. https://doi.org/10.1152/ajpgi.00157.2022
273. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. *JAMA*. 2004;292(14):1724-1737. https://doi.org/10.1001/jama.292.14.1724
274. Sjöström 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(3):219-234. https://doi.org/10.1111/joim.12012
275. Sjöström L. Bariatric surgery and reduction in morbidity and mortality: experiences from the SOS study. *Int J Obes*. 2008;32(Suppl 7):S93-S97. https://doi.org/10.1038/ijo.2008.244
276. Cancello R, Henegar C, Viguerie N, et al. Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss. *Diabetes*. 2005;54(8):2277-2286. https://doi.org/10.2337/diabetes.54.8.2277
277. Genua I, Tuneu L, Ramos A, et al. Effectiveness of bariatric surgery in patients with the metabolically healthy obese phenotype. *Obes Surg*. 2021;31(2):517-522. https://doi.org/10.1007/s11695-020-04967-6
278. Goday A, Benaiges D, Parri A, et al. Can bariatric surgery improve cardiovascular risk factors in the metabolically healthy but morbidly obese patient? *Surg Obes Relat Dis Off J Am Soc Bariatr Surg*. 2014;10(5):871-876. https://doi.org/10.1016/j.soard.2014.04.022
279. Rubin R. What's the best way to treat normal-weight people with metabolic abnormalities? *JAMA*. 2018;320(3):223-225. https://doi.org/10.1001/jama.2018.8188
280. Park YMM, Fung TT, Steck SE, et al. Diet quality and mortality risk in metabolically obese normal-weight adults. *Mayo Clin Proc*. 2016;91(10):1372-1383. https://doi.org/10.1016/j.mayocp.2016.06.022

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Agius R, Pace NP, Fava S. Phenotyping obesity: a focus on metabolically healthy obesity and metabolically unhealthy normal weight. *Diabetes Metab Res Rev*. 2024;e3725. https://doi.org/10.1002/dmrr.3725

15207560, 2024, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3725 by CAS - Wuhan Library of CAS, Wiley Online Library on [11/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License