

# Metabolically healthy obesity: it is time to consider its dynamic changes

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Obesity reduces life expectancy, lowers quality of life, and causes numerous cardiometabolic diseases and some cancers. However, the individual risk of developing obesity-associated comorbidities is highly variable and cannot be explained only by body mass index. Observations that some obese people have a low risk for cardiometabolic disorders gave rise to the notion of metabolically healthy obesity (MHO). Despite the lack of a precise definition, MHO is typically identified by normal glucose and lipid metabolism indices, as well as the absence of hypertension. In individuals with MHO, the absence of metabolic abnormalities may minimize the risk of mortality, cardiovascular diseases, chronic kidney disease, dementia, and cancer, compared to metabolically unhealthy individuals with obesity. However, MHO appears to be a temporary phenotype that may not confer permanent benefits to individuals with obesity, further justifying therapeutic efforts to maintain metabolic fitness. In this review, we describe the traits of the MHO phenotype, its changeable nature, and the factors associated with phenotype change. In addition, we discuss the clinical outcomes of the MHO phenotype, particularly focusing on the transition of metabolic health over time and its effect on cardiometabolic disorders. Finally, the clinical importance of maintaining metabolic health is emphasized.

**Keywords:** Metabolic syndrome; Obesity; Weight reduction; Weight gain

## INTRODUCTION

Obesity is a complex, multifactorial chronic disease associated with a higher risk of comorbidities such as metabolic syndrome, cardiovascular disease (CVD), and several types of cancer, as well as a higher risk of death from those comorbidities [1,2]. Obesity has a significant impact on patients' quality of life, limits economic and social activity, and imposes a significant financial burden on society as a whole. Despite several efforts to address the obesity pandemic and its consequences, obesity remains a serious public health concern globally [1,2]. The Korean Society for the Study of

Obesity (KSSO) defines obesity as a body mass index (BMI)  $\geq 25$  kg/m<sup>2</sup> according to the Asia-Pacific criteria of the World Health Organization guidelines, which is different from that used in Western countries [3,4]. According to the 2020 Obesity Fact Sheet by KSSO using the Korean definition, the prevalence of overall obesity was 32.6% in 2009 and increased by 1.18-fold to 38.5% in 2018, respectively [5]. Therefore, obesity is clearly a major public health problem in Korea and across the world.

However, not all obese people are at an elevated risk of obesity-related comorbidities and mortality, implying that there is a subset of healthy obese people, who have a con-

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dition known as "metabolically healthy obesity (MHO)" [6–10]. Metabolic abnormalities, such as dyslipidemia, insulin resistance, hypertension, and an unfavorable inflammatory profile, are absent in MHO [7–10]. Numerous studies have demonstrated that people with MHO have a lower risk of mortality and other comorbidities than those with metabolically unhealthy obesity (MUO) and are not at a higher risk than people who are normal weight [7–10]. However, so far, the predictive value of the MHO phenotype, as well as its clinical definition and criteria, remains a subject of debate [11,12]. Furthermore, the clinical implications of the MHO phenotype may be dependent on the health outcomes being studied [12]. Furthermore, as evidence mounts that MHO is changeable across time, researchers' focus has shifted to the consequences of phenotypic shifts in MHO individuals. In this context, the purpose of the present review was to address numerous contemporary issues concerning MHO, such as its natural course and clinical consequences, with a special emphasis on its dynamic and variable nature.

## DYNAMIC AND CHANGEABLE ASPECTS OF MHO

Obesity has been considered to be a chronic and easily relapsing disease [13–15]; these traits of obesity also apply to MHO. Individuals in long-term obesity treatment programs may experience cycles of weight reduction and weight return, with their phenotypic shifting from MUO to MHO and back again. Furthermore, nearly half of the MHO participants in the Multi-Ethnic Study of Atherosclerosis (MESA) acquired metabolic abnormalities by the end of the 12-year follow-up period [16]. This conclusion is corroborated by a meta-analysis based on estimates from 40 studies, which showed that MHO individuals had higher risk of progressing to the abnormal metabolic state than their counterparts with metabolically healthy nonobesity (MHNO), and half of the MHO individuals would lose their metabolic health over time [17]. Similarly, in a 6-year follow-up study of the prospective Pizarra trial, 30% of people classified with MHO at baseline transitioned to MUO [18]. Using the Korean National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS), our study team demonstrated the transitional character of the MHO phenotype [19]. Only 57.2% of the initial MHO group in the Korean cohort remained metabolically healthy after 2 years, whereas 42.8% experienced aggravation in their metabolic health—in

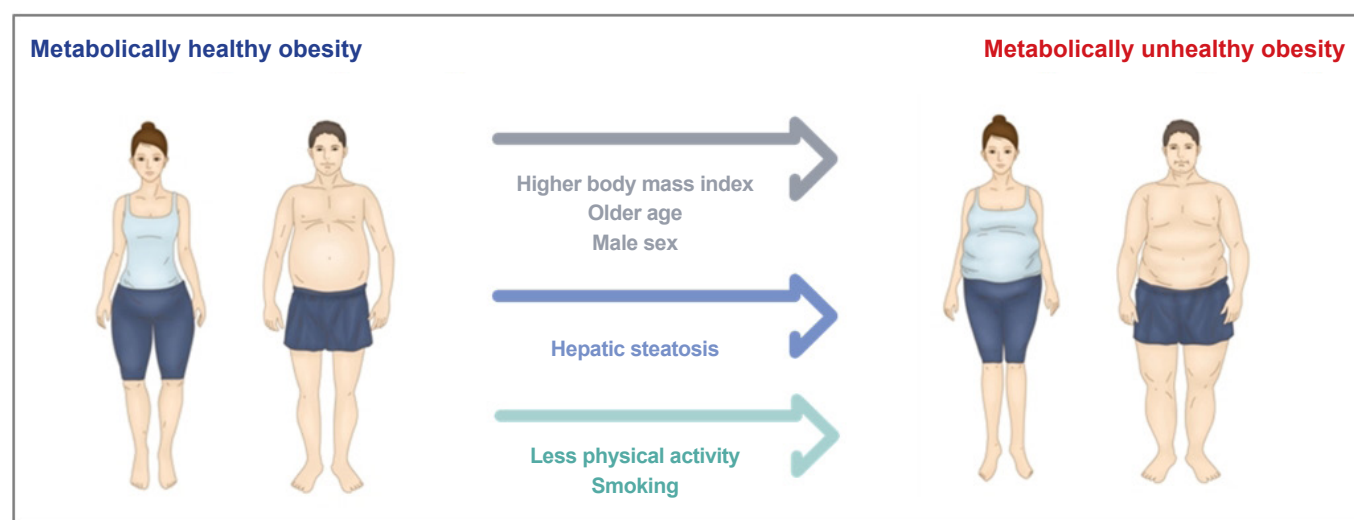
other words, transition to MUO status. However, MUO also showed a transient and reversible nature, as 11.8% of the baseline MUO group restored their metabolic health (i.e., transitioned from MUO to MHO) [19]. Therefore, the shift from MHO to MUO is not always a one-way street. Finally, as the phenotypic transition frequently occurs in both MHO and MUO, we need to focus on the implications of these transitions in health outcomes in obese patients.

High BMI, older age, evidence of more severe metabolic dysfunction (i.e., the presence of hepatic steatosis, number of abnormal metabolic criteria, and values closer to the upper limit of the normal range), and a poor lifestyle index (a composite of diet composition, leisure time physical activity, and cigarette smoking) all increase the risk of transitioning from MHO to MUO (Fig. 1) [16,20–24]. The North West Adelaide Health Study (NWAHS) of 4,056 randomly selected adults revealed that maintenance of an MHO phenotype, which was associated with favorable outcomes, was related to younger age and a more peripheral fat distribution [25]. Female sex, younger age, and lower initial weight and BMI were found to be significant predictors of sustained metabolic health in a primary care cohort from the Clinical Practice Research Datalink in the United Kingdom [22]. Our cohort study on the MHO phenotype and its CV outcomes also showed that a higher BMI and the presence of any risk factor at baseline were associated with a higher likelihood of incident impaired metabolic state [19].

## CLINICAL OUTCOMES OF MHO WITH CONSIDERATION OF ITS DYNAMIC CHANGES

### CV outcomes and mortality

The notion of MHO was derived from evidence indicating that a subgroup of obese adults lacks relevant cardiometabolic risk factors, hence reducing their risk of CVD [20,26,27]. Despite this notion, numerous studies have revealed detrimental long-term effects in MHO populations [27–29]. Indeed, previous research showed that patients with MHO had a higher risk of CVD than MHNO individuals [28]. Using a Korean nationwide population-based cohort, our research team discovered that MHO status was associated with a significant risk of CV events, showing that MHO is not a benign condition in terms of CVD [19]. The risk of CV events was greater in the MHO group than in the MHNO



**Fig. 1.** Risk factors for transition from metabolically healthy obesity to metabolically unhealthy obesity.

group (hazard ratio [HR], 1.14; 95% confidence interval [CI], 1.05–1.24). In an updated analysis of metabolic health status and BMI 2 years after the baseline examination, we further discovered that the cardiovascular outcomes of the MHO group varied substantially according to their status change over time. Among participants with MHO initially, those who transitioned to MUO had a higher risk of CV events than those who maintained MHO status (HR, 1.24; 95% CI, 1.00–1.54). Several cohort studies found poor CV outcomes in individuals who moved from MHO to a metabolically unhealthy phenotype [16,30,31]. In accordance with these prior studies, our findings demonstrated that MHO at baseline does not ensure a favorable CV outcome for patients, especially when the switch to a metabolically unhealthy phenotype occurs.

The term "obesity paradox" was adopted to explain the observation that, although higher BMI is associated with higher rates of diabetes, hypertension, dyslipidemia, and CVD, obese individuals with these conditions may have better survival outcomes than leaner individuals [32,33]. Similarly, those classed as normal weight or underweight may have a worse prognosis for CVD than those who are overweight, a phenomenon known as the "lean paradox" [34]. Our research indicated that, despite the higher incidence of cardiovascular events in obese people regardless of their metabolic health, their all-cause mortality was comparable to or lower than that of nonobese, healthy people [19]. Indeed, MHO status at baseline was related to lower

mortality than MHNO (HR, 0.86; 95% CI, 0.79–0.93) [19]. Those who transitioned from the MHO to the metabolically unhealthy nonobesity (MUNO) group—that is, shifting to a metabolically unhealthy status while concurrently losing body weight—had a higher all-cause mortality rate than those who remained in the MHO status (HR, 1.96; 95% CI, 1.45–2.65). These data provide support for the "lean paradox" and highlight the heterogeneous nature of the MHO population. Interestingly, the shift from MUO to MUNO was also associated with significantly increased all-cause mortality (HR, 1.31; 95% CI, 1.15–1.49) when the persistent MUO group was used as the reference, but the transition from MUO to MHO was associated with lower all-cause mortality (HR, 0.77; 95% CI, 0.64–0.93). These findings further reinforce the "lean paradox" by demonstrating that a catabolic condition, as indicated by weight loss, may be a powerful predictor of a poor prognosis. Further research on therapeutic interventions to prevent progression to a metabolically unhealthy phenotype might aid in improving the health effects of obesity.

### Diabetes

Diabetes is a major public health issue causing several comorbidities and mortality worldwide, with an increasing incidence and prevalence [35]. According to the International Diabetes Federation Diabetes Atlas, 537 million adults aged 20 to 79 years had diabetes in 2021, and this number is

expected to climb to 783 million by 2045 [36]. The reasons for the diabetes epidemic are numerous, including an increased prevalence of obesity-related to a sedentary lifestyle and unhealthy diet [37].

Large-scale epidemiological studies conducted in Europeans, Japanese, and Koreans found that MHO adults had a significantly higher risk of developing type 2 diabetes (T2D) than the respective MHNO reference groups [12,25,38,39]. The risk of developing T2D is substantially lower in those with MHO than in those with MUO, but it is still approximately fourfold higher than in those with MHNO [38] and is strongly related to the number of metabolic abnormalities [40–42]. In a 6-year follow-up cohort study of a rural Chinese population, the participants with baseline MHO had an elevated risk of T2D, with an adjusted HR of 1.94 (95% CI, 1.33–2.81) [43]. However, the risk of T2D was higher for people who experienced the transition from MHO to MUO when compared to stable MHNO, but not for participants who did not experience this transition [43]. As a result, maintaining a metabolically healthy status is clinically important to alleviate the risk of incident diabetes in patients with obesity.

### Chronic kidney disease

Obesity is an established risk factor for chronic kidney disease (CKD) [44–46]. To date, few longitudinal studies have investigated the risk of developing CKD in individuals with MHO [45,47–49]. In 2015, a Japanese study group reported that the MHO phenotype was not associated with a higher risk of developing CKD [49]. On the contrary, more recent studies have consistently proposed a significant association between MHO phenotype and incident CKD [45,47,50]. For example, a prospective cohort study including 62,249 metabolically healthy, young, and middle-aged men and women without CKD or proteinuria at baseline, showed that overweight and obesity were associated with an increased incidence of CKD [47]. Our research group investigated CKD risk in individuals with the MHO phenotype, with consideration of its phenotypic transition over time [51]. Based on initial health examination results, MHO status was associated with an elevated incidence of CKD (HR, 1.23; 95% CI, 1.12–1.36), suggesting that MHO is not a benign condition in the context of renal outcomes. In a follow-up analysis of metabolic health status and BMI, we found that the risk of

incident CKD in the MHO group was highly variable according to the phenotypic transition. The risk of incident CKD was particularly high in people who had progressed to a metabolically unhealthy phenotype (i.e., MHO to MUNO or MUO) compared with the stable MHNO group (MHO to MUNO group: HR, 1.60; 95% CI, 1.16–2.20; MHO to MUO group: HR, 1.68; 95% CI, 1.45–1.96). In contrast, people who reduced their body weight and maintained metabolic health were not at a higher risk for developing CKD than the stable MHNO group (MHO to MHNO group: HR, 0.98; 95% CI, 0.72–1.32). These data suggest that although people with MHO are at a high risk of CKD development, the risk of developing CKD could be mitigated if their body weight is well controlled while maintaining metabolic health. In other words, our results have important clinical implications that obesity is a modifiable risk factor in preventing CKD development in people with MHO, as well as emphasizing the significance of metabolic health in CKD development.

### Colorectal cancer

Obesity is also related to the incidence of certain forms of cancer [52]. Obesity, in particular, is a risk factor for colorectal cancer (CRC), one of the most frequent gastrointestinal malignant tumors globally [53]. To date, investigations have yielded contradictory results about the risk of CRC in MHO patients; nevertheless, an elevated risk of CRC has been found to be strongly related to MUO [54–58]. As a result, it is uncertain whether obesity, independent of obesity-related metabolic abnormalities, plays a role in the development of CRC. We investigated the relationship between obesity, metabolic health, and the transition of metabolic phenotype with CRC risk. The study comprised 319,397 patients from the Korean nationwide health examination cohort, and we divided obese patients into four groups based on their dynamic metabolic health status: MHO, MHO to MUO, MUO to MHO, and stable MUO [59]. We observed no significant difference in incident CRC risk in the stable MHO group, compared to the stable MHNO group (HR, 0.97; 95% CI, 0.83–1.14). The MHO to MUO group, in contrast, had a higher incidence of incident CRC than the stable MHNO group (HR, 1.34; 95% CI, 1.15–1.57). Among patients with MUO at baseline, those who transitioned to the MHO group had no elevated risk of CRC (HR, 1.06; 95% CI, 0.91–1.25), but those who stayed in the stable MUO group had a higher

risk of incident CRC than those who moved to the stable MHNO group (HR, 1.29; 95% CI, 1.19–1.41). Therefore, we suggest that when assessing the relationship between obesity and CRC, physicians should examine patients' metabolic health conditions and counsel them on the necessity of metabolic fitness.

## Dementia

Obesity, as previously noted, is a well-known risk factor for a variety of cardiometabolic disorders and some types of cancer. However, obesity has been found to be protective against dementia in recent studies [60–64]. Recently, two cohort studies evaluated the effects of obesity without metabolic abnormalities on Alzheimer's disease (AD) incidence [65,66]. A Korean study employing a nationwide cohort found that the MHO group had the lowest risk of AD (HR, 0.87; 95% CI, 0.86–0.88) compared to the MHNO group [66]. Similarly, in a longitudinal study of 1,199 Europeans (drawn from the Alzheimer's Disease Neuroimaging Initiative database) who were initially free of AD, the risk of AD among elderly obese individuals was significantly reduced after adjusting for metabolic status (HR, 0.70; 95% CI, 0.56–0.89) [65]. Our findings, which were obtained from a Korean nationwide health examination cohort, are consistent with those of prior research, which found that MHO individuals had a much lower risk of AD (HR, 0.73; 95% CI, 0.65–0.81). Furthermore, we discovered that AD risk was significantly dependent on changes in BMI and metabolic health phenotypes, as well as baseline status. Maintaining the MHO phenotype, in particular, was associated with a much lower chance of developing AD even compared to the MHNO phenotype (HR, 0.62; 95% CI, 0.50–0.77). Among MUO participants at baseline, those who converted to the MUNO phenotype had a higher risk of AD, but those who transitioned to the MHO phenotype were protected from AD development (HR, 0.62; 95% CI, 0.50–0.78). In contrast, our additional analyses revealed that the MHO phenotype had no protective impact against vascular dementia. The pathophysiology of vascular dementia is most likely linked to stroke, as vascular insufficiency is the predominant pathophysiologic mechanism underlying both stroke and vascular dementia [67]. Previous research has found that MHO subjects have a similar or slightly higher risk of stroke than MHNO patients [19,28,68–71]. Because the patho-

physiology of vascular dementia differs from that of AD, the effects of fat on vascular dementia may differ from those of obesity on AD.

In summary, the MHO phenotype has distinct clinical consequences for a variety of outcomes, which are largely different from those of MUO. Furthermore, the clinical implications of MHO should also be considered in a context in which metabolic health is a transitory, not a permanent, state, as this aspect of MHO phenotype significantly impacts the clinical outcomes (Table 1) [19,43,51,59,72]. In general, recovery or maintenance of metabolic health could lead to a more favorable prognosis; therefore, clinicians should counsel obese patients about metabolic fitness to help prevent the development of obesity-related comorbidities.

## PERSPECTIVES ON THE MUNO PHENOTYPE

For a long time, the critical finding of very high CV risk and mortality in subjects with MUNO was underappreciated in research on the cardiometabolic risk of individuals according to the obese metabolic health phenotype [73–77]. MUNO patients had a considerably higher risk of all-cause mortality, CKD, and colorectal cancer in our studies [19,51,59]. Moreover, MHO individuals who changed to the MUNO status had substantially higher all-cause mortality than the stable MHO group, indicating the deleterious nature of this phenotype. Stefan et al. [78] recently summarized the features of the MUNO phenotype; these lean subjects with metabolic risk factors have an unfavorable body fat distribution, such as a low leg fat mass, visceral obesity, or fatty liver. This phenotype is also characterized by decreased insulin secretion capacity and increased insulin resistance, as well as poor cardiorespiratory fitness and carotid atherosclerosis [78]. These findings urge clinicians to develop clinical interventions to improve metabolic health in these individuals, despite not being classed as traditional obesity. Indeed, well-defined phenotyping strategies will help to precisely understand the pathophysiology of cardiometabolic disease, allowing for targeted lifestyle and pharmacological interventions to prevent adverse outcomes, including the ultimate goal of reducing mortality.

## CONCLUSIONS

In the modern era of precision medicine, the heterogeneity



**Table 1.** Heterogeneous outcomes of the MHO phenotype<sup>a)</sup> according to the phenotypic transitions over time

Variable	Mortality <sup>b)</sup>	CV events <sup>b)</sup>	T2D <sup>c)</sup>	CKD <sup>d)</sup>	CRC <sup>e)</sup>	AD <sup>f)</sup>
Study	Cho et al. [19]	Cho et al. [19]	Wang et al. [43]	Cho et al. [51]	Cho et al. [59]	Cho et al. [72]
Baseline						
MHNO	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
MHO	0.86 (0.79–0.93)	1.14 (1.05–1.24)	1.94 (1.33–2.81)	1.23 (1.12–1.36)	1.14 (1.04–1.26)	0.73 (0.65–0.81)
Transition						
Stable MHNO	NA	NA	1 (Reference)	1 (Reference)	1 (Reference)	NA
MHO to MHNO	1.18 (0.87–1.61)	1.02 (0.74–1.40)	NA	0.98 (0.72–1.32)	NA	0.98 (0.71–1.34)
Stable MHO	1 (Reference)	1 (Reference)	0.31 (0.10–0.97)	1.23 (1.04–1.44)	0.97 (0.83–1.14)	0.62 (0.50–0.77)
MHO to MUNO	1.96 (1.45–2.65)	1.23 (0.86–1.78)	4.52 (1.28–16.04)	1.60 (1.16–2.20)	NA	1.23 (0.86–1.76)
MHO to MUO	1.19 (0.96–1.48)	1.24 (1.00–1.54)	3.54 (1.80–6.96)	1.68 (1.45–1.96)	1.34 (1.15–1.57)	0.97 (0.81–1.17)

Values are presented as hazard ratio (95% confidence interval).

MHO, metabolically healthy obesity; CV, cardiovascular; T2D, type 2 diabetes; CKD, chronic kidney disease; CRC, colorectal cancer; AD, Alzheimer's disease; MHNO, metabolically healthy nonobesity; NA, not applicable; MUNO, metabolically unhealthy nonobesity; MUO, metabolically unhealthy obesity.

<sup>a)</sup>Metabolically healthy subjects were defined according to the Adult Treatment Panel III criteria as having none or one of the following risk factors: (1) systolic blood pressure  $\geq 130$  mmHg and/or diastolic blood pressure  $\geq 85$  mmHg and/or taking antihypertensive treatment; (2) triglyceride  $\geq 150$  mg/dL and/or taking antidiabetic medications; (3) fasting plasma glucose  $\geq 100$  mg/dL and/or taking antidiabetic medications; and (4) high-density lipoprotein cholesterol  $< 40$  mg/dL in men and  $< 50$  mg/dL in women. <sup>b)</sup>Adjusted for baseline age, sex, smoking, alcohol drinking, physical activities, and low-density lipoprotein cholesterol level. <sup>c)</sup>Adjusted for age, sex, education level, marital status, smoking, alcohol drinking, family history of diabetes, family history of hypertension, body mass index, systolic and diastolic blood pressure, fasting plasma glucose, total cholesterol, triglyceride, and high-density lipoprotein cholesterol level. <sup>d)</sup>Adjusted for baseline age, sex, smoking, alcohol drinking, physical activity, low-density lipoprotein cholesterol level, and the baseline estimated glomerular filtration rate. <sup>e)</sup>Adjusted for baseline age, sex, smoking, alcohol drinking, income, and the presence of inflammatory bowel disease. <sup>f)</sup>Adjusted for baseline age, sex, smoking, alcohol drinking, physical activity, and income.

of clinical outcomes in obese people has significant implications. As the likelihood of developing cardiometabolic diseases is reliant on the presence of metabolic abnormalities, a definition of obesity based purely on BMI status does not provide sufficient insight into current and future health outcomes. Previous research has demonstrated that those with MHO had a lower risk of future CVD, CKD, cancer, and mortality than people with MUO; nevertheless, an elevated risk for the majority of those outcomes was observed in MHO people compared to those with MHNO. Obesity appears to be protective against AD, particularly in the absence of metabolic abnormalities. Currently, there are no randomized, controlled trials on the effectiveness of obesity treatment between individuals with MHO and MUO; however, a substantial amount of evidence suggests that maintenance or recovery of metabolic fitness in obese individuals protects them from obesity-related adverse outcomes. Further epidemiological research may discover modifiable risk factors and therapeutic interventions to prevent conversions from MHO to MUO, thereby affecting the future cardiometabolic fate of obese patients.

## ARTICLE INFORMATION

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Not applicable.

### Conflicts of interest

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