METABOLICALLY HEALTHY OBESITY AND HEALTH RISKS – A REVIEW OF META-ANALYSES

Erika Čermáková, Martin Forejt
Department of Public Health, Faculty of Medicine, Masaryk University, Brno, Czech Republic

SUMMARY

Objective: This article briefly summarizes the results of existing research on metabolically healthy obesity in the context of health risks.

Methods: The PubMed database was searched for relevant meta-analyses addressing metabolically healthy obesity in the context of health risks.

Results: We included a total of 17 relevant meta-analyses in this review. The results of the studied meta-analyses showed that metabolically healthy obesity may be only a transient condition associated with an increased risk of developing metabolic abnormalities in the future. People with obesity without metabolic abnormalities have an increased risk of type 2 diabetes, cardiovascular disease, cancer, chronic kidney disease, and depressive syndrome. In addition, all people with obesity are at risk of pathogenesis resulting from the mechanical stress caused by presence of abnormal adipose tissue, such as sleep apnoea syndrome or skin problems.

Conclusion: Based on the results of meta-analyses, we recommend motivating all obese patients to change their lifestyle regardless of the presence of metabolic defects.

Key words: metabolically healthy obesity, fit and fat phenomenon, pathogenesis of obesity, visceral fat, body fat percentage, meta-analysis

Address for correspondence: E. Čermáková, Faculty of Medicine, Masaryk University, Kamenice 5, 625 00 Brno, Czech Republic. E-mail: 211678@muni.cz

https://doi.org/10.21101/cejph.a7806

INTRODUCTION

A permanently increasing number of individuals with obesity is a global problem that gains epidemic proportions. Many studies have already shown an association of obesity with the comorbid chronic non-infectious diseases of mass incidence, such as cardiovascular disease, type 2 diabetes, and cancer. In the context of the tendency to destigmatize obese people in recent years, the term metabolically healthy obesity (MHO) is increasingly emerging. This has given rise to the "fit and fat" phenomenon, which has become an argument for many obese people to delay obesity treatment. As a result, the term "healthy obesity", which some experts consider to be a higher BMI without the accompanying expected laboratory markers, has recently been explored. This article aims to concisely and clearly describe the results of existing research on MHO in the context of health risks.

Definition of Obesity

According to the WHO definition, overweight and obesity are characterized by an abnormal or excessive accumulation of fat tissue that poses a health risk. For the diagnosis of obesity, the body mass index (BMI) is currently the most commonly used parameter. People with BMI over 25 are considered overweight and people with BMI above 30 are considered obese (1). The problem is that BMI does not include the amount of adipose tissue and especially visceral fat, which excessive amounts are associated with the occurrence of chronic inflammation of low grades in the body. This increases the risk of developing chronic non-infectious diseases with mass incidence. For this reason, it is not uncommon to see individuals who have a BMI in the normal weight range, but may be at increased risk of cardiometabolic disease due to increased intra-abdominal fat (2). The opposite is the case when an individual falls into the overweight or obese category according to BMI, but the distribution of adipose tissue is not associated with an inflammatory condition related to a higher proportion of abdominal fat. An example of a wrong BMI value could be a bodybuilder, where a higher BMI may not be associated with a high percentage of body fat. Also, individuals with gynoid-type obesity may not have increased visceral fat present.

Therefore, besides BMI, it is important to consider body fat percentage and the distribution of adipose tissue when assessing overweight and obesity. Body composition, including visceral fat content, can be more accurately determined, for example, by an analyser based on the principle of bioelectrical impedance measurement. In addition, we can estimate visceral fat content simply by measuring waist circumference. Waist circumference in women up to 80 cm and men up to 94 cm is considered normal, above 88 cm in women and 102 cm in men is associated with a high risk of comorbid cardiometabolic diseases (3).

Definition of Metabolically Healthy Obesity

The fundamental problem is that there is currently no internationally accepted definition of MHO. This fact greatly complicates prevalence research and limits the study of the health risks associated with obesity in the absence of metabolic syndrome. Over 30 different definitions of metabolic health have been used

in clinical trials to date (4, 5). Although MHO is usually defined by the absence of a metabolic defect, some studies have accepted selected cardiometabolic abnormalities (6, 7). In many studies, the presence of no more than one abnormal component of the metabolic syndrome has been tolerated to define MHO (high systolic and diastolic blood pressure, high plasma TG concentration, low HDL-C concentration, high fasting blood glucose). Therefore, many people who are categorized as MHO are not truly healthy, but simply have fewer cardiometabolic abnormalities than people who fall into the category of unhealthy obese (5).

MATERIALS AND METHODS

We searched the PubMed database (National Library of Medicine) for all English-language relevant meta-analyses from January 2000 to March 2023. The terms "metabolically healthy obesity" and "meta-analysis" were searched for in the title/abstract text. A total of 21 results were found, of which 17 relevant meta-analyses were included in the review. We selected the meta-analyses focused on the risk of developing chronic non-infectious diseases, including cardiovascular disease, type 2 diabetes, chronic kidney disease, and cancer.

RESULTS

The results of the review of meta-analyses are presented in Table 1. None of these meta-analyses have confirmed that the risk of developing chronic non-infectious diseases in MHO is comparable to that of metabolically healthy normal-weight individuals. On the contrary, the results of all these meta-analyses suggested that MHO may be only a transient condition that is associated with an increased risk of developing metabolic abnormalities in the future. The same results were confirmed by the findings of the PRISMA study, which analysed 12 cohorts and 7 intervention studies. According to the authors, nearly one-third of all obese people were in a metabolically healthy state, but at the same time, they had a higher risk of developing metabolic abnormalities and half of them would go into a metabolically unhealthy condition (8).

MHO and Cardiovascular Disease

All studied meta-analyses confirmed an increased risk of cardiovascular disease (CVD) in the MHO phenotype compared to healthy normal-weight individuals (RR from 1.45 to 1.58; 95% CI: 1.20–1.70 and 1.34–1.85, respectively) (9–14). The risk of developing CVD was linearly increased with each additional unit of BMI ($p < 0.001$) (12). A positive association of MHO was also found for the risk of stroke and coronary atherosclerosis (15, 16).

MHO and Diabetes Mellitus Type 2

Adults with MHO had a significantly higher risk of developing type 2 diabetes compared with metabolically healthy adults with normal weight (RR = 4.03; 95% CI: 2.66–6.09). Prospective studies have suggested that MHO is not a benign condition (17).

Comparable results were reached by the authors of a meta-analysis that focused on the development of diabetes in individuals with MHO without fatty liver. They were also found at increased risk of developing diabetes as individuals with fatty liver. Therefore, both groups should be carefully monitored (18).

MHO and Cancer

MHO has been confirmed to have an increased risk of cancer. The results of the meta-analysis, which included 8 studies with more than 12.5 million participants, showed a significantly increased risk of developing cancer in the case of individuals with MHO compared to metabolically healthy with normal weight (OR = 1.14; 95% CI: 1.05–1.23) (19). An increased risk of colorectal cancer has been found in people with obesity regardless of metabolic status (20). On the other hand, another meta-analysis found a lower risk of cancer in MHO than in people with obesity with metabolic abnormalities (21).

MHO and Chronic Kidney Diseases

Increased risk of chronic kidney disease has been found in individuals with overweight and individuals with obesity without metabolic abnormalities compared to people with normal weight (RR = 1.47; 95% CI: 1.31–1.65) (22).

MHO and Osteoporosis

A meta-analysis studying the association between MHO and osteoporosis was not found. However, an interesting result was reported in a study by Chen et al. (23), that explore the association between different obesity phenotypes and bone mass density. According to the conclusions of this study, it depends on how obesity is defined. When defined with a higher percentage of body fat, a reduced amount of mineral density was observed. On the other hand, increased BMI is closely associated with increased bone mass density. These different results are probably related to the protective effect of muscle mass in people with higher BMI and, in contrast, the negative effect of chronic inflammation low-grade with increased body fat. Still, there is a need for further research in this area, as in this study the authors found different results for male and female subjects. Reduced bone mass density was observed in male subjects and on the contrary, this effect was not observed in female subjects. Probably the protection of female sex hormones also can be an important factor here (23). In postmenopausal women, as sex hormones decline, the increased amount of adipose tissue may have a beneficial effect on oestrogen production (24). For this reason, obesity was previously thought to be a protective factor in the development of osteoporosis, but this has been questioned due to the presence of pro-inflammatory cytokines and further research is needed in this area (25).

MHO Other Health Risks

In addition to diseases caused directly by metabolic abnormalities obesity causes other health problems. According to a recent meta-analysis, people with MHO also have an increased risk of depressive syndrome compared to non-obese people (OR = 1.19; 95% CI: 1.03–1.37) (26).

On the other hand, some study results have suggested that MHO status may be associated with metabolic abnormalities

***Table 1**. Overview of meta-analyses studying the health risks of MHO*

Author and year	Title of meta-analysis	Number of included studies	Total sample size	Quantitative risk	Meta-analysis conclusions
Eckel et al. 2016 (9)	Metabolically healthy obesity and cardiovascular events: a systematic review and meta-analysis	22 studies	Sample size is not reported	Relative risk (RR) = 1.45; 95% confidence interval (CI) 1.20–1.70	Metabolically healthy obese (MHO) individuals without metabolic syndrome had an increased risk of CVD compared with healthy normal-weight participants.
Zheng et al. 2016 (11)	The long-term prognosis of cardiovascular disease and all-cause mortality for metabolically healthy obesity: a systematic review and meta-analysis	22 prospective studies	584,799 participants	Cardiovascular disease (CVD): RR = 1.50; 95% CI: 1.27–1.77 Risk of all-cause mortality: RR = 1.18; 95% CI: 0.83–1.66	A positive association between MHO phenotype and CVD risk was confirmed. However, a higher risk of all-cause mortality is not evident in MHO individuals.
Yeh et al. 2019 (12)	The relationship between metabolically healthy obesity and the risk of cardiovascular disease: a systematic review and meta-analysis	43 studies	4,822,205 participants	OR = 1.52; 95% CI: 1.38–1.66 Relationship between BMI and CVD risk among metabolically healthy individuals ($p < 0.001$)	MHO individuals compared with metabolically healthy normal-weight individuals had a higher risk of CVD and all-cause mortality. Every unit BMI increases the risk of CVD.
Huang et al. 2020 (10)	The association between metabolically healthy obesity, cardiovascular disease, and all-cause mortality risk in Asia: a systematic review and meta-analysis	17 studies included in meta-analysis evaluating primary outcome (19 studies included in systematic review)	1,637,994 participants (in systematic review)	Odds ratio (OR) = 1.36; 95% CI: 1.13–1.63	MHO individuals compared with metabolically healthy normal-weight individuals had a higher risk of CVD and all-cause mortality. MHO individuals had a significantly lower risk of all-cause mortality than metabolically healthy nonobese individuals (including overweight and underweight), but a borderline significantly higher risk of all-cause mortality than metabolically healthy normal-weight individuals.
Abiri et al. 2022 (13)	Transition from metabolically healthy to unhealthy overweight/obesity and risk of cardiovascular disease incidence: a systematic review and meta-analysis	7 prospective observational studies	7,720,165 participants	Hazard ratio (HR) 1.42; 95% CI: 1.24–1.60	The transition from MHO to unhealthy status during monitoring increased the risk of CVD. This may explain the association between MHO and the incidence of cardiovascular events.
Opio et al. 2020 (14)	Metabolically healthy overweight/obesity are associated with increased risk of cardiovascular disease in adults, even in the absence of metabolic risk factors: a systematic review and meta-analysis of prospective cohort studies	23 prospective cohort studies	4,492,723 participants	Overweight RR = 1.34; 95% CI: 1.23–1.46 Obesity RR = 1.58; 95% CI: 1.34–1.85	There was an increased risk of CVD in MHO compared to healthy normal weight. The risk was elevated regardless of the number of metabolic risk factors.
Hsueh et al. 2020 (16)	Association of metabolically healthy obesity and elevated risk of coronary artery calcification: a systematic review and meta-analysis	6 studies	23,543 participants	OR = 1.36; 95% CI: 1.11–1.66	Compared with metabolically healthy non-obese individuals, the MHO phenotype had a higher probability of coronary artery calcification. Meta-analysis showed that MHO phenotypes were associated with an increased risk of coronary artery calcification compared with metabolically healthy nonobese individuals, reflecting the extent of coronary atherosclerosis.
Ma et al. 2021 (15)	Metabolically healthy obesity and risk of stroke: a meta-analysis of prospective cohort studies	8 studies	4,256,888 participants	RR = 1.17; 95% CI: 1.11–1.23	Meta-analysis confirms a positive association between MHO phenotype and stroke risk.

Continued on the next page

Continued from the previous page

Bell et al. 2014 (17)	Metabolically healthy obesity and risk of incident type 2 diabetes: a meta-analysis of prospective cohort studies	7 studies and ELSA (English Longitudinal Study of Ageing)	1,770 healthy obese participants; 98 type 2 diabetes cases	RR = 4.03; 95% CI: 2.66–6.09	MHO adults have a significantly increased risk of developing type 2 diabetes compared to metabolically healthy adults of normal weight. Prospective evidence does not suggest that healthy obesity is a harmless condition.
Hashimoto et al. 2018 (18)	Metabolically healthy obesity without fatty liver and risk of incident type 2 diabetes: A meta-analysis of prospective cohort studies	3 studies from the databases and the NAGALA study (NAfld in Gifu Area, Longitudinal Analysis)	A total of 134,667 participants (including 8,675 MHO subjects without fatty liver and 7,218 MHO subjects with fatty liver)	RR of incident diabetes: without fatty liver (FL) 1.42; 95% CI: 1.1–1.77 MHO with FL 3.28; 95% CI: 2.30–4.67	MHO with or without fatty liver had a risk of developing type 2 diabetes. Individuals with MHO who do not have fatty liver should be closely monitored – similar to those with fatty liver – for the development of diabetes.
Lin et al. 2020 (19)	The association between metabolically healthy obesity and risk of cancer: A systematic review and meta-analysis of prospective cohort studies	8 studies	12,542,390 participants	MHO increased risk of developing cancer than in metabolically healthy nonobese: OR = 1.14; 95% CI: 1.05–1.23	A positive association between MHO and cancer risk was confirmed.
Zheng et al. 2022 (21)	The association between metabolic status and risk of cancer among patients with obesity: metabolically healthy obesity vs. metabolically unhealthy obesity	11 studies	1,020,341 MHO participants 1,036,695 metabolically unhealthy obese (MUO) participants	MHO phenotype versus MUO OR = 0.71; 95% CI: 0.61–0.84	The study suggests a reduced risk of cancer for MHO compared with metabolically unhealthy obesity regardless of population heterogeneity or definitions of obesity and metabolic status.
Goodarzi et al. 2022 (20)	Metabolic phenotypes and risk of colorectal cancer: a systematic review and meta-analysis of cohort studies	7 cohort studies	759,066 participants	Increased risk 1.14; 95% CI: 1.06–1.22	Individuals with MA, even if they are of normal weight, have an increased risk of colorectal cancer (CRC). In addition, obesity is associated with CRC regardless of metabolic status.
Kanbay et al. 2023 (22)	The risk for chronic kidney disease in metabolically healthy obese patients: a systematic review and meta-analysis	16 studies	4,965,285 participants	Overweight RR = 1.29; 95% CI: 1.27–1.32 ($p < 0.001$) Obese RR = 1.47; 95% CI: 1.31–1.65 ($p < 0.001$)	Metabolically healthy overweight and obese individuals have a higher risk of chronic kidney disease compared to non-overweight individuals.
Jokela et al. 2014 (26)	Association of metabolically healthy obesity with depressive symptoms: pooled analysis of eight studies	8 studies	30,337 participants	OR = 1.19; 95% CI: 1.03–1.37	MHO has a slightly increased risk of depressive symptoms compared to the non-obese, but the risk is greater when obesity is combined with an adverse metabolic profile.
Lin et al. 2017 (8)	The prevalence, metabolic risk, and effects of lifestyle intervention for metabolically healthy obesity: a systematic review and meta-analysis: a PRISMA-compliant article	12 cohort studies and 7 intervention studies	5,914 MHO participants 26,203 metabolically healthy normal weight (MHNW) participants	Risk of incident metabolic abnormalities (MA) compared with MHNW RR = 1.80; 95% CI: 1.53–2.11	Almost a third of obese individuals are in metabolic health. However, the MHO phenotype has a higher risk of developing metabolic abnormalities, and half of them go on to a metabolically unhealthy state.
Ortega et al. 2018 (28)	Role of physical activity and fitness in the characterization and prognosis of the metabolically healthy obesity phenotype: a systematic review and meta-analysis	35 studies	Sample size is not reported	Metabolically healthy obese (MHO) individuals have a 24–33% higher risk of all-cause mortality and CVD mortality/morbidity compared to MHNW	MHO individuals are more active, spend less time sedentary, and have higher levels of cardiorespiratory fitness than individuals with metabolically unhealthy obesity, suggesting that their healthier metabolic profile could be due, at least in part, to these factors of a healthier lifestyle.

with similar (15, 27) or less (9) risk in the future than in the case of normal-weight obese people. The association with central fat distribution is particularly important in the occurrence of metabolic dysregulation and systemic inflammation (2).

Physical activity is one of the most important factor influencing health of obese people and seems to play an important role in the MHO phenotype (28). However, it is also necessary to take into consideration the fact that excessive weight during physical activity in obese people represents significant stress on the musculoskeletal system manifested by joint pain or back pain (29–31). Therefore, it is recommended to choose physical activity wisely and concerning physical constitution. Or it is also possible to consult a physiotherapist or other specialist in the field about the inclusion of appropriate physical activity. In addition, all obese individuals are at risk of skin problems related to skin overhangs and subsequent problems with atopic dermatitis or infections of mycotic origin. The other problem can be an increased incidence of stretch marks, painful cellulite and other skin diseases (32). Last but not least, the increased risk of sleep apnoea syndrome, which aetiology is closely related to the presence of excessive adipose tissue in the neck and the resulting airway obstruction, regardless of the presence of metabolic abnormalities (33). Long-term reduced sleep quality may result in decreased metabolic health parameters in the future caused by hormonal changes, worsened regeneration and reduced spontaneous physical activity.

DISCUSSION

The aim of this review of meta-analyses was to summarise the current evidence on the health risks of metabolically healthy obesity and to provide a position statement for assessing these risks. To our knowledge, this is the first such comprehensive review of meta-analyses on this topic and we consider it to be highly topical. On the one hand, opinion on this phenomenon is strongly influenced by the body positivity trend. On the other hand, there is the ever-increasing prevalence of obesity, which has reached epidemic proportions worldwide, with far-reaching health, economic and psychosocial consequences.

In our review, we collected a total of 17 meta-analyses from the MEDLINE database (PubMed) on the health risks associated with metabolically healthy obesity. Individual meta-analyses were reviewed and categorised by type of disease. The results were presented in narrative form, with quantified data in a summary table.

A comparable review of meta-analyses is not available. Qualitatively comparing the results of our review, our results are consistent with those of the PRISMA study, which assessed the metabolic risk of MHO in general (8). MHO were found to have a higher risk of developing one or more metabolic abnormalities within 10 years.

On the other hand, we found some evidence that the normal-weight obesity has a similar (15, 27) or even higher (9) risk of cardiometabolic disease. MHO have a higher risk than non-obese people and a lower risk than obese patients. Metabolic health status and the presence of metabolic abnormalities are critical to health risk. A significant effect on cardiovascular health has been found in relation to cardiorespiratory fitness (27).

A major limitation not only of this review, but of research on the health risks associated with metabolically healthy obesity in general, is its globally inconsistent definition. Obesity is defined by the WHO as an abnormal or excessive amount of adipose tissue, but its diagnosis is based on knowledge of BMI, which does not include information on the amount of adipose tissue. Future research should therefore focus on determining a healthy amount of body fat for the general population, which could lead to a consensus on a uniform definition of MHO.

Another limitation of the study was the heterogeneity of the data available in the meta-analyses. Each meta-analysis also had its own methodology for analysing and interpreting the results. This review also did not consider the quality of the conduct of the trials included in each meta-analysis, which may be reflected in the results of this umbrella review.

Conversely, a strength of this review is the use of meta-analyses, which should eliminate any potential bias in the results, for example, influenced by the incorrect choice of methodology in an individual study. Thus, this review may provide a more objective results on the status of metabolically healthy obesity.

CONCLUSION

Research on the prevalence of MHO and its associated risks is limited by the missing internationally accepted definition. Current studies suggest that the MHO phenotype is in many cases a temporary condition associated with a higher risk of developing metabolic abnormalities. Moreover, based on the current definitions, not all metabolically healthy individuals can be considered healthy, but only those with a lower occurrence of metabolic abnormalities. MHO are in higher risk than non-obese people and in smaller risk than obese patients. Probably not only the amount but especially the distribution of adipose tissue, which is related to the prevalence of systemic inflammation, has a major influence on the incidence of metabolic abnormalities. In the future, the definition of MHO and metabolically unhealthy obesity needs to be clarified because even normal-weight people are at risk of metabolic abnormalities depending on the amount and distribution of adipose tissue. In addition to the potential development of metabolic abnormalities, all MHO patients are at risk for pathogenesis resulting from the presence of excessive adipose tissue, which represents a significant mechanical burden. Therefore, all obese patients should be motivated to improve their lifestyle. The focus should be on continuous and thus sustainable changes in eating habits without unnecessary prohibitions and extreme restrictions. It should be recommended a wholesome balanced diet offering a rich spectrum of foods. Instead of, patients should be warned against the practice of unsuitable diets that unreasonably eliminate a particular macronutrient or whole food group. Keeping to them puts the body at risk of nutrient deficiencies and unwanted loss of muscle mass, which can result in a decrease in basal metabolic rate. By rational modification of dietary habits and inclusion of appropriate physical activity, it is possible to improve body composition parameters by reducing the amount of adipose tissue and reducing waist circumference even if the same body weight is maintained. This usually results in an improvement in metabolic parameters and can even change from a condition of unhealthy obesity to “metabolically healthy obesity”. This can significantly increase the length and quality of life of an individual.

Acknowledgement

The study was supported by specific research/Masaryk University (MUNI/A/1623/2023).

Conflicts of Interest

None declared

REFERENCES

1. World Health Organization. Obesity and overweight [Internet]. Geneva: WHO; 2023 [cited 2022 Sep 30]. Available from: https://www.who.int/health-topics/obesity.
2. Oliveros E, Somers VK, Sochor O, Goel K, Lopez-Jimenez F. The Concept of normal weight obesity. Prog Cardiovasc Dis. 2014 Jan-Feb;56(4):426-33.
3. World Health Organization. Waist circumference and waist-hip ratio: report of a WHO expert consultation, Geneva, 8-11 December 2008 [Internet]. Geneva: WHO; 2011 [cited 2022 Oct 13]. Available from: https://apps.who.int/iris/bitstream/handle/10665/44583/?sequence=1.
4. Blüher M. Metabolically healthy obesity. Endocr Rev. 2020 May 1;41(3):bnaa004. doi: 10.1210/endrev/bnaa004.
5. Smith GI, Mittendorfer B, Klein S. Metabolically healthy obesity: facts and fantasies. J Clin Invest. 2019 Oct 1;129(10):3978-89.
6. Ogorodnikova AD, Kim M, McGinn AP, Muntner P, Khan U, Wildman RP. Incident cardiovascular disease events in metabolically benign obese individuals. Obesity (Silver Spring). 2012 Mar;20(3):651-9.
7. Mongraw-Chaffin M, Foster MC, Anderson CAM, Burke GL, Haq N, Kalyani RR, et al. Metabolically healthy obesity, metabolic syndrome, and cardiovascular risk. J Am Coll Cardiol. 2018 May 1;71(17):1857-65.
8. 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 (Baltimore). 2017 Nov;96(47):e8838. doi: 10.1097/MD.0000000000008838.
9. 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 Jun;23(9):956-66.
10. Huang MY, Wang MY, Lin YS, Lin CJ, Lo K, Chang IJ, et al. The Association between metabolically healthy obesity, cardiovascular disease, and all-cause mortality risk in Asia: a systematic review and meta-analysis. Int J Environ Res Public Health. 2020 Feb 19;17(4):1320. doi: 10.3390/ijerph17041320.
11. Zheng R, Zhou D, Zhu Y. 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. 2016 Oct;70(10):1024-31.
12. Yeh TL, Chen HH, Tsai SY, Lin CY, Liu SJ, Chien KL. The Relationship between metabolically healthy obesity and the risk of cardiovascular disease: a systematic review and meta-analysis. J Clin Med. 2019 Aug 15;8(8):1228. doi: 10.3390/jcm8081228.
13. Abiri B, Koohi F, Ebadinejad A, Valizadeh M, Hosseinpanah F. Transition from metabolically healthy to unhealthy overweight/obesity and risk of cardiovascular disease incidence: a systematic review and meta-analysis. Nutr Metab Cardiovasc Dis. 2022 Sep;32(9):2041-51.
14. Opio J, Croker E, Odongo GS, Attia J, Wynne K, McEvoy M. Metabolically healthy overweight/obesity are associated with increased risk of cardiovascular disease in adults, even in the absence of metabolic risk factors: a systematic review and meta-analysis of prospective cohort studies. Obes Rev. 2020 Dec;21(12):e13127. doi: 10.1111/obr.13127.
15. Ma LZ, Sun FR, Wang ZT, Tan L, Hou XH, Ou YN, et al. Metabolically healthy obesity and risk of stroke: a meta-analysis of prospective cohort studies. Ann Transl Med. 2021 Feb;9(3):197. doi: 10.21037/atm-20-4387.
16. Hsueh YW, Yeh TL, Lin CY, Tsai SY, Liu SJ, Lin CM, et al. Association of metabolically healthy obesity and elevated risk of coronary artery calcification: a systematic review and meta-analysis. PeerJ. 2020 Mar 26;8:e8815. doi: 10.7717/peerj.8815.
17. 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. 2014 Jun;15(6):504-15.
18. Hashimoto Y, Hamaguchi M, Tanaka M, Obora A, Kojima T, Fukui M. Metabolically healthy obesity without fatty liver and risk of incident type 2 diabetes: a meta-analysis of prospective cohort studies. Obes Res Clin Pract. 2018 Jan-Feb;12(1):4-15.
19. Lin CJ, Chang YC, Cheng TY, Lo K, Liu SJ, Yeh TL. The association between metabolically healthy obesity and risk of cancer: a systematic review and meta-analysis of prospective cohort studies. Obes Rev. 2020 Oct;21(10):e13049. doi: 10.1111/obr.13049.
20. Goodarzi G, Mozaffari H, Raeisi T, Mehravar F, Razi B, Ghazi ML, et al. Metabolic phenotypes and risk of colorectal cancer: a systematic review and meta-analysis of cohort studies. BMC Cancer. 2022 Jan 21;22(1):89. doi: 10.1186/s12885-021-09149-w.
21. Zheng X, Peng R, Xu H, Lin T, Qiu S, Wei Q, et al. The Association between metabolic status and risk of cancer among patients with obesity: metabolically healthy obesity vs. metabolically unhealthy obesity. Front Nutr. 2022 Feb 25;9:783660. doi: 10.3389/fnut.2022.783660.
22. Kanbay M, Copur S, Siriopol D, Yildiz AB, Berkkan M, Tuttle KR, et al. The risk for chronic kidney disease in metabolically healthy obese patients: a systematic review and meta-analysis. Eur J Clin Invest. 2023 Jan;53(1):e13878. doi: 10.1111/eci.13878.
23. Chen YY, Fang WH, Wang CC, Kao TW, Chang YW, Wu CJ, et al. Body fat has stronger associations with bone mass density than body mass index in metabolically healthy obesity. PLoS One. 2018 Nov 8;13(11):e0206812. doi: 10.1371/journal.pone.0206812.
24. Migliaccio S, Greco EA, Fornari R, Donini LM, Lenzi A. Is obesity in women protective against osteoporosis? Diabetes Metab Syndr Obes. 2011;4:273-82.
25. Cao JJ. Effects of obesity on bone metabolism. J Orthop Surg Res. 2011 Jun 15;6:30. doi: 10.1186/1749-799X-6-30.
26. Jokela M, Hamer M, Singh-Manoux A, Batty GD, Kivimäki M. Association of metabolically healthy obesity with depressive symptoms: pooled analysis of eight studies. Mol Psychiatry. 2014 Aug;19(8):910-4.
27. Hart SM, Keirns BH, Sciarrillo CM, Malin SK, Kurti SP, Emerson SR. Cardiorespiratory fitness and submaximal exercise dynamics in normal-weight obesity and metabolically healthy obesity. Eur J Appl Physiol. 2023 Nov 2. doi: 10.1007/s00421-023-05344-8.
28. Ortega FB, Cadenas-Sanchez C, Migueles JH, Labayen I, Ruiz JR, Sui X, 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 Jul-Aug;61(2):190-205.
29. Jinks C, Jordan K, Croft P. Disabling knee pain - another consequence of obesity: results from a prospective cohort study. BMC Public Health. 2006 Oct 19;6:258. doi: 10.1186/1471-2458-6-258.
30. Shiri R, Karppinen J, Leino-Arjas P, Solovieva S, Viikari-Juntura E. The Association between obesity and low back pain: a meta-analysis. Am J Epidemiol. 2010 Jan 15;171(2):135-54.
31. Silverwood V, Blagojevic-Bucknall M, Jinks C, Jordan JL, Protheroe J, Jordan KP. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage. 2015 Apr;23(4):507-15.
32. Darlenski R, Mihaylova V, Handjieva-Darlenska T. The Link between obesity and the skin. Front Nutr. 2022 Mar 10;9:855573. doi: 10.3389/fnut.2022.855573.
33. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. Lancet. 2014 Feb 22;383(9918):736-47.

Received March 27, 2023
Accepted in revised form February 16, 2024