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REVIEW

Metabolic health in normal-weight and obese individuals

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Abstract

Cardiovascular complications are commonly associated with obesity. However, a subgroup of obese individuals may not be at an increased risk for cardiovascular complications; these individuals are said to have metabolically healthy obesity (MHO). In contrast, metabolically unhealthy individuals are at high risk of cardiovascular disease (CVD), irrespective of BMI; thus, this group can include individuals within the normal weight category (BMI 18.5–24.9 kg/m^2). This review provides a summary of prospective studies on MHO and metabolically unhealthy normal-weight (MUHNW) phenotypes. Notably, there is ongoing dispute surrounding the concept of MHO, including the lack of a uniform definition and the potentially transient nature of metabolic health status. This review highlights the relevance of alternative measures of body fatness, specifically measures of fat distribution, for determining MHO and MUHNW. It also highlights alternative approaches of risk stratification, which account for the continuum of risk in relation to CVD, which is observable for most risk factors. Moreover, studies evaluating the transition from metabolically healthy to unhealthy phenotypes and potential determinants for such conversions are discussed. Finally, the review proposes several strategies for the use of epidemiological research to further inform the current debate on metabolic health and its determination across different stages of body fatness.

Keywords Cardiovascular diseases · Cohort studies · Metabolically benign · Obesity · Review

Abbreviations

CVD	Cardiovascular disease
MHO	Metabolically healthy obesity
MUHNW	Metabolically unhealthy normal-weight

Introduction

Obesity is a worldwide epidemic that poses considerable problems for an individual's health and has large cost implications associated with its prevention and the treatment of its complications [1, 2]. More specifically, cardiovascular complications are particularly common with obesity. However, a subgroup of obese individuals may not be at an increased risk for cardiovascular complications; these individuals are said to have metabolically healthy obesity (MHO) [3, 4]. Distinguishing MHO from obesity with substantially elevated risk of cardiovascular complications would allow us to focus interventions, such as weight loss, on those likely to benefit most. This may be a practical and important step towards personalised medicine for obesity [4]. Yet, the concept of MHO has been disputed for several reasons, including the lack of a uniform definition of the condition and risks associated with obesity other than cardiovascular disease (CVD) [3, 5].

On the other hand, metabolically unhealthy subgroups of individuals are at high risk of CVD irrespective of BMI; this group may include individuals within the normal weight category, with a BMI of 18.5–24.9 kg/m^2 (the metabolically unhealthy normal-weight [MUHNW] phenotype) [6, 7]. Importantly, individuals in the MUHNW group have not been focused on with regards to the prevention of diseases more commonly related to obesity, such as CVD.

This review discusses several aspects of metabolic health in obese and normal-weight individuals, including: (1) the

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evidence from prospective studies on MHO and MUHNW phenotypes; (2) the role of body-fat distribution patterns in MHO and MUHNW; (3) prospective studies on the transition from metabolically healthy to unhealthy phenotypes and its consequences; and (4) potential determinants for such conversions in metabolic health status.

Evidence for an MHO phenotype

Individuals within specific BMI groups can be further stratified for the absence or presence of cardiometabolic risk factors (other than BMI). The term 'MHO' thus applies to obese individuals in whom cardiometabolic risk factors are (largely) absent. The use of the term 'healthy' implies here that individuals who fall into the MHO category are not at an increased risk of cardiometabolic complications compared with individuals with a normal weight. Several studies have evaluated subgroups of individuals categorised by BMI and cardiometabolic risk factors (determined at baseline) to assess their subsequent risk of CVD and/or mortality [8–11]. In addition to BMI, the criteria used to define subgroups in the context of metabolic health is frequently based on: (1) the absence/presence of the metabolic syndrome; and (2) insulin sensitivity. Interestingly, findings from several meta-analyses [8–11] and recent large-scale cohort studies [12–14] do not clearly support the notion that MHO subgroups, as currently defined, are protected from cardiometabolic complications (Table 1).

The absence of the metabolic syndrome in obesity has most commonly been used to define MHO. Although various definitions have been considered, most studies include measures of blood pressure, triacylglycerols, HDL-cholesterol and plasma glucose [8–11]. Importantly, the mere absence of the metabolic syndrome alone does not mean that individual risk factors will not be present. However, more rigorous definitions of metabolic health, e.g. absence of all individual components of the metabolic syndrome, have rarely been investigated [8, 11]. Importantly, the proportion of obese individuals considered to be metabolically healthy varies largely depending on the definition of MHO used. To illustrate this point, Fig. 1 shows prevalence estimates of MHO using different definitions, using data from the Third National Health and Nutrition Examination Survey (NHANES III), which has formed the basis for several prospective studies on MHO [3, 8]. The prevalence of MHO in this survey varied between 47% when classified based on the absence of the metabolic syndrome as defined by the National Cholesterol Education Program Adult Treatment Panel III [15], 32% if based on insulin sensitivity (using a HOMA-IR cut-off of 2.5, similar to several previous studies [3]) and 10% if based on all components of the metabolic syndrome being simultaneously absent (Fig. 1). Moreover, the different definitions of MHO in Fig. 1 only partly overlap in terms of identifying those with MHO; for example, only approximately one-third of those identified as having MHO based on insulin sensitivity are also identified as having MHO based on absence of the metabolic syndrome. This becomes even more complicated when considering that individual metabolic risk factors are defined differently between studies, ranging from the presence/absence of manifest diagnosed conditions (e.g. type 2 diabetes) [12, 13] to risk factor levels prior to disease onset [8–11], the latter identifying a smaller proportion of individuals with MHO. For example, if only excluding individuals with manifest diagnosed conditions from the MHO group, this group would have higher cardiovascular risk than if individuals with pre-clinical risk factors were also excluded. However, the same exclusions should be applied to the normal-weight metabolic healthy reference group, for comparison. Whether the choice of risk factor-thresholds actually affects the associations between MHO and risk of cardiometabolic complications observable in studies has not yet been evaluated. Overall, the heterogeneity of the methods used to define metabolic health across studies poses as a major limitation of this line of research.

The MUHNW phenotype

In studies related to metabolic health, the highest risk for cardiometabolic complications has been found among the group considered to be metabolically unhealthy, irrespective of BMI. This includes individuals within the normal-weight category according to BMI [16]. For example, according to prospective studies [8–10, 13, 14], risk for CVD among MUHNW individuals is about 1.5–3-fold higher than among metabolically healthy individuals with normal weight (Table 1); this risk was higher than the relative risk in those with MHO. In prospective studies, characteristics that were used to define metabolically unhealthy subgroups were similar between individuals with a normal BMI and those who fell within BMI categories of overweight and obesity. Thus, as with obese individuals, the presence of the metabolic syndrome has primarily been used to reflect an unhealthy phenotype in individuals with normal weight [8–10]. However, among individuals with CVD events, the metabolic syndrome has been found to be present in a much smaller fraction of individuals with normal weight as compared with overweight and obese individuals. As an example, in the European Prospective Investigation into Cancer and Nutrition (EPIC-CVD) study, only 20% of incident CVD cases among normal-weight participants were observed in those with the metabolic syndrome at baseline; this is a considerably smaller proportion than in overweight (52%) and obese (76%) individuals [14]. This clearly points towards variation in the sensitivity of the metabolic syndrome to predict future CVD cases across the BMI range; its absence is unlikely to rule out CVD risk in normal-weight individuals. Still, the risk factors used to define the metabolic syndrome might be useful for quantifying risk in those with a normal

Table 1 Summary of selected prospective cohort studies on cardiometabolic complications in MHO and MUHNW phenotypes

Author/Study	Definition of metabolic health	Outcome measure	MHO RR (95% CI)[a]	MUHNW RR (95% CI)[a]
Meta-analyses				
Kramer et al, 2013 (8 cohorts) [10]	Absence of the metabolic syndrome	CVD and total mortality	1.19 (0.98, 1.38)	3.14 (2.36, 3.93)
Fan et al, 2013 (8 cohorts) [9]	Absence of the metabolic syndrome or insulin resistance	CVD	1.56 (1.40, 1.92)	1.81 (1.56, 2.10)
Eckel et al, 2016 (13 cohorts) [8]	Absence of the metabolic syndrome	CVD	1.45 (1.20, 1.75)	2.07 (1.62, 2.65)
Eckel et al, 2016 (5 cohorts) [8]	Absence of insulin resistance	CVD	1.39 (1.14, 1.69)	1.41 (0.79, 2.53)
Zheng et al, 2016 (18 cohorts) [11]	Various definitions, predominantly related to absence of the metabolic syndrome	CVD	1.60 (1.38, 1.84)	ND
Individual cohort studies				
EPIC-CVD [14]	Absence of the metabolic syndrome	Coronary heart disease	1.28 (1.03, 1.58)	2.15 (1.79, 2.57)
THIN [12]	Absence of diabetes, hypertension and lipid-lowering drugs	Coronary heart disease	1.49 (1.45, 1.54)	Increasing with number of metabolic abnormalities
		Cerebrovascular disease	1.07 (1.04, 1.11)	Increasing with number of metabolic abnormalities
Nurses' Health Study [13]	Absence of diabetes, hypertension and hypercholesterolaemia	CVD	1.39 (1.15, 1.68)	2.43 (2.19, 2.68)
		Myocardial infarction	1.44 (1.11, 1.86)	2.60 (2.26, 2.99)
		Stroke	1.37 (1.04, 1.81)	2.22 (1.92, 2.57)

[a] Reference: metabolically healthy normal-weight group

EPIC, European Prospective Investigation into Cancer and Nutrition; ND, no data; THIN, The Health Improvement Network

weight since there is limited evidence to show that risk factors are overall different for those with normal weight compared with those in the overweight and obese BMI subgroups. According to the results of the Emerging Risk Factor Collaboration, the associations between blood lipids [17] and hyperglycaemia [18] with CVD risk are generally not modified by BMI. The same has been reported for waist circumference and waist-to-hip ratio, although the risk gradients appear to be more pronounced for individuals with normal weight compared with those who are obese [1].

In the context of MHO and MUHNW phenotypes, the clear-cut classification of individuals according to BMI and metabolic risk factors ignores the fact that the associations between cardiometabolic disease and its risk factors are a continuum. This applies to BMI as well as other factors determining metabolic health. For example, the risk of coronary heart disease associated with BMI increases continuously with increasing BMI within the overweight and obese range [1]. Similarly, there is a stepwise increase in risk of coronary heart disease with increasing fasting glucose values within the prediabetes range (5.6–6.9 mmol/l) [18] and a more linear association with increasing HbA_{1c} (even within the normal range) [19]. In addition, CVD risk increases with increasing blood pressure [17, 18], with risk gradients already observed within the blood pressure range considered to be normal [20]. An alternative approach would be to use risk factor information on a continuous scale, as is already done, for example, in the context of global cardiovascular risk estimation. For example, the Pooled Cohort Equation [21] considers total cholesterol, HDL-cholesterol and systolic blood pressure levels on a continuous scale to estimate absolute risk of major cardiovascular events.

Relevance of body-fat distribution in the MHO and MUHNW phenotypes

A central problem of research related to the MHO and MUHNW phenotypes is that BMI is the anthropometric measure used to classify individuals. Although BMI is widely used in clinical practice and shows reasonable correlation with body fatness, it may result in misclassification on an individual level because of the varying contributions of bone mass, muscle mass and fluid to body weight [22]. Also, BMI does not reflect body-fat distribution. Waist circumference and waist-to-hip ratio better predict cardiovascular events than BMI, although this may differ across populations [1]. While this suggests that measures of body fat distribution would more accurately allow identification of individuals at cardiometabolic risk, as compared with BMI, their relative contribution to overall risk prediction is only moderate and substantially smaller than information on metabolic risk factor levels [1].

Noteworthy in this context is that few studies have used measures of body-fat distribution, such as waist circumference, to define MHO, despite these being an integral part of

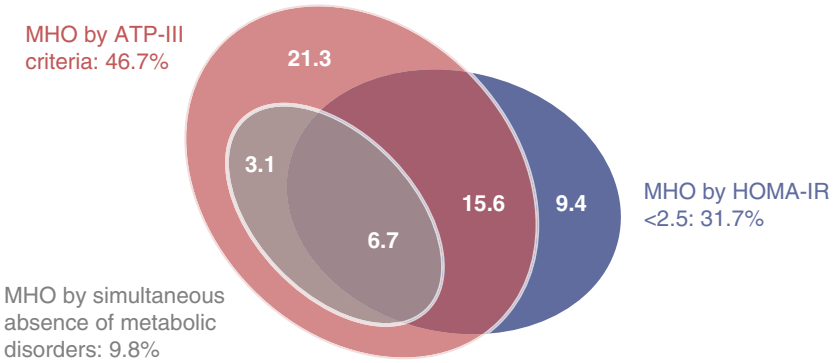

Fig. 1 Illustration of the variation in the prevalence of MHO, classified using different definitions, using data from the Third National Health and Nutrition Examination Survey (NHANES III). Criteria for metabolic health: (1) absence of the metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III (ATP-III) criteria (healthy if ≤2 of the following criteria are present: waist circumference >102 cm for men or >88 cm for women; blood pressure ≥130/85 mmHg or blood pressure lowering medication; triacylglycerols ≥1.69 mmol/l or lipid-lowering medication; HDL-cholesterol <1.04 mmol/l for men or <1.29 mmol/l for women; fasting glucose ≥6.1 mmol/l or prevalent diabetes [15]; (2) the absence of insulin resistance based on HOMA-IR (<2.5); (3) simultaneous absence of the following metabolic disorders: elevated blood pressure (≥130/85 mmHg or blood pressure lowering medication), elevated glucose/HbA_{1c} levels (fasting glucose ≥5.55 mmol/l, HbA_{1c} ≥39 mmol/mol [5.7%] or glucose-lowering medication) and impaired lipid homeostasis (triacylglycerols ≥1.69 mmol/l, total cholesterol ≥6.21 mmol/l, HDL-cholesterol <1.04 mmol/l for men or <1.29 mmol/l for women, or lipid-lowering medication) . The figure is based on data from non-pregnant participants between 18 and 75 years of age, without a history of CVD, with BMI ≥18.5 kg/m^2 and who fasted for at least 6 h before the examination (n = 12,341). Calculation of frequencies accounted for the complex survey design and was carried out using the operation 'PROC SURVEYFREQ' in SAS (version 9.4, Enterprise Guide 6.1; SAS Institute, Cary, NC, USA). This figure is available as part of a downloadable slideset

classification of the metabolic syndrome [8]. This may be explained by the high correlation between BMI and waist circumference: the vast majority of individuals with a BMI in the obese range also have a large waist circumference (>88 cm for women and >102 cm for men), according to the National Cholesterol Education Program Adult Treatment Panel III [15]. Individuals with obesity can be assumed to have an abnormal waist circumference, as defined by the International Diabetes Federation (≥80 cm for women and ≥94 cm for men) [23]. Similarly, abdominal obesity is rare among individuals with normal weight according to their BMI (Fig. 2a). Still, for a given BMI there is considerable heterogeneity in waist circumference across the range of BMI, including within the normal weight category. Instead of categorising normal weight and obesity using established cut-offs for waist circumference, stratification by measures of relative fat distribution for a given degree of overall body fatness might be more informative (Fig. 2b). This approach is strongly supported by the observation that differences in waist circumference are related to increased metabolic risk in individuals with normal weight, even if waist circumference measures are within a range that is considered normal [24]. A strong linear increase in risk for cardiovascular mortality has been described for waist circumference adjusted for BMI [25], which is different from the rather J-shaped association of BMI and waist circumference observed if these anthropometric measures are modelled individually [1, 2].

Waist circumference is a measure of central obesity and, if adjusted for BMI (thus keeping overall body fatness comparable), it more strongly reflects the accumulation of fat in the abdominal region relative to other body parts. However, metabolic abnormalities in both obese and normal-weight individuals seem to be linked to visceral or ectopic fat (specifically in the liver) [3, 5], which are only partly reflected by overall abdominal fat accumulation. Genetic analyses suggest that lipodystrophy-like mechanisms are related to insulin resistance [26], supporting the notion that metabolically unhealthy phenotypes may be associated with body-fat distribution patterns that favour visceral and ectopic fat accumulation over fat deposition in the periphery [27]. This phenomenon might particularly be present in the MUHNW phenotype [6]. Still, the relative contribution of different fat compartments, including those in the periphery, to metabolic risk in the context of the MHO and MUHNW phenotype is, so far, understudied. Data suggest that among normal-weight individuals, subcutaneous thigh fat mass is more strongly related to abnormal metabolic risk factors than liver fat, while among obese individuals, thigh fat mass seems largely unrelated to these risk factors [6]. The long-term relevance of such phenotypes in the context of metabolic health for hard endpoints such as CVD has not been studied yet.

Long-term trajectories of metabolic health

A major point of critique of the MHO concept relates to the potential conversion of individuals with MHO to an unhealthy phenotype over time [3]. Such conversion would be expected to result in an increased CVD risk. Cohort studies found higher CVD risk for MHO subgroups with longer duration of follow-up, indicating a transient nature for the phenotype

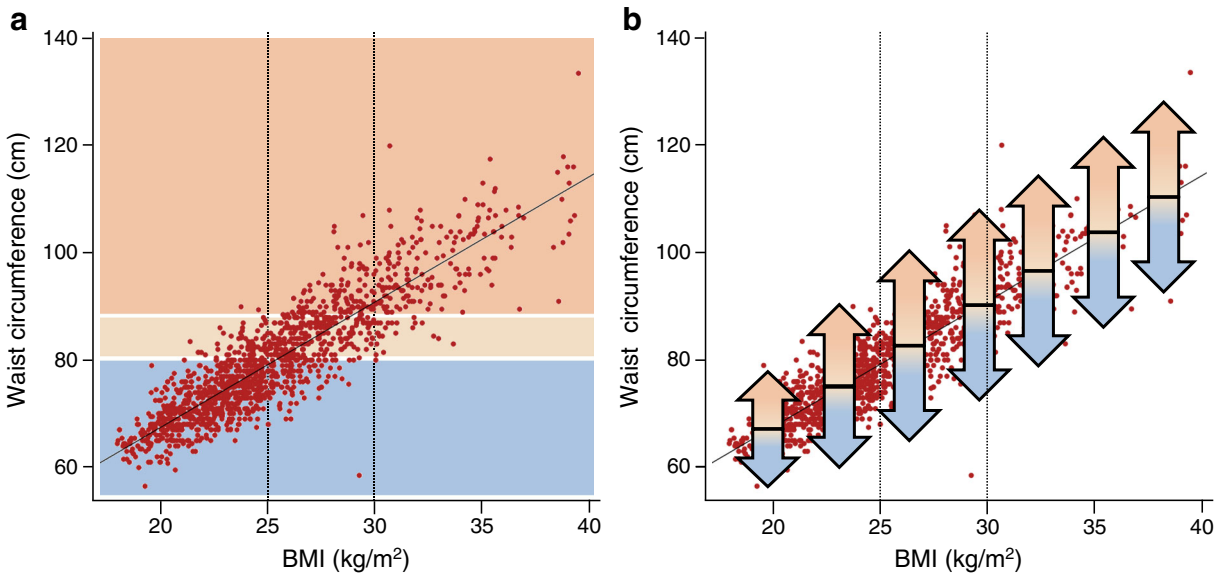

Fig. 2 Illustrative example of quantifying cardiovascular risk by BMI and waist circumference as indicators of metabolic health. (**a**) Stratification into distinct risk groups is possible using cut-offs for BMI (vertical dotted lines; 25 kg/m^2 and 30 kg/m^2) and waist circumference (white horizontal lines; 80 cm [23] and 88 cm [15] in women). However, the strong correlation between BMI and waist circumference indicates that it is unlikely that obese women will have a normal waist circumference (<80 cm) and that women within the normal weight BMI category will have a waist circumference >88 cm. Strict categorisation of waist circumference also ignores differences in risk with increasing waist circumference within these categories. (**b**) Variation in waist circumference at any given BMI can be used to quantify risk for CVD, in addition to the risk that is associated with BMI alone. This approach would better reflect the continuum of risk associated with most cardiometabolic risk factors with regards to CVD. This figure is available as part of a downloadable slideset

[8, 10]. This has been confirmed by studies with follow-up of up to 10 years, the majority of which suggest that between one-third and one-half of individuals with MHO convert to an unhealthy phenotype [13, 28–37] (Table 2). Very few studies have been conducted over longer time periods. In the Whitehall II study [30], about half of initially healthy obese individuals converted to an unhealthy phenotype over 20 years. This proportion was larger in the Nurses' Health Study [13], where only 16% and 6% of women with MHO remained metabolically healthy after 20 and 30 years, respectively. Interestingly, metabolic health is also a transient phenotype among normal-weight individuals. While ~60% of individuals with normal weight were observed to remain metabolically healthy after 10 years of follow-up in a variety of cohort studies [13, 29, 32], only ~30% remained metabolically healthy after 20 years in the Nurses' Health Study and ~15% remained metabolically healthy after 30 years of follow-up [13]. Again, the use of different definitions and measures of risk factors to define metabolic health complicates comparisons across studies. Still, it is clear that metabolic health appears to be a transient phenotype. This finding implies that, by only considering baseline metabolic health status in prospective studies, there is a real risk of harbouring considerable misclassification over time. If possible, repeated measures should be used in studies of metabolic health to update exposure status over time.

So, how is long-term risk affected by maintenance of metabolic health vs transition to unhealthy phenotypes? Studies do not clearly show that persistent MHO is unrelated to CVD risk, even if maintained over a long time. In the Nurses' Health Study, those who maintained an MHO phenotype over 20 years still had a higher risk of CVD over the 10 years' follow-up when compared with individuals who were metabolically healthy and within the normal weight category over the same time period [13]. On the other hand, conversion to a metabolically unhealthy phenotype increased CVD risk similarly among obese individuals and individuals with normal weight. The effect of conversion from metabolically healthy to unhealthy phenotypes on subsequent CVD risk may also depend on the effectiveness of pharmacological interventions. For example, hypercholesterolaemia may be less detrimental with regards to CVD risk as compared with the development of type 2 diabetes or hypertension [13], possibly due to more effective treatment regimens to lower blood cholesterol levels (and, hence, CVD risk).

Determinants for conversion from metabolically healthy to unhealthy phenotypes

With the observation that maintenance of metabolic health seems to be difficult for many, if not most,

Table 2 Summary of prospective cohort studies on long-term stability of metabolic health

Author	Study	Definition of metabolic health	Follow-up time	Findings for the MHO phenotype	Findings for the MHNW phenotype
Appleton et al, 2013 [29]	North West Adelaide Health Study	Absence of the metabolic syndrome	~8 years	Transition to MUHO: 31%	Remaining MHNW: 59%
Soriguer et al, 2013 [37]	Pizarra Study	Absence of the metabolic syndrome and/or insulin resistance	6 years	Transition to MUHO: 37%	ND
Achilike et al, 2015 [28]	San Antonio Heart Study	Absence of the metabolic syndrome, including insulin resistance	~8 years	Transition to MUHO: 48%	ND
Bell et al, 2015 [30]	Whitehall II Study	Absence of the metabolic syndrome, including insulin resistance	5, 10, 15 and 20 years	Transition to MUHO: 32% at 5 years; 41% at 10 years; 35% at 15 years; 52% at 20 years	ND
Lee et al, 2015 [33]	Chungju Metabolic Disease Cohort	In the lower 3 quartiles for fasting glucose and triacylglycerol indexes	4 years	Transition to MUHO: 15%	ND
Hamer et al, 2015 [34]	English Longitudinal Study of Ageing	Absence of the metabolic syndrome, including inflammation	8 years	Transition to MUHO: 45%	ND
Hwang et al, 2015 [39]	Japanese American Community Diabetes Study	Absence of the metabolic syndrome	10 years	Transition to MUHO[a]: 65%	ND
Kim et al, 2016 [32]	Korean Genome Epidemiology Study	Absence of the metabolic syndrome	10 years	Transition to MUHO[a]: 45%	Remaining MHNW: 60%
Kabat et al, 2017 [31]	Women's Health Initiative	Absence of the metabolic syndrome	6 years	Transition to metabolically unhealthy phenotypes: 34%	ND
Eckel et al, 2018 [13]	Nurses' Health Study	Absence of diabetes, hypertension and hypercholesterolaemia	10, 20 and 30 years	Transition to metabolically unhealthy phenotypes: 57% at 10 years; 84% at 20 years; 94% at 30 years	Remaining metabolically healthy: 63% at 10 years; 32% at 20 years; 15% at 30 years
Mongraw-Chaffin et al, 2018 [35]	Multi-Ethnic Study of Atherosclerosis	Absence of the metabolic syndrome	10 years	Transition to MUHO: 48%	ND
Moussa et al, 2018 [36]	UK Clinical Practice Research Datalink	Absence of diabetes, hypertension, hyperlipidaemia, CVD, cerebrovascular disease, liver disease, renal disease and obstructive sleep apnoea	~9 years	Transition to metabolically unhealthy phenotypes[b]: 44%	ND

[a] Obesity defined as BMI ≥ 25 kg/m^2

[b] Obesity defined as BMI ≥ 35 kg/m^2

MHNW, metabolically healthy normal-weight; MUHO, metabolically unhealthy obesity; ND, no data

irrespective of their BMI, but that conversion to unhealthy phenotypes markedly increases CVD risk [13], the question arises as to which risk factors trigger such a conversion. Conversion from metabolically healthy to unhealthy phenotypes has been related to higher baseline BMI or waist circumference [28, 29, 36] and also to longer duration of obesity [38]. Furthermore, in a study of 85 Japanese-American men and women, transition from MHO to metabolically unhealthy obesity (MUHO) was associated with greater visceral fat, but significant associations were not observed with greater abdominal subcutaneous fat [39]. Weight loss can improve metabolic risk profiles [7], even among individuals with the MUHNW phenotype, and it is also likely that weight loss is an important strategy to lower risk of conversion of metabolically healthy individuals to metabolically unhealthy phenotypes. Notably, metabolic risk factors are not merely markers of body fatness or fat distribution; instead, lifestyle choices (specifically diet) has been shown to be related to many of the metabolic risk markers used to define unhealthy phenotypes. For example, landmark trials, such as The Dietary Approaches to Stop Hypertension (DASH) trial [40], have shown that a diet rich in fruits and vegetables can reduce blood pressure. In addition, the reanalysis of the retracted PREDIMED (Prevención con Dieta Mediterránea) diet trial has not only observed lower CVD risk among those assigned to a Mediterranean diet supplemented with olive oil or with nuts [41], but also found that marked improvements in risk factor profiles were observed with little effect on body weight. Moreover, isoenergic studies suggest that modification of macronutrient composition can affect lipid levels [42]. The vast majority of premature deaths due to CVD events appear to be attributable to high-risk lifestyle patterns in combination with body fatness [43]. Still, the relative contribution of different lifestyle factors and weight gain to different cardiometabolic risk factors may be heterogeneous. For example, the relationship between fruits and vegetables with blood pressure and CVD risk have been well documented, but the level of consumption of these dietary items seem less important with regard to type 2 diabetes risk [44].

Outlook

Although an increasing number of prospective cohort studies have evaluated subgroups of obese and normal-weight individuals, the concept of metabolic health remains controversial. Epidemiological research could inform this debate, as shown in the Text box. In summary, it is hoped that ongoing research in this area will eventually allow clinicians and researchers to come to an agreement with regards to the definition of metabolic health so that it may be monitored in obese and normal-weight individuals. This may enable optimal targeting for the prevention of complications associated with poor metabolic health, including CVD, to reduce the associated health and cost burdens.

Epidemiological research in the classification of metabolic health status

- Systematic evaluation of existing and alternative strategies to define metabolic health would help us to come to an agreement upon a common definition for metabolic health phenotypes, providing information on the metabolic risk factors that should be assessed and their thresholds for diagnosis.
- Studies using repeated measures account for the time-varying nature of metabolic health and body weight. More research on the transition from metabolically healthy to unhealthy phenotypes over long periods of time would be informative.
- Identification of determinants, specifically modifiable lifestyle factors, for the transition from metabolically healthy to unhealthy phenotypes would help to identify targets for prevention. This might be specifically relevant for different groups according to body fatness.
- The evaluation of body-fat distribution patterns as potential main determinants of metabolic health and subsequent cardiometabolic risk may substantiate the notion that BMI is suboptimal for the classification of individuals with regard to cardiometabolic risk and may point towards alternative anthropometric measures for clinical use.
- Comparative evaluation of continuous risk-assessment strategies may highlight alternative approaches to the categorical classification of metabolically healthy/unhealthy individuals.

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References

1. Emerging Risk Factors Collaboration, Wormser D, Kaptoge S et al (2011) Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. Lancet 377(9771):1085–1095. https://doi.org/10.1016/S0140-6736(11)60105-0
2. Global BMI Mortality Collaboration, Di Angelantonio E, Bhupathiraju Sh N et al (2016) Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet 388:776–786. https://doi.org/10.1016/S0140-6736(16)30175-1
3. Stefan N, Haring HU, Hu FB, Schulze MB (2013) Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. Lancet Diabetes Endocrinol 1(2):152–162. https://doi.org/10.1016/S2213-8587(13)70062-7
4. Stefan N, Haring HU, Schulze MB (2018) Metabolically healthy obesity: the low-hanging fruit in obesity treatment? Lancet Diabetes Endocrinol 6(3):249–258. https://doi.org/10.1016/S2213-8587(17)30292-9
5. Neeland IJ, Poirier P, Despres JP (2018) Cardiovascular and metabolic heterogeneity of obesity: clinical challenges and implications for management. Circulation 137(13):1391–1406. https://doi.org/10.1161/CIRCULATIONAHA.117.029617
6. Stefan N, Schick F, Haring HU (2017) Causes, characteristics, and consequences of metabolically unhealthy normal weight in humans. Cell Metab 26(2):292–300. https://doi.org/10.1016/j.cmet.2017.07.008
7. Rubin R (2018) What's the best way to treat normal-weight people with metabolic abnormalities? JAMA 320(3):223–225. https://doi.org/10.1001/jama.2018.8188
8. Eckel N, Meidtner K, Kalle-Uhlmann T, Stefan N, Schulze MB (2016) Metabolically healthy obesity and cardiovascular events: a systematic review and meta-analysis. Eur J Prev Cardiol 23(9):956–966. https://doi.org/10.1177/2047487315623884
9. Fan J, Song Y, Chen Y, Hui R, Zhang W (2013) Combined effect of obesity and cardio-metabolic abnormality on the risk of cardiovascular disease: a meta-analysis of prospective cohort studies. Int J Cardiol 168(5):4761–4768. https://doi.org/10.1016/j.ijcard.2013.07.230
10. Kramer CK, Zinman B, Retnakaran R (2013) Are metabolically healthy overweight and obesity benign conditions?: A systematic review and meta-analysis. Ann Intern Med 159(11):758–769. https://doi.org/10.7326/0003-4819-159-11-201312030-00008
11. Zheng R, Zhou D, Zhu Y (2016) The long-term prognosis of cardiovascular disease and all-cause mortality for metabolically healthy obesity: a systematic review and meta-analysis. J Epidemiol Community Health 70(10):1024–1031. https://doi.org/10.1136/jech-2015-206948
12. Caleyachetty R, Thomas GN, Toulis KA et al (2017) Metabolically healthy obese and incident cardiovascular disease events among 3.5 million men and women. J Am Coll Cardiol 70(12):1429–1437. https://doi.org/10.1016/j.jacc.2017.07.763
13. Eckel N, Li Y, Kuxhaus O, Stefan N, Hu FB, Schulze MB (2018) 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 6(9):714–724. https://doi.org/10.1016/S2213-8587(18)30137-2
14. Lassale C, Tzoulaki I, Moons KGM et al (2017) Separate and combined associations of obesity and metabolic health with coronary heart disease: a pan-European case-cohort analysis. Eur Heart J 39:397–406. https://doi.org/10.1093/eurheartj/ehx448
15. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (2002) 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 106:3143–3421
16. Ruderman N, Chisholm D, Pi-Sunyer X, Schneider S (1998) The metabolically obese, normal-weight individual revisited. Diabetes 47(5):699–713. https://doi.org/10.2337/diabetes.47.5.699
17. Emerging Risk Factors Collaboration, Di Angelantonio E, Sarwar N et al (2009) Major lipids, apolipoproteins, and risk of vascular disease. JAMA 302(18):1993–2000. https://doi.org/10.1001/jama.2009.1619
18. Emerging Risk Factors Collaboration, Sarwar N, Gao P et al (2010) Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 375(9733):2215–2222. https://doi.org/10.1016/S0140-6736(10)60484-9
19. Selvin E, Steffes MW, Zhu H et al (2010) Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 362(9):800–811. https://doi.org/10.1056/NEJMoa0908359
20. Vasan RS, Larson MG, Leip EP et al (2001) Impact of high-normal blood pressure on the risk of cardiovascular disease. N Engl J Med 345(18):1291–1297. https://doi.org/10.1056/NEJMoa003417
21. Goff DC Jr, Lloyd-Jones DM, Bennett G et al (2014) 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 129(25 suppl 2):S49–S73. https://doi.org/10.1161/01.cir.0000437741.48606.98
22. World Health Organization (1995) Physical status: the use and interpretation of anthropometry. Technical Report Series No. 854; p. 327
23. Alberti KG, Zimmet P, Shaw J (2005) The metabolic syndrome—a new worldwide definition. Lancet 366(9491):1059–1062. https://doi.org/10.1016/S0140-6736(05)67402-8
24. Eckel N, Muhlenbruch K, Meidtner K, Boeing H, Stefan N, Schulze MB (2015) Characterization of metabolically unhealthy normal-weight individuals: risk factors and their associations with type 2 diabetes. Metabolism 64(8):862–871. https://doi.org/10.1016/j.metabol.2015.03.009
25. Pischon T, Boeing H, Hoffmann K et al (2008) General and abdominal adiposity and risk of death in Europe. N Engl J Med 359(20):2105–2120. https://doi.org/10.1056/NEJMoa0801891
26. Lotta LA, Gulati P, Day FR et al (2017) Integrative genomic analysis implicates limited peripheral adipose storage capacity in the pathogenesis of human insulin resistance. Nat Genet 49(1):17–26. https://doi.org/10.1038/ng.3714
27. Wittemans LBL, Lotta LA, Langenberg C (2018) Prioritising risk factors for type 2 diabetes: causal inference through genetic approaches. Curr Diab Rep 18(7):40. https://doi.org/10.1007/s11892-018-1009-1
28. Achilike I, Hazuda HP, Fowler SP, Aung K, Lorenzo C (2015) Predicting the development of the metabolically healthy obese phenotype. Int J Obes 39(2):228–234. https://doi.org/10.1038/ijo.2014.113

29. Appleton SL, Seaborn CJ, Visvanathan R et al (2013) Diabetes and cardiovascular disease outcomes in the metabolically healthy obese phenotype: a cohort study. Diabetes Care 36(8):2388–2394. https://doi.org/10.2337/dc12-1971
30. Bell JA, Hamer M, Sabia S, Singh-Manoux A, Batty GD, Kivimaki M (2015) The natural course of healthy obesity over 20 years. J Am Coll Cardiol 65(1):101–102. https://doi.org/10.1016/j.jacc.2014.09.077
31. Kabat GC, Wu WY, Bea JW et al (2017) Metabolic phenotypes of obesity: frequency, correlates and change over time in a cohort of postmenopausal women. Int J Obes 41(1):170–177. https://doi.org/10.1038/ijo.2016.179
32. Kim NH, Seo JA, Cho H et al (2016) Risk of the development of diabetes and cardiovascular disease in metabolically healthy obese people: The Korean Genome and Epidemiology Study. Medicine 95(15):e3384. https://doi.org/10.1097/MD.0000000000003384
33. Lee SH, Yang HK, Ha HS et al (2015) Changes in metabolic health status over time and risk of developing type 2 diabetes: a prospective cohort study. Medicine 94(40):e1705. https://doi.org/10.1097/MD.0000000000001705
34. Hamer M, Bell JA, Sabia S, Batty GD, Kivimaki M (2015) Stability of metabolically healthy obesity over 8 years: the English Longitudinal Study of Ageing. Eur J Endocrinol 173(5):703–708. https://doi.org/10.1530/EJE-15-0449
35. Mongraw-Chaffin M, Foster MC, Anderson CAM et al (2018) Metabolically healthy obesity, transition to metabolic syndrome, and cardiovascular risk. J Am Coll Cardiol 71(17):1857–1865. https://doi.org/10.1016/j.jacc.2018.02.055
36. Moussa O, Arhi C, Ziprin P, Darzi A, Khan O, Purkayastha S (2018) Fate of the metabolically healthy obese-is this term a misnomer? A study from the Clinical Practice Research Datalink. Int J Obes. https://doi.org/10.1038/s41366-018-0096-z
37. Soriguer F, Gutierrez-Repiso C, Rubio-Martin E et al (2013) Metabolically healthy but obese, a matter of time? Findings from the prospective Pizarra study. J Clin Endocrinol Metab 98(6):2318–2325. https://doi.org/10.1210/jc.2012-4253
38. Mongraw-Chaffin M, Foster MC, Kalyani RR et al (2016) 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 101(11):4117–4124. https://doi.org/10.1210/jc.2016-2460
39. Hwang YC, Hayashi T, Fujimoto WY et al (2015) Visceral abdominal fat accumulation predicts the conversion of metabolically healthy obese subjects to an unhealthy phenotype. Int J Obes 39(9):1365–1370. https://doi.org/10.1038/ijo.2015.75
40. Appel LJ, Moore TJ, Obarzanek E et al (1997) A clinical trial of the effects of dietary patterns on blood pressure. N Engl J Med 336(16):1117–1124. https://doi.org/10.1056/NEJM199704173361601
41. Estruch R, Ros E, Salas-Salvado J et al (2018) Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. N Engl J Med 378(25):e34. https://doi.org/10.1056/NEJMoa1800389
42. Mensink RP, Zock PL, Kester AD, Katan MB (2003) Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. Am J Clin Nutr 77(5):1146–1155. https://doi.org/10.1093/ajcn/77.5.1146
43. Li Y, Pan A, Wang DD et al (2018) Impact of healthy lifestyle factors on life expectancies in the US Population. Circulation 138(4):345–355. https://doi.org/10.1161/CIRCULATIONAHA.117.032047
44. Schulze MB, Martinez-Gonzalez MA, Fung TT, Lichtenstein AH, Forouhi NG (2018) Food based dietary patterns and chronic disease prevention. BMJ 361:k2396. https://doi.org/10.1136/bmj.k2396