

# Quick Facts on Metabolically Healthy Obesity

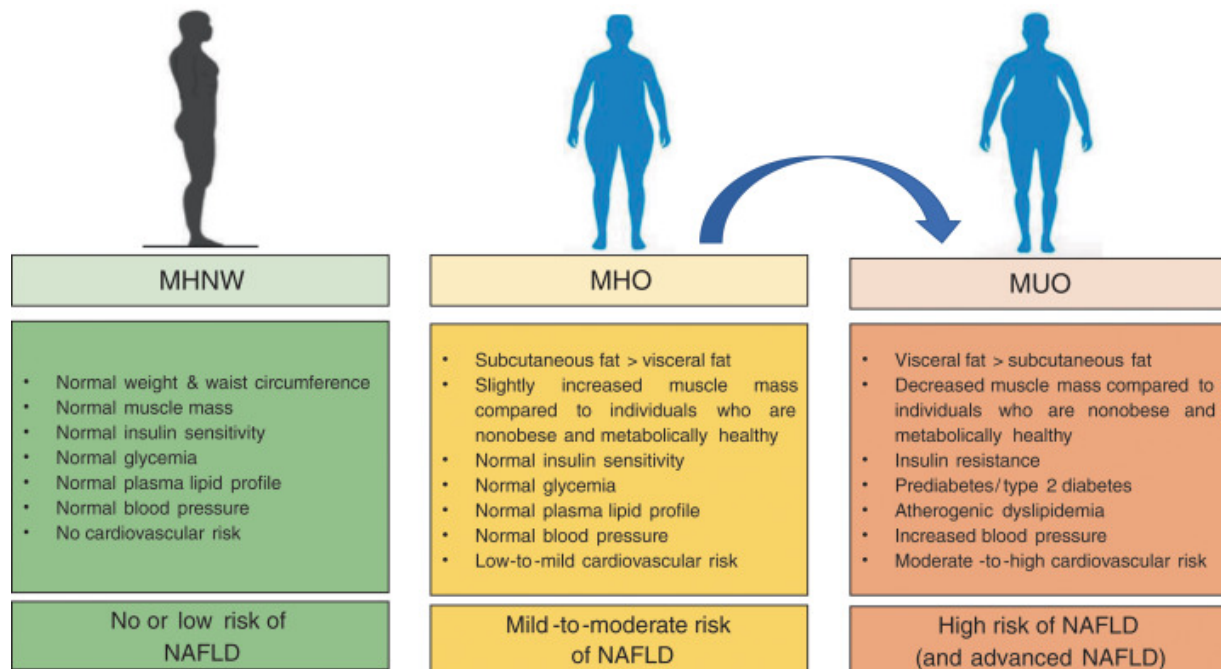
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## Introduction

Overweight and obesity are states of excessive fat accumulation that present risks to health. With their increased prevalence over the last half century, obesity and its many complications have become a leading major public health problem. Obesity is typically diagnosed by calculation of the body mass index, which also can be used to classify the severity of obesity. Body mass index correlates moderately well with adiposity, although there is considerable variability in percentage body fat and presence of comorbidities and health risk factors on an individual level for a given BMI value <sup>1</sup>.

Obesity is often associated with a constellation of metabolic abnormalities, including hypertension, glucose intolerance, insulin resistance, dyslipidemia, nonalcoholic fatty liver disease, and the metabolic syndrome, which are important risk factors for type 2 diabetes and atherosclerotic cardiovascular disease. (see Figure 1)

**Figure 1. Main cardiometabolic parameters among individuals with healthy normal weight versus metabolically healthy obesity and metabolically unhealthy obesity<sup>8</sup>.**



However, not all people with obesity have metabolic complications. Metabolically healthy obesity is a concept derived from clinical observations that a subgroup of people with obesity do not exhibit cardiometabolic abnormalities. The identification of this group came from analysis of data showing that this subgroup of obese individuals appear to have a lower risk of obesity-related cardiometabolic diseases than that which would be estimated from the positive association between body mass index and cardiometabolic risk <sup>2</sup>. Based on such data, it was subsequently suggested, albeit controversially, that identifying such individuals would be useful since these patients may not require aggressive treatment as they were thought to be less likely to develop subsequent cardiometabolic complications <sup>3</sup>. However, more recent data from long-term outcome studies demonstrate that a substantial proportion of metabolically healthy obese patients often convert to a metabolically unhealthy state, and do in fact

develop cardiometabolic disease, including overt coronary artery disease itself<sup>4-6</sup>. The finding that conversions from metabolically healthy to metabolically unhealthy obesity occur regularly suggests that metabolically healthy obesity represents a transient state, rather than a defined subgroup of obesity that remains stable.

## Description, criteria, and prevalence of metabolically unhealthy obesity

The concept of metabolically healthy obesity developed from observations made decades ago that individuals with obesity have a different susceptibility to diabetes and atherosclerosis, which, in part, could be related to body fat distribution.

At present, a set of universally accepted defining criteria for metabolically healthy obesity has not been established. Most experts agree that metabolically healthy obesity is typically marked by the absence of any metabolic and cardiovascular disease, including type 2 diabetes, dyslipidemia, hypertension, and atherosclerotic cardiovascular disease ASCVD in a person with obesity. One set of practical criteria for metabolically healthy obesity that has been proposed for adults includes (1) a diagnosis of obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) AND (2) demonstration of the following: serum triglycerides  $\leq 150$  mg/dl, serum HDL-cholesterol concentrations  $>40$  mg/dl (in men) or  $>50$  mg/dl (in women), systolic blood pressure (SBP)  $\leq 130$  mmHg, diastolic blood pressure  $\leq 85$  mmHg, no antihypertensive drug treatment and no drug to lower serum glucose<sup>7</sup>.

Additional physiologic traits of a metabolically healthy state include adequate cardiorespiratory fitness, preserved insulin secretion and sensitivity, and a predilection for lower body subcutaneous fat distribution (as opposed to liver or visceral fat)<sup>8</sup>. (Figure 1)

Data on the prevalence of metabolically healthy obesity show a great range of variation and are confounded by the lack of standardized criteria for this phenotype. One recent meta-analysis that included 12 cohort and 7 intervention studies found that  $\sim 35\%$  of the obese patients were considered metabolically healthy, though there were significant regional, ethnic, age, and sex differences and results were influenced by the criteria used to define metabolic health<sup>9</sup>.

## Natural history of metabolically unhealthy obesity

Metabolically healthy obesity is a transient phenotype which can convert into and from metabolically unhealthy obesity during cycles of weight loss and weight regain in response to obesity treatments and recidivism, respectively<sup>10</sup>. Data from longitudinal studies indicate that  $\sim 30\%$  to  $50\%$  of people with metabolically unhealthy obesity convert to a state of metabolically healthy obesity over the course of 4 to 20 years of follow-up<sup>4,5</sup>. 30-year follow-up data from over 90,000 participants of the Nurses' Health Study verified the frequent transition from metabolically healthy to metabolically unhealthy obesity and demonstrated a decline in metabolic health with age across the entire BMI range<sup>6</sup>. These findings are corroborated by a meta-analysis of 12 studies including more than 5900 individuals with 3–10-year follow-up, which demonstrated that almost half of the participants classified with metabolically healthy obesity developed at least 1 metabolic abnormality<sup>9</sup>.

The major factors associated with the conversion of metabolically healthy obesity to metabolically unhealthy obesity are a decline in insulin sensitivity and an increase in fasting blood glucose<sup>11</sup>. The risk of transitioning from metabolically healthy obesity to metabolically unhealthy obesity is greater in those with a very high BMI, older age, presence of hepatic steatosis, higher number of abnormal metabolic criteria (especially values that are close to the upper limit of the normal range), a poor lifestyle index (a composite of diet composition, leisure time physical activity, and cigarette smoking), and weight gain during the observation period<sup>5,12-14</sup>. Taken together, these longitudinal studies demonstrate that

metabolic health among those who are obese is not a stable condition and is prone to deteriorate with aging and continued weight gain.

## Cardiovascular risk in in metabolically unhealthy obesity

In general, the risks of type 2 diabetes, cardiovascular disease, and all-cause mortality are greatest in people with metabolically unhealthy obesity, followed by those with metabolically healthy obesity and least in those who are metabolically healthy and lean <sup>5,11,15–18</sup>.

The risk of cardiovascular events (myocardial infarction, sudden cardiac death, heart failure, and peripheral vascular disease) is lower in people with metabolically healthy obesity than in those with metabolically unhealthy obesity, but is still higher than in people who are metabolically healthy and lean <sup>16,17</sup>. A report from The Health Improvement Network study demonstrated that those with metabolically healthy obesity still had an increased risk of cardiovascular disease, particularly heart failure, and even coronary artery disease <sup>16</sup>. Likewise, an analysis of participants of the Nurses' Health Study found that metabolically healthy obese individuals who were able to maintain metabolic health over a long time still had a 57% higher risk of cardiovascular disease than those women with a stable normal body weight <sup>6</sup>. In the same study it was shown that the risk of cardiovascular disease clearly increased in women who converted from metabolically healthy to metabolically unhealthy obesity compared to those with stable metabolically healthy obesity <sup>6</sup>. Finally, a meta-analysis that pooled data from 18 prospective observational studies and included 585,000 participants followed over a median of 10 years found that the risk of cardiovascular events was about 50% greater in people with metabolically healthy obesity at baseline than in people who were metabolically healthy and lean <sup>15</sup>.

Hence, the risk of developing cardiovascular events depends on whether the metabolic profile phenotype remains stable and healthy, or worsens and converts to metabolically unhealthy obesity and the risk is directly related to the number of metabolic abnormalities that develop from baseline <sup>5,16</sup>.

## Risk of diabetes in metabolically unhealthy obesity

The risk of developing type 2 diabetes is substantially elevated in obese individuals who are metabolically unhealthy; it is moderately high in individuals who are obese but metabolically healthy and relatively low in people who are metabolically healthy and lean. A meta-analysis of prospective cohort studies estimated that the risk of developing type 2 diabetes is 5- to 20-fold greater in obese people who are metabolically unhealthy compared to those who are healthy and lean, whereas those with metabolically healthy obesity have a 4-fold greater risk of developing type 2 diabetes compared to those who are healthy and lean <sup>11</sup>. One cohort study that followed body weight and metabolic parameters among 34,000 young men over a 6-year time frame found that overweight and obese individuals who were metabolically healthy at baseline still had an increased risk of developing type 2 diabetes, as compared to healthy lean individuals <sup>19</sup>. The summation of these studies demonstrates that over time, metabolically healthy obesity confers less risk for developing incident diabetes compared to obesity with metabolic dysfunction, but the long-term metabolic status still remains unfavorable.

## Mortality risk in in metabolically unhealthy obesity

In general, overweight and obesity are associated with an excess risk of all-cause mortality <sup>20</sup>. Whether obese individuals who are metabolically fit are at increased risk for death is uncertain as the available data on risk of mortality is conflicting <sup>15,18,21–23</sup>. There is some evidence that the risk of mortality is elevated for individuals with metabolically healthy obesity. One prospective cohort study that included over 10,000 individuals followed for 20 years found that those individuals who were obese but without any

cardiometabolic abnormalities still had a 2-fold greater risk of mortality as compared to the reference group of healthy non-obese individuals <sup>22</sup>. A systematic review and meta-analysis that combined data from eight cohorts and 61,000 patients found that metabolically healthy obese individuals had a higher rate of mortality compared with metabolically healthy normal-weight individuals <sup>23</sup>. Notably, the mortality risk for those categorized as overweight did not achieve statistical significance, corroborating previous results that mortality risks fall along a continuum in proportion to body mass index <sup>24</sup>.

## Clinical implications

Treatment of overweight and obesity remains an arduous challenge both at the individual and public health levels. There is strong evidence from epidemiological studies that obesity, independently of other cardiometabolic risk factors, including high LDL-cholesterol, smoking, or diabetes, increases the risk for cardiovascular disease and diabetes. Collectively, the accumulating evidence over the past decade supports the notion that obesity has long-term harmful consequences on cardiometabolic health even in those individuals who are initially metabolically fit <sup>7</sup>.

The designation of metabolically healthy obesity applies to individuals fulfilling the aforementioned criteria and should not be misconstrued that such individuals with obesity have no other obesity-related health impairments. In addition to metabolic diseases (e.g., type 2 diabetes, dyslipidemia, fatty liver disease) and cardiovascular diseases (e.g., hypertension, myocardial infarction, stroke), obesity is associated with osteoarthritis, reproductive abnormalities, asthma, depression, cognitive impairment, and selected malignancies (e.g., breast, ovarian, prostate, liver, kidney, colon)—all of which can reduce quality of life, and lead to unemployment, lower productivity, and social stigma <sup>25</sup>. Therefore, the state of obesity remains an indication to initiate a treatment plan—even in those individuals without any cardiometabolic abnormalities at the time of diagnosis.

Presently, there are no randomized controlled obesity treatment trials comparing cardiometabolic outcomes between groups of individuals with metabolically healthy obesity and metabolically unhealthy obesity, which would support treatment stratification depending on metabolic status <sup>7</sup>. Until such data are available, recognizing and identifying obese individuals who are metabolically healthy provides an opportunity to intervene early and minimize the risks of developing overt cardiometabolic disease. Interventions should aim to prevent further weight gain to prevent the natural course of metabolically healthy obesity to convert into metabolically unhealthy obesity, particularly with aging.

Specific measures for clinicians treating obese individuals who are metabolically healthy to employ include (1) encourage efforts to at least maintain their current weight and avoid any further weight gain as a first step; (2) monitor the period of the menopausal transition given that this is a frequent point of conversion to metabolically healthy obesity; and (3) routinely measure the fasting blood glucose, since rising values of this parameter even within the normal range are highly predictive of conversion to metabolically unhealthy obesity.

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