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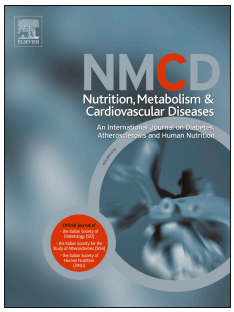

Influence of dietary patterns on the metabolically healthy obesity phenotype: A Systematic Review

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PII: S0939-4753(21)00228-3

DOI: https://doi.org/10.1016/j.numecd.2021.05.007

Reference: NUMECD 2686

To appear in: *Nutrition, Metabolism and Cardiovascular Diseases*

Received Date: 8 March 2021

Revised Date: 4 May 2021

Accepted Date: 6 May 2021

Please cite this article as: Vilela DLS, Fonseca PG, Pinto SL, Bressan J, Influence of dietary patterns on the metabolically healthy obesity phenotype: A Systematic Review, *Nutrition, Metabolism and Cardiovascular Diseases*, https://doi.org/10.1016/j.numecd.2021.05.007.

Influence of dietary patterns on the metabolically healthy obesity phenotype: A Systematic Review

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Competing Interests: The authors declare no competing financial interests.

Keywords: Metabolically Healthy Obesity; Phenotype; Dietary Patterns; Healthy Diet.

Word counts:

Abstract: 200 words

Text: 4.902 words

Number of references: 81

Number of figures: 2

Number of tables: 3

Number of supplementary tables: 3

Number of supplementary figures: 1 (ABCD)

1. INTRODUCTION

Obesity is defined as excess body fat that can cause health risks; the body mass index (BMI) ≥ 30 kg/m² is the most widely used criteria for its diagnosis [1]. It is a complex disease with a multifactorial etiology [2] that has nearly tripled since 1975 [3], affecting 13% of the global adult population (around 650 million people) [1]. Obesity is one of the main risk factors for cardiovascular disease, non-alcoholic liver steatosis, type 2 diabetes mellitus (T2D), some types of cancer [4], and has a high mortality burden [5]. Furthermore, in the current context, obesity and impaired metabolic health are relevant risks factors of severe coronavirus disease 2019 (COVID-19) [6]. However, despite the associated health risks, many individuals with obesity (35%) do not have metabolic disorders, a condition referred to as metabolically healthy obesity (MHO) [7–9].

The etiological mechanisms of MHO are not entirely clear, but it is claimed that this phenotype is likely the result of greater genetic resistance to noncommunicable diseases, lifestyle, or a combination of both [10]. In addition, there are many controversies regarding current MHO research. While some cutting-edge studies state that MHO is a transient condition associated to a high risk of progression to metabolic syndrome and cardiovascular diseases [7,11,12], others suggest it is a stable condition linked to a better prognosis for lower risk of comorbidities and mortality [13,14].

Perhaps one of the possible reasons for these contrasting results is that despite the genetic basis, MHO's prognosis may vary according to the numerous factors to which the individual may be subject throughout life [10,15], for example, aging causes a redistribution of body fat and senescence of preadipocytes contributing to inflammatory processes that affect metabolic health [16]. Among these factors especially those related to lifestyle – such as food – has a relevant influence, although there is no consensus on the role of diet in this phenotype [10,15]. Current evidence suggests that MHO individuals have similar caloric and

macronutrient intake compared to the metabolically unhealthy obese (MUO)[17–20]. There is also evidence that MHO individuals respond differently to MUO in relation to dietary interventions [21,22]. A recent systematic review with meta-analysis that compared dietary interventions with different macronutrient compositions in this population found no evidence to support the recommendation of any specific diet in MHO [23].

Hence, the aforementioned data indicate the relevance of investigating dietary patterns in this group of individuals, for it is a more comprehensive method than the analysis of isolated nutrients or foods. That is because meals are composed of multiple foods that interact and synergize, and their effects cannot be solely attributed to a single nutrient [24,25]. Taking into account the importance of acknowledging the factors that interfere in the MHO condition, improving care and reducing the risk of comorbidities in these individuals, this study aimed to systematically review the literature about eating pattern adopted by MHO individuals or interventions with specific dietary patterns and their repercussions on cardiometabolic status and mortality.

2. METHODS

▪ 2.1 *Protocol and registration*

The present review was conducted according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement [26] and was registered under PROSPERO (International Prospective Register of Ongoing Systematic Reviews; [registration number CRD42020159783; available on https://www.crd.york.ac.uk/prospero/]). The PRISMA checklist is provided in **Table S1** in the online Supporting Information.

▪ 2.2 *Search strategy*

The articles were found in six electronic databases, including MEDLINE/PubMed, SCOPUS, Web of Science, ScienceDirect, LILACS, and SciELO. **Chart 1** displays the

PICOS (Participants, Intervention, Comparison, Outcomes, and Study design) criteria adopted in this review. The following search terms were used to search in titles and abstracts papers that reported the effects of dietary patterns on the health of people with metabolically healthy obesity: ('Dietary Pattern' OR 'Mediterranean Diet' OR 'Dietary Approaches to Stop Hypertension Diet' OR 'DASH Diet' OR 'Western Diet' AND 'Metabolically Healthy Obesity' OR 'Metabolically Benign Obesity'). The search was conducted in June 2020, and was not restricted by either language or publication date. The detailed search is described in **Table S2**.

- 2.3 *Eligibility criteria*

Papers meeting the following criteria were included: (1) interventional and observational original studies (randomized controlled trials, non-randomized trials, case-control, cohort and cross-sectional); (2) studies including humans with metabolically healthy obesity (BMI ≥30 Kg/m²), adults and elderly (aged 18 years or over); (3) studies using dietary patterns as an intervention or exposure; (4) studies investigating changes in health parameters such as mortality, cardiometabolic risk, transition to classic obesity or maintenance of MHO as the outcome of interest. The following exclusion criteria were applied: (1) non-original articles, such as letters, commentaries, or reviews; (2) investigations of outcome measures other than changes in the health parameters mentioned above; (3) studies that analyzed metabolically healthy overweight adults along with MHO and did not report data stratified by BMI class; (4) interventions mainly focusing on behavioral changes, such as physical activity; (5) studies addressing weight loss interventions rather than assessing the relationship between dietary pattern and metabolic phenotype.

- 2.4 *Study selection and data collection process*

Study selection was performed independently in an unblinded standardized manner by 2 authors (D.L.S.V. and P.G.F.). Disagreements were resolved by consensus or by consulting a third author (J.B.). The following data were extracted from each study: authors; year of publication; country, sample size, characteristics of study participants; intervention design; dietary pattern, dietary pattern assessment method, clinical parameters, and main results. The selected studies were imported into the Mendeley® reference management software [27] to exclude duplicates, and the peer-review process was carried out using the Rayyan® QCRI Software [28]. Data were extracted by the first reviewer (P.G.F) using a standardized form containing the variables of interest, and independently checked by the second reviewer (D.L.S.V), whereas discrepancies were solved by consensus.

- 2.5. *Risk of bias assessment*

All seven articles selected for inclusion in the systematic review were subject to rigorous evaluation by two independent reviewers (D.L.S.V and P.G.F) and disagreements were solved by an independent evaluation of a third author. The risk of bias of the included studies was assessed following the Joanna Briggs Institute (JBI) Reviewer's Manual [29], through Critical Analysis Tools, specific to each study design, developed by the JBI and approved by the JBI Scientific Committee after an extensive peer review. Since there is no established score to determine the level of bias on set of articles, the reviewers resorted to a classification of the risk of bias according to the percentage of affirmative responses ('yes'), as follows: low (≥70%), moderate (between 50 and 70%) and high risk of bias (< 50%) [26] (**Fig. S1** ABCD), and more details on **Table S3** (ABCD).

3. RESULTS

- 3.1 *Description of identified/included studies: Study selection*

A total of 236 records were identified through searches in the MEDLINE/PubMed, SCOPUS, LILACS, ScienceDirect, Web of Science and, SciELO databases. Duplicate records were removed using Mendeley reference manager software, resulting in 198 records. Following title and abstract screening, 172 records were removed as they did not meet the inclusion criteria. The remaining 26 records were retrieved and reviewed for further assessment, whereas 19 articles were excluded after full-text screening. The most common reasons for study exclusion were: dietary pattern was not assessed (7 studies); evaluation of patients with obesity and overweight without sample stratification (6 studies); the relationship between dietary pattern and metabolic phenotype was not assessed (4 studies); the BMI cut-off point for defining obesity was ≥ 25 (2 studies). After reviewing the full-texts for eligibility, seven studies were included **(Figure 1).**

- 3.2 *Study characteristics*

3.2.1. Study Design

The designs of the studies included in this review were: cross-sectional (n=3; 42.85%) [30–32], prospective cohorts (n=3; 42.85%) [33–35] and non-randomized quasi-experimental (n=1; 14.3%)[22].

3.2.2. Study Participants

The total sample consisted of 23.997 adult and elderly individuals (>18 and <90 years old), mostly females (58.1%). For diagnosing MHO, evaluation parameters included BMI ≥30 kg/m² associated with metabolic syndrome to assess metabolic health, such as fasting blood glucose, lipid profile, blood pressure, waist circumference, Insulin Resistance Index (HOMA-IR), and C-reactive protein (CRP) whose selection criteria and cut-off points (36–40) varied among studies, as well as the number of modified parameters that was still classified as metabolic health. Two studies classified as metabolically healthy the individuals with no

changes except for the waist circumference (WC). Three studies considered one change, and two studies considered individuals with zero to two abnormal parameters as metabolically healthy.

Among the selected articles, only 19.5% of individuals were classified as MHO. Moreover MHO, studies have also included the following phenotypes: Metabolically Unhealthy Obese (MUO), Metabolically Abnormal Non-Obese (MANO), Metabolically Obese Normal Weight (MONW) (MANO and MONW are synonymous and refer to eutrophic individuals with metabolic diseases), Intermediate (INT), Metabolically Healthy Non-Obese (MHNO) that corresponds to eutrophic and healthy individuals. The absolute frequency of individuals per phenotype was described in **Table 1**.

Three of these used MUO, MANO, MHNO and MHO (32–34), two used MUO, MHO and INT [30,35], one used MUO, MHO, MHNO and MONW [31] and one used only MHO [22].

3.2.3. Type of Intervention

Among the dietary patterns, four studies addressed the Mediterranean diet (57,1%) [19,30–32], one the Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diets (14,3%) [31], and two healthy and unhealthy eating patterns classified according to nutrients and food groups (28,6%) [30,32] In five studies the assessment of dietary patterns resorted to *a priori* methods: dietary indexes or scores for adherence to the diet [22,31,33–35], whereas two employed *a posteriori* approaches: 24-hour recall and food frequency questionnaire; two different statistical techniques to identify dietary patterns: principal component analysis [30] and factor analysis [32] (**Table 2)**.

3.2.4. *Evaluated outcomes*

Observational study with food pattern

The Mediterranean dietary pattern was positively linked to healthier metabolic phenotypes. It was observed that individuals with obesity with lower Med Diet Score (MDS) values were less likely to be metabolically healthy [34]. However, in the study by Park *et al.* (2017) the authors only observed this relationship in specific age groups. The increase in the Mediterranean diet score was associated to a higher prevalence of the MHO phenotype in the younger group [31].

The possible decline of metabolic health following the transition to MUO was assessed in the studies included in this review and, among the different metabolic phenotypes, MHO was more likely to shift to MUO in relation to the other phenotypes. A significant portion of MHO individuals (between 31% and 33%) will experience this transition in five years of follow-up [33,34]. Evidence suggests that the MHO individuals who maintained their metabolically healthy status for ten years had greater adherence to the Mediterranean diet [34]. It was also observed that individuals with temporary MHO had higher values of CRP and HOMA-IR, and higher Low Density Lipoprotein (LDL) and systemic blood pressure at the starting point of the studies, compared to their stable MHO counterparts [34].

Furthermore the benefits for metabolic health, the Mediterranean diet also reduced the mortality risk in MHO. In general, there was a higher mortality risk in MUO compared to MHO individuals. A five-point increase in adherence to the Mediterranean diet (MDS) reduced all-cause mortality risk in MHO by 41%, even among those with noncommunicable diseases, including T2D and systemic arterial hypertension. However, there was no reduction in the mortality risk in the MUO phenotypes with the increase in MDS, and neither an association between MDS and cardiovascular diseases (CVD) mortality in both groups. In MUO individuals, a higher MDS score tended to increase the mortality risk for those physically active and reduce the risk for sedentary ones [35].

Regarding the other dietary patterns evaluated, there was also a correlation between feeding and metabolic health. Healthy patterns were associated to a better metabolic health condition, while unhealthy patterns generated the opposite effect. There was no difference in energy and macronutrient consumption between individuals with different metabolic health phenotypes [30].

MHO women had a healthier diet when compared to MUO. The pattern rich in healthy foods (such as fruit, vegetables, and fish) was positively associated to MHO, while a Western-like pattern (rich in refined carbohydrate sources such as white bread and sweets) was inversely related to MHO [30]. A study by Bell *et al*. (2015) reported similar results, as a correlation between dietary patterns and the metabolic phenotype was found. Each increment in the standard deviation of unhealthy dietary patterns (rich in high glycemic index foods, saturated fats and fruit, and vegetables low) reduced by 14% participants' likelihood of displaying a metabolically healthy profile. In contrast, each increment in the standard deviation of the healthy diet (rich in vegetables, fruit, whole grains, and lean meats) increased participants' likelihood of displaying good metabolic health by 18% [32].

The DASH diet also provided an improvement in metabolic health, but not in MHO individuals. Adherence to the DASH diet was inversely proportional to the likelihood of having a metabolic disease phenotype in normal-weight metabolically obese individuals (NWMO) [31]. Further are summarized in **Table 2**.

Prospective studies of intervention with dietary pattern

Intervention with the Mediterranean diet (supplemented with extra-virgin olive oil or nuts), without caloric restriction, contributes to preventing the transition from MHO to MUO [33]. The study of Konieczna *et al*. (2019) showed that each 2-point increase in the adherence score (MEDAS) was followed by a 14% reduction in the risk of deterioration of metabolic health in five years [33]. Adherence to the Mediterranean diet was also associated to reversals

224 of metabolic abnormalities and transition to healthy metabolic phenotypes in metabolically
225 unhealthy participants with obesity. Every 2-point increase in MEDAS was associated with a
226 16% higher probability of becoming MHO [33].

227 However, the intervention using a hypocaloric Mediterranean diet and physical
228 exercises resulted in low adherence and few metabolic benefits in addition to a negative
229 change in the adipokine profile. After two years of intervention with a hypocaloric
230 Mediterranean diet and physical exercise, 52% of the female MHO sample dropped out. There
231 was a significant reduction in body weight, BMI and WC. There were no significant changes
232 in cardiometabolic status, except for a reduction in glycaemia and triglycerides. Adiponectin
233 concentrations also decreased with the intervention, and resistin concentrations increased
234 [22]. Further are summarized in **Table 2**.

235

236 3.2.5. *Risk of bias within studies*

237 Since a tool was used for each study design, the bias was also analyzed based on the
238 isolation results. The critical analysis of the selected studies is described in **Table S3** (ABC).
239 The articles were grouped according to their experimental designs. In general, 76% of the
240 responses were positive, indicating that the studies had a low risk of bias. Therefore, it is
241 concluded that the high quality of the studies selected for this review is due to the low risk of
242 predominant bias (**Figure S1**).

243 One of the main points of bias among the selected studies was related to the MHO
244 diagnosis, since the authors did not employ a standardized protocol. Another issue that caused
245 this variation among authors was the use of dietary patterns assessment methods that are not
246 validated for the studied population. There were no standardized methods for assessing and
247 classified dietary patterns, so the studies used different methodologies, causing a bias in the
248 measurement of sample exposure and clinical heterogeneity (**Figure S1**).

Despite the differences between the studies and mainly between MHO diagnoses, the overall methodological quality used was considered good, with a low risk of bias, thus enabling more reliable results, since most of the articles carried out adjustments and corrections with respect to the confounding variables (**Figure S1**).

4. DISCUSSION

To our knowledge this is the first review that assessed the dietary patterns of MHO people. This systematic review included data from seven articles with a total population of 23.997 individuals: 19.5% of whom were MHO, mostly female, and aged between 18 and 90 years. The metabolic health diagnosis varied among studies with respect to the number of comorbidities considered as good metabolic health, as well as to the cut-off points of the adopted parameters. The Mediterranean dietary pattern was the most assessed in the studies. Results indicated that greater adherence to healthy dietary patterns was likely to prevent the transition from MHO to MUO phenotypes, besides improving metabolic health, and reducing the risk of CVD and all-cause mortality.

The prevalence of MHO individuals in our study was 19.5%, a low percentage compared to those reported in other studies, that ranged between 30% and 35% [7,41]. This prevalence may vary according to factors such as sex, age, ethnicity and definition of metabolic health [7]. In this review, although the diagnosis of obesity in all studies was carried out considering BMI ≥30kg/m², the different concepts of metabolic health among the articles generated bias and clinical heterogeneity, thus making comparisons difficult.

These data emphasize the relevance of standardizing the criteria for defining MHO, especially in light of the recurring controversies regarding this situation, such as the lack of consensus about the risk of mortality and metabolic syndrome [7,11–14]. Such aspects become even more controversial when one considers that the presence of one or more

metabolic abnormalities is classified as good metabolic health. The need to standardize MHO definitions was recently addressed by the BioShare-EU project who suggested adopting a single and more rigorous criterion based on obesity with no metabolic syndrome components except for the waist circumference [8,42].

A recent review by Brandão et al. (2020) claims that the existence of individuals with the MANO/MONW [8] – reaching values around 20-30% – [43] and MHO phenotype suggests the presence of risk factors for cardiometabolic diseases regardless of overweight, and that obesity is not always related to metabolic, inflammatory, and/or fibrinolytic disorders [8].The factors that explain the existence of the MHO phenotype are the greater expansion capacity of the adipose tissue and its location. The higher proportion of hyperplasia in relation to hypertrophy generates smaller adipocytes (multilocular). Consequently, there is a reduction in the secretion of pro-inflammatory cytokines, as well as a greater production of adiponectin and low infiltration of macrophages. There is also a low percentage of visceral and ectopic fat and greater accumulation of subcutaneous fat, besides greater intestinal integrity. These attributes prompt a reduction in systemic inflammation and greater insulin sensitivity, which would justify the absence of metabolic abnormalities [8].

Even though genetics partially explains the development of some of these characteristics, it does not, *per se*, justify the reason why not every individual with obesity has metabolic diseases [44]. This fact highlights the relevance of environmental factors such as feeding. Feeding may modulate inflammation levels, oxidative stress, regulate gene expression, epigenetic mechanisms and modify the intestinal microbiota (45–50). Therefore, we hypothesized that the association between dietary patterns and metabolic health is due to changes in the factors that are crucial for the development of cardiometabolic diseases.

Dietary patterns are defined as a set of foods consumed that are assessed as a single exposure [51]. In general, balanced diets that are based on fresh and low processed foods,

299 mainly fruit and vegetables, white meats, whole grains, legumes, oils sources of unsaturated
300 fats are considered “healthy patterns” [52] examples of patterns are the DASH and
301 Mediterranean, other patterns with characteristics similar to these are called “healthy” or
302 “prudent” or named only according to the foods that compose it.

303 The studies included in this review suggest that, regardless of the diagnosis used,
304 individuals with MHO have a healthy dietary pattern (such as the Mediterranean diet, DASH
305 and general healthy patterns). These patterns play an important role in maintaining or
306 recovering metabolic health, reducing the risk of comorbidities and mortality, while less
307 healthy dietary patterns produce the opposite effect **(Figure 2)**.

308 Pathological obesity is directly related to systemic, chronic and low-grade
309 inflammation, which is generated by the dysfunction of adipose tissue homeostasis with
310 infiltration of immune cells and an increase in inflammatory mediators, a process called
311 “metainflammation”. Moreover, obesity intensifies the appearance of diseases related to
312 aging, further emphasizing the changes that adipose tissue undergoes with advancing age
313 [53]. Aging causes a decline in the capacity for adipogenesis and storage of adipose tissue due
314 to the senescence of pre-adipocytes. These senescent adipocytes also secrete more pro-
315 inflammatory cytokines that induce insulin resistance and increased lipolysis – called
316 inflammaging – which predisposes to the development of NCDs. This is aggravated by age-
317 related hormonal changes that promote the redistribution of adipose tissue from the
318 gluteofemoral region to the abdominal region and increased visceral and ectopic fat [16,53].

319 Healthy dietary patterns can attenuate subclinical inflammation since they consist of
320 bioactive compounds rich food, such as polyphenols, antioxidants, micronutrients and
321 polyunsaturated fatty acids. Together, these compounds reduce oxidative stress and metabolic
322 syndrome risk [10,46,54–61] and, therefore, the risk of pathological obesity. A recent study
323 that assessed the relationship between the dietary inflammatory index and metabolic

syndrome corroborates this hypothesis. With 3.042 volunteers and ten years of follow-up, this research concluded that the highest anti-inflammatory load diet was effective in maintaining a healthy metabolic state [62] .

Furthermore, healthy eating patterns and other lifestyle interventions are effective in improving metabolic health because they can treat metabolically unhealthy fat distribution [16,53]. A weight loss of 5% reduces visceral fat and healthy diets, such as Mediterranean, regardless of weight loss, decrease cardiometabolic risk [16,30,35,53]. This is probably due to the functional foods present in these dietary patterns (such as polyunsaturated and monounsaturated fatty acids, eicosanoids, micronutrients and phenolic compounds) that may mitigate inflammaging by being agonists of the nuclear receptor Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) as well as some drugs of the thiazolidinedione class. This receptor promotes adipogenesis by favoring free fatty acid uptake and storage and insulin sensitivity, in addition to stimulating adiponectin and leptin synthesis and suppressing levels of cytokines such as TNF-α, IL1-β [63,64].

Less healthy dietary patterns, such as the Western-type ones, are rich in high-calorie foods of low nutritional density. These combined factors contribute to a diet low in micronutrients and fibers, with excess sugar, additives, as well as trans and saturated fatty acids [65]. This may positively modulate inflammation levels, promote dysbiosis and increase intestinal permeability by producing chemical mediators that exacerbate inflammation levels and that are related to noncommunicable diseases [46,66–68]. This possibly contributes to the transition to classic obesity patterns.

Subclinical inflammation is linked to metabolic abnormalities due to the disturbance in the homeostasis of pro and anti-inflammatory transcription factors. This imbalance causes an increase in pro-inflammatory adipokines and cytokines and a reduction in anti-inflammatory ones. In addition to impaired intracellular hormonal signaling, promoting a pro-inflammatory

environment with an increase of oxygen and nitrogen reactive species [69–71] leads to metabolic disorders and to the development of metabolic syndrome [72].

Although most articles included in this review did not assess the modification of diet-related inflammatory markers, previous studies indicate that chronic low-grade inflammation may be the factor that defines whether an individual is an MHO [73]. In adults, this phenotype is related to lower levels of complement factor 3, CRP, Tumor Necrosis Factor-α (TNF-α), Interleukin 6 (IL-6), and reduced number of white blood cells. Moreover, individuals with temporary MHO had higher values of CRP [34], reinforcing the concept MHO had a beneficial inflammatory profile compared to individuals of different phenotypes [74].

A study that evaluated the relationship between inflammatory markers and dietary pattern found out an inverse association between a prudent dietary pattern and plasma concentrations of CRP and E-selectin, as well as a positive relationship between a Western dietary pattern and concentrations of CRP, IL-6, E-selectin, Soluble Intercellular Adhesion Molecule-1 (sICAM-1) and soluble Vascular Cell Adhesion Molecule 1 (sVCAM-1) [75]. This chronic low-grade inflammation is associated to insulin resistance and elevated CRP, a predictor of vascular inflammation, metabolic syndrome and cardiovascular diseases [72].

Intervention with the Mediterranean diet (supplemented with extra-virgin olive oil or nuts and without caloric restriction) also appears to be beneficial in maintaining good metabolic health in MHO individuals because it can contribute to preventing the transition from MHO to MUO and favored the transition of MUO individuals to the MHO phenotype [33]. Moreover, a five-point increase in adherence to the Mediterranean diet (MDS) reduced all-cause mortality risk in MHO by 41% [35]. Despite the benefits of healthy dietary patterns, the study by Gomes-Huelgas et al. (2019) observed a decline in the profile of adipokines in MHO individuals submitted to intervention with Mediterranean low-calorie diet, evidenced by increased levels of resistin and reduced adiponectin [22]. Resistin is related to

inflammation through and increase in CRP and other pro-inflammatory cytokines [76]. Adiponectin is the main adipokine with anti-inflammatory and cardioprotective action. It inhibits the activation of Nuclear Factor Kappa B (NF-κB) and Alpha Interferon (IFN-α) besides mitigating the action of TNF-α and increases the levels of cytokines such as Interleukin 10 (IL-10) and Interleukin-1 receptor (IL-1R) [77]. This disturbance in the adipokine profile may lead to an increase in chronic low-grade inflammation associated to cardiometabolic abnormalities, such as insulin resistance [45].

This controversial result calls into question whether hypocaloric diets are beneficial for maintaining the metabolic status of MHO individuals; however, they can reduce the non-metabolic causes of morbidity and mortality in MHO people. A recent literature review pointed out that this treatment prompted a reduction in BMI, blood pressure, and triglycerides in MHO patients [23]. However, Karelis et al. (2008) showed that MHO individuals in a balanced hypocaloric diet intervention displayed a significant reduction in insulin sensitivity, while in MUO, an improvement in insulin resistance was observed. Results were contrasting despite the similar weight loss, suggesting that MHO may respond differently to hypocaloric diets [21]. Another study, using accurate phenotyping, corroborates these findings because the calorie-restricted healthy diet was not very effective in improving insulin sensitivity in MHO individuals. In contrast, for MUO individuals, the benefits of this intervention were more expressive [78]. This emphasizes that in addition to assessing the weight, it is important to monitor the individuals' health conditions as a whole to provide them with a global evaluation since weight loss does not always promote improvements in cardiometabolic parameters.

The study by Park et al. (2016) also reported this difference in diet response, as only MHO individuals displayed a reduced risk of mortality with the unrestricted calorie Mediterranean diet [35]. This finding suggests that subjects with obesity are a heterogeneous

group concerning their metabolic state. It may be beneficial to adopt different dietary strategies for MHO, and MUO still current guidelines not considering these factors [78].

It is noteworthy that although several individuals with obesity have an absence or a lesser number of metabolic abnormalities, there is an association that has been shown between increased BMI per se and mortality [79,80]. Although MHO individuals display lower mortality risk and about half the risk of developing CVD and T2D compared to MUO [9,13], they are subject to considerably greater risk – ranging between 50 and 300% – of long-term negative outcomes such as morbidity and mortality. Besides have a considerable chance of progressing to MUO phenotypes [7] compared to metabolically healthy eutrophic individuals [9,13].

Furthermore, regardless of the onset of cardiometabolic diseases, obesity may prompt the development of non-metabolic comorbidities that reduce the individual's quality of life, such as asthma, gallbladder disease, osteoarthritis, and chronic low back pain [81]. This emphasizes the importance of encouraging the adoption of a healthy lifestyle among these individuals to reduce disease risk and improve health.

The strengths of this study include the fact that it presented a comprehensive review about the relationship between dietary patterns and the metabolic phenotype, with a large sample of individuals of different ethnicities, although including only seven studies, and some these are studies of long term. In addition, most of the studies included had a low risk of bias. The main limitations of this review included the fundamentals for the diagnosis of MHO. We emphasize the need to standardize the diagnosis of this condition so that future studies on MHO may benefit from more comprehensive, reproducible, and comparable approaches. Furthermore, there is a lack of standardization in the analysis of the dietary patterns used as intervention/exposure in this population, and eating pattern data for evaluation are derived from food frequency questionnaires or 24-hour dietary recalls. These self-reporting methods

may lead to measurement errors but are validated tools, and correct application reduces the risk of failure.

5. CONCLUSION

In conclusion, despite the divergences regarding the diagnostic criteria of MHO, adherence to a healthy dietary pattern helps to maintain metabolic health and reducing morbidity and mortality risks, while less healthy dietary patterns produce the opposite effect.

Findings suggest that MHO individuals possibly respond differently to diet than MUO individuals since there is a disparity between their metabolic states. However, it is noteworthy that there is no consensus on the concept of metabolic health, which may effect on the possible differences between the MHO and MUO responses to diet. Further studies with a standardized concept are necessary to verify this association's consistency and mechanisms to define conducts for the dietary intervention of individuals with obesity according to their metabolic phenotype.

Acknowledgements and funding: We thanks to the Coordination for the improvement of higher level personnel - CAPES Foundation (Ministry of Education, Brazil) conceded grants to D.L.S.V and funding for grammar and spelling review of the article; and National Council for Scientific and Technological Development- CNPq (Ministry of Science, Technology and Innovation, Brazil) for conceded research productivity grants to J.B. The funding sources played no role in the study design, collection, and analysis, interpretation of data; and in the writing of the manuscript or decision to publish.

Competing Interests: The authors declare no competing financial interests.

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TABLES AND FIGURES LEGENDS

Chart 1. PICOS criteria for inclusion of studies

Table 1. Absolute frequency of individuals per phenotype used in the studies

Table 2. Study characteristics and main effects of dietary patterns on the metabolically healthy obesity phenotype

Figure 1. Flow diagram of the literature search process

Figure 2. Effects of dietary patterns on metabolic phenotypes of obesity (Graphic Abstract). The dietary components of a healthy eating pattern can positively modulate aspects related to the occurrence of NCDs. They promote anti-inflammatory and antioxidant activity, intestinal integrity, and beneficial epigenetic regulation, and therefore decrease insulin resistance, lipid atherogenicity and, hepatic/ ectopic fat, while adherence to an unhealthy eating pattern would do the opposite. These factors directly affect the main characteristics of the metabolic phenotypes -MHO and MUO-, thus healthy eating pattern prevents the transition from MHO to MUO, decreases the risk of death from any cause, as well as cardiovascular risk in general.

Description	Abbreviation	Inclusion criteria
Participants	P	Metabolically Healthy Obese (MHO)
Intervention	I	Dietary patterns (Mediterranean Diet, DASH, Healthy and Unhealthy Patterns)
Comparison	C	Metabolically Unhealthy Obese (MUO)
Outcomes	O	Effects on health (mortality, cardiometabolic risk, transition to classic obesity or metabolic health maintenance)
Study design	S	Randomized and Non-randomized, Cross-Sectional, Case-Control and Cohort Trials

	Gomes-Huelgas et al. 2019[22]	Konieczna et al. 2019[33]	Kouvari et al. 2019[34]	Slagter et al. 2018[30]	Park et al. 2017[31]	Park et al. 2016[35]	Bell et al. 2015(32)[28]
MUO/MAO	0	2154	425	4017	687	1141	483
MANO	0	1553	672	0	0	0	483
MHNO	0	1501	686	0	1340	0	1159
MHO	115	593	107	1774	353	598	290
INT	0	0	0	3479	0	0	0
MONW	0	0	0	0	387	0	0
Total	115	5801	1890	9270	2767	1739	2415

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738 **Abbreviations:** Metabolically Unhealthy Obese (MUO), Metabolically Abnormal Non-Obese (MANO), Metabolically Healthy Non-Obese (MHNO), Metabolically Healthy
739 Obese (MHO), Intermediate (I) e Metabolically Obese Normal Weight (MONW).

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Reference	Study design	Sample	MHO diagnosis	Dietary pattern and method of assessment	Clinical parameters	Main results
Gomes-Huelgas et al. 2019 [22]	Non-Randomized Clinical	n= 115 Spanish women (100%) 35-55 years; MHO n = 115 (100% of the total sample)	≤1 of the metabolic syndrome criteria: fasting blood glucose ≥99 mg/dL; BP ≥135/85mmHg (or use of hypotensive agents); HDL-C ≤50 mg/dL or TG ≥150 mg/dL (or use of lipid-lowering therapy)	Hypocaloric Mediterranean Diet; Previous FFQ, Validated Mediterranean Diet Adherence Questionnaire	Weight, height, BMI, WC, BP (DBP and SBP), Glycemia, HbA1c, TC, LDL-c, HDL-c and TG, CRP-high sensitivity, IL-6, TNF-alpha, Resistin, Adiponectin	Weight loss reduces inflammatory biomarkers in MHO, but it induces a deterioration in the adipokine profile, which does not improve with diet and exercise intervention
Konieczna et al. 2020 [33]	Cohort	n=5801 2.437 Spanish men 55-80 years old (42%) and 3364 Spanish women 60-80 years old (58%); MHO n = 593 (10.2% of the total sample)	0-2 metabolic syndrome criteria: WC ≥102cm for men and ≥88 cm for women; fasting glucose ≥ 100 mg/dL (or drug treatment for hyperglycemia); SBP ≥130 mmHg and / or DBP ≥85mmHg (or use of hypotension); TG ≥150mg/dL (or treatment for elevated triglycerides); HDL-C <40 mg/dL for men and <50 mg/dL for women (or drug treatment for reduced HDL-C)	Validated Mediterranean Diet Adherence Questionnaire (MEDAS) and FFQ (dietary composition of macro and micronutrients)	Weight, height, WC, SBP and DBP, BMI, fasting plasma glucose, HDL-c and TG.	Adherence to the traditional Mediterranean Diet was associated with the transition to healthy phenotypes and promoted an improvement in metabolic health in MHO
Kouvari et al. 2019 [34]	Cohort	n=1890 937 Greek men 46±13 (49.6%) and 953 Greek women 45±14 (50.4%); MHO n=107 (5.66% of the total sample)	Absence of hypertension (SBP <130 mmHg and DBP <85 mmHg), dyslipidemia (TG ≥ 150mg/dL or treatment for high triglycerides, HDL-C <40 mg/dL for men and <50mg/dL for women or drug treatment for HDL-C reduced); glycemic abnormality (fasting blood glucose ≥ 100 mg/dL)	Mediterranean Diet Adherence Questionnaire (MedDietScore)	Weight, height, PCR, HOMA-IR, PRA, LDL-c, HDL-c, TG, fasting glycemia, TGO, TGP, Clearance Creatinine	High transition rate from MHO to MUO (52%), with low adherence to the Mediterranean Diet being associated with high CVD risk. Greater adherence to this pattern may be a potential preventive mechanism for the transition to metabolically unhealthy phenotypes

Slagter et al. 2018 [30]	Cross-cut	n= 9270 3442 Dutch men (37.1%) e 5828 Dutch women (62.9%) 30-69 years old; MHO n=1774 (19.1% of the total sample)	Absence of SAH (SBP <130 mmHg and SBP <85 mmHg), dyslipidemia (TG ≥150mg/dL or treatment for high triglycerides, HDL-C <40 mg/dL for men and <50mg/dL for women or drug treatment for HDL -C reduced); glycemic abnormality (fasting blood glucose ≥100 mg/dL)	4 subtypes of dietary patterns; FFQ and Principal Component Analysis	Body weight, height, BMI, WC, BP (DBP and SBP), fasting glucose, HDL-c, TG	Only 10% of men and 25% of women had MHO. Comparing MHO and MUO, only women with MHO had a healthy diet, rich in fruit, vegetables, fish and unsweetened fermented dairy products, avoiding sweetened drinks and snacks (savory and sweet). The pattern of food products rich in refined carbohydrates with a high glycemic index and low fiber content was inversely associated with MHO.
Park et al. 2017[31]	Cross-cut	n= 2767 1.299 American men (47%) and 1468 American women (53%) 30 -65 years old; MHO n= 353 (12.75% of the total sample)	0-1 metabolic syndrome criteria: fasting glucose ≥100 mg/dL (or drug treatment for hyperglycemia); HOMA –IR >90th percentile; PCR >90th percentile; SBP ≥130 mmHg and / or DBP ≥ 85 mmHg (or use of hypotension); TG ≥ 150mg/dL (or treatment for high triglycerides); HDL-C <40 mg/dL for men and <50 mg/dL for women (or drug treatment for reduced HDL-C)	Mediterranean diet assessed by FFQ (NHANES III), 24hDR and Mediterranean Diet Adherence Questionnaire; DASH assessed using 24hDR and Mellen's Index	Weight, height, BMI, WC, Fasting glucose, insulin, BP, TG, HDL-C and High sensitivity PCR	The highest count on the Mediterranean Diet score was associated with a higher probability of the MHO phenotype only in younger individuals (men <45 years and pre-menopausal women) and greater adherence to DASH was associated with lower probabilities of MONW phenotype. It is suggested that interventions for the prevention of CVD and metabolic disease differ by age group.

Park et al. 2016 [35]	Cohort	n= 1.739 769 American men (44.2%) and 970 American women (55.8%) 20-88 years old; MHO n=598 (34.38% of the total sample)	<2 criteria for metabolic syndrome: fasting glucose ≥ 100 mg/dL (or drug treatment for hyperglycemia); HOMA –IR >90th percentile; PCR >90th percentile; SBP ≥130 mmHg and / or DBP ≥85 mmHg (or use of hypotension); TG ≥150mg/dL (or treatment for high triglycerides); HDL-C <40 mg/dL for men and <50 mg/dL for women (or drug treatment for reduced HDL-C)	Mediterranean diet assessed by FFQ (NHANES III) and Mediterranean Diet Adherence Questionnaire	Weight, height, BMI, WC, fasting glucose, HOMA-IR, TG, HDL-c, CRP-high sensitivity, BP (SBP and DBP)	There were fewer deaths in MHO than in MUO. Better adherence to the Mediterranean diet was associated with a lower risk of death from any cause in MHO, but not in MUO.
Bell et al. 2015 [32]	Cross-cut	n = 2415 1159 Australian men (48%) e 1256 Australian women (52%) >45 years old; MHO n=290 (12% of the total sample)	0-2 of the abnormality criteria (TC ≥213 mg/dL or diagnosis of high cholesterol; LDL-c ≥135 mg/dL; HDL-c <39 mg/dL for men and <50 mg/dL for women; TG ≥177 mg / dL; fasting blood glucose> 108 mg / dL or diagnosis of diabetes; WC in men ≥102 cm or in women ≥88 cm; SBP ≥140 mmHg or DBP ≥90 mmHg or diagnosis of SAH) + BMI> 30 kg/m²	3 subtypes of dietary patterns; 24hDR (two days), eating behavior questionnaire; Factor Analysis	Weight, Height, BMI, TC, HDL-c, LDL-c, TG, fasting glucose	Having a healthier dietary pattern plays a role in the metabolic system and obesity phenotypes. Each increased standard deviation in the unhealthy pattern reduced the chance of having a metabolically healthy profile by 14%; while for each increased standard deviation in the healthy eating pattern, the chances of having a metabolically healthy profile increased by 18%.

Abbreviations: HDL-c: high density lipoprotein; TG: triglycerides; FFQ: food frequency questionnaire; BMI: Body Mass Index; WC: waist circumference; BP: blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure; HbA1c: glycated hemoglobin; TC: total cholesterol; LDL-c: low density lipoprotein; CRP: C-reactive protein; IL-6: interleukin 6; TNF-alpha: tumor necrosis factor alpha; MHO: metabolically healthy obesity; HOMA-IR: insulin resistance index; 24hDR: 24-hour dietary recall;; TGO: glutamic-oxalacetic transaminase; TGP: glutamic-pyruvic transaminase; MUO: metabolically unhealthy obesity; CVD: cardiovascular disease; DASH: Dietary Approaches to Stop Hypertension; SAH: Systemic arterial hypertension; MONW: metabolically obese of normal weight.

ICMJE DISCLOSURE FORM

Date: March-06 -21
Your Name: Josefina Bressan
Manuscript Title: Influence of Dietary Patterns on the Metabolically Healthy Obesity Phenotype: A Systematic Review
Manuscript number (if known):_____

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In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

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Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	____None	The Coordination for the improvement of higher level personnel - CAPES Foundation (Ministry of Education, Brazil) conceded grants to D.L.S.V and funding for grammar and spelling review of the article; and National Council for Scientific and Technological Development-CNPq (Ministry of Science, Technology and Innovation, Brazil) for conceded research productivity grants to J.B. The funding sources played no role in the study design, collection, and analysis, interpretation of data; and in the writing of the manuscript or decision to publish. I declare no competing financial interests.
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_x_ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

HIGHLIGHTS

- Individuals with MHO have a healthy dietary pattern;
- Healthy dietary patterns play a role in maintaining or recovering metabolic health;
- Mediterranean diet without caloric restriction prevents transition from MHO to MUO;
- MHO individuals possibly respond differently to diet than MUO;
- The MHO diagnosis varied much among studies which impairs assessment of prognosis.

ICMJE DISCLOSURE FORM

Date: March-06 -21
Your Name: Pâmela Gracielle da Fonseca
Manuscript Title: Influence of Dietary Patterns on the Metabolically Healthy Obesity Phenotype: A Systematic Review
Manuscript number (if known):_____

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Date: March-06 -21
Your Name: Sônia Lopes Pinto
Manuscript Title: Influence of Dietary Patterns on the Metabolically Healthy Obesity Phenotype: A Systematic Review
Manuscript number (if known):_____

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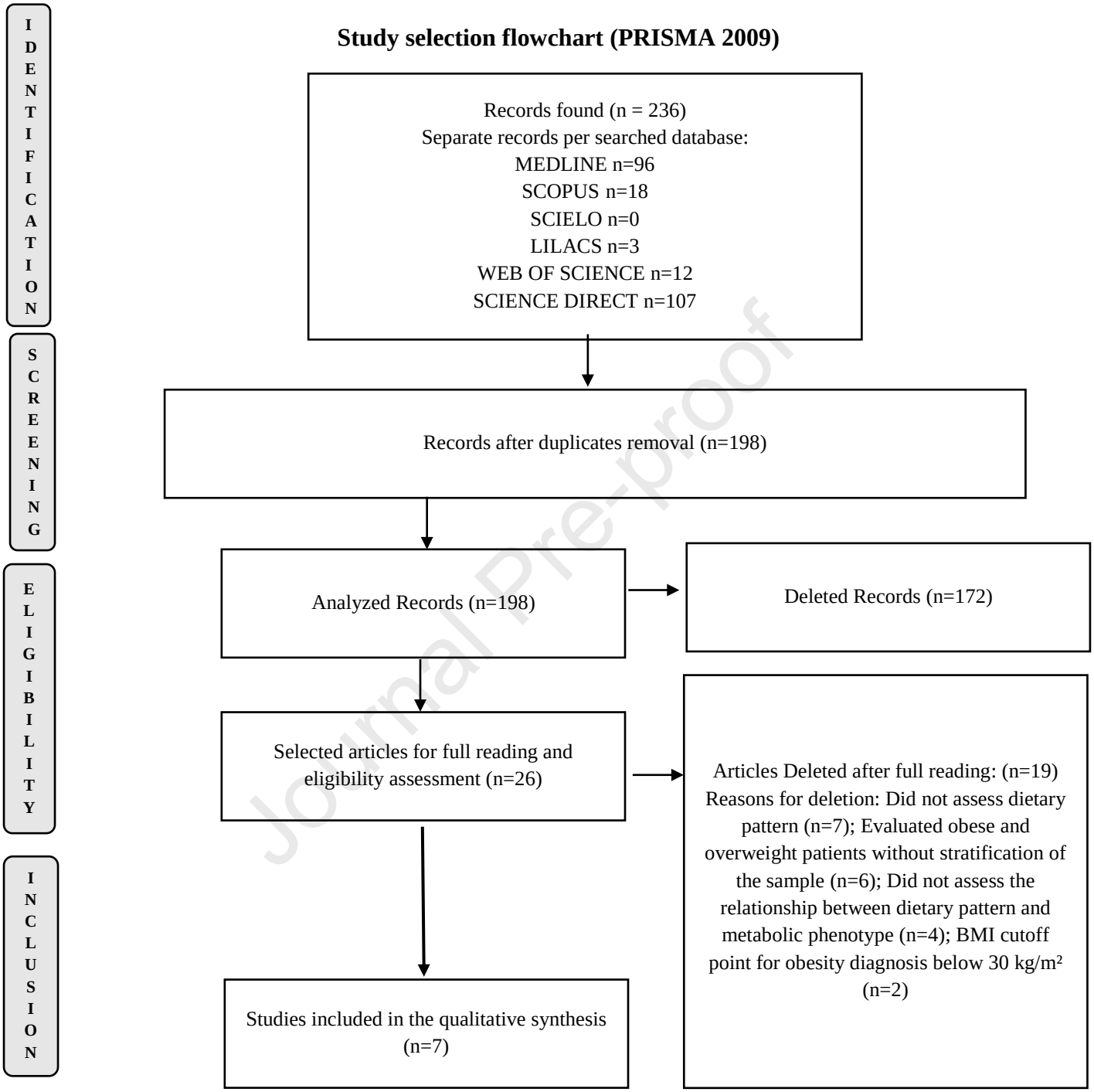
Figure 1

Study selection flowchart (PRISMA 2009)



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