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Dietary patterns according to gender and ethnicity associated with metabolic syndrome: a systematic review and meta-analysis

Padrões alimentares segundo gênero e etnia associados com a síndrome metabólica: uma revisão sistemática e meta-análise

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Abstract *The objective of this systematic review (SR) with meta-analysis (MA) was to identify the dietary patterns of the population, regarding ethnicity and gender, and their association with the metabolic syndrome and its risk factors (MetS-RF). The literature search was performed using Medline, Scopus, Ebsco, SciELO, and BVS databases. Studies with adult participants that identified dietary patterns associated with MetS-RF were included. Pooled odds ratio (OR) and 95%CI were calculated using a random-effect, generic inverse variance method. Statistical heterogeneity and publication bias were explored. The dietary patterns were classified as healthy or unhealthy. Studies were categorized into three groups: Women (all ethnicities), Afro-descendant (men and women), and General Population (both genders and ethnicity). Among the articles found (n=8,496), 22 integrated the SR and 11 the MA. The adherence to the healthy dietary pattern was negatively associated (protective factor) with MetS-RF only in the General Population (OR=0.77; 95%CI: 0.61-0.98). Nevertheless, the unhealthy dietary pattern was associated with the higher prevalence of MetS-RF in all analyzed groups. It was concluded that an unhealthy eating pattern increases the chances of SM-RF in adults, regardless of gender and ethnicity.*

Key words *Metabolic syndrome, Feeding behavior, Western diet*

Resumo *Esta revisão sistemática (RS) com meta-análise (MA) teve por objetivo identificar os padrões alimentares da população, segundo sexo e etnia, e sua associação com a síndrome metabólica e seus fatores de risco (SM-FR). Foram consultadas as seguintes bases de dados: Medline, Scopus, Ebsco, SciELO e BVS. Foram incluídos estudos com participantes adultos e que identificaram padrões alimentares associados à SM-FR. Na MA empregou-se o modelo de efeitos aleatórios para estimativa do odds ratio (OR) combinado. A heterogeneidade estatística e o viés de publicação foram explorados. Os padrões alimentares foram agrupados em saudável ou não saudável. Conforme a composição das amostras, os estudos foram assim categorizados: Mulheres (sem definição de etnia), Afrodescendentes (homens e mulheres), e População Geral (ambos os sexos e etnia). Foram encontrados 8.496 artigos, dos quais 22 compuseram a RS e 11 a MA. A adesão ao padrão alimentar saudável associou-se negativamente com SM-FR (fator de proteção) apenas para População Geral (OR=0,77; IC95%: 0,61-0,98). No entanto, o padrão alimentar não saudável esteve associado a maiores prevalências de SM-FR em todos os grupos analisados. Concluiu-se que um padrão alimentar não saudável aumenta as chances de SM-FR em adultos, independentemente de gênero e etnia.*

Palavras-chave *Síndrome metabólica, Comportamento alimentar, Dieta ocidental*

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Introduction

The dietary pattern can be defined as the set of food and beverages that are usually consumed by individuals and populations[1,2]. Unhealthy dietary patterns, allied to a sedentary lifestyle, contribute to the increased prevalence of chronic non-communicable diseases (NCDs)[3], for instance, metabolic syndrome (MetS). This is characterized by the presence of certain conditions such as central obesity, dyslipidemia, hypertension (SAH), insulin resistance, and hyperglycemia[4].

The association between dietary patterns and MetS has been quite studied. Some studies show it as a protective factor, while others indicate an increased risk of developing MetS[5-8]. A healthy dietary pattern, as the one based on characteristic food of the Mediterranean diet, improves the HDL profile and of the MetS components[9,10]. The Brazilian cardioprotective dietary pattern[11] contributes to the reduction of LDL levels. In contrast, an unhealthy pattern, characterized by the presence of fried meat, processed meat, sugars, fast food, alcoholic beverages, among others, is associated with a greater risk for MetS[12,13].

Studies on the relationship between diet and NCDs have increased[14], but most of the research has been conducted in North America, Europe, and Asia[14-16], with minimal focus on Afro-descendant populations, particularly those that differentiate results by gender. Research carried out in the USA revealed that the black population had a greater probability of adopting an unhealthy dietary pattern compared to the white population[17].

Certain MetS components, for instance, SAH, are more prevalent in Afro-descendant individuals[18], but little is known about the MetS characteristics in black populations[19]. Furthermore, there seems to be a higher susceptibility of the women population to MetS[20,21]. In this context, little is known about the dietary patterns practiced by this public, which indicates the necessity of such relations to be further clarified.

This study aimed to identify the dietary patterns of the population, according to ethnicity and gender, and their association with the MetS or its risk factors (MetS-RF).

Methods

This is a systematic review (SR) with meta-analysis (MA) developed to answer the following question: Which dietary patterns adopted by women and afro-descendants are associated with MetS-RF? In the search for articles, an adaptation of the PICO strategy[22] was used. This study used "exposure" instead of "intervention" due to its observational nature and did not include a "comparator", which is typically used in efficacy comparison studies. The recommendations contained in PRISMA were followed[23]. The research protocol was previously registered (PROSPERO ID CRD42020148478).

Search Strategy

The search for articles was carried out on the following electronic databases: MEDLINE (via PubMed), SciELO, Virtual Health Library (VHL - the Brazilian Virtual Health Library - BVS); EBSCO and, Scopus. The following limits were used: human beings, age ≥18 years, and English, Portuguese and Spanish languages. The terms employed in the search were identified on the DeCS and the MeSH. In MEDLINE (PubMed) the search strategy was established using the alternative "advanced search" and the logical operators OR and AND. Thus, having MEDLINE as a reference, the search strategy was organized as follows: ((Adult# OR "middle age" OR "young adult" OR Women)) AND ("African Continental Ancestry Group" OR Black OR negro OR "Negroid Race" OR "Races, Negroid" OR "black-slaves descendant" OR Quilombolas) AND (Eating OR "food analysis" OR food# OR "Feeding Behavior" OR "Feeding Behaviors" OR "Feeding Patterns" OR "Feeding Pattern" OR "food habit" OR "food habits" OR Diet OR "food consumption") AND ("Metabolic Syndrome" OR "Metabolic Syndrome X" OR "excess weight" OR overweight OR obesity OR "abdominal obesity" OR hypertension OR "High Blood Pressure" OR "dyslipidemia" OR "total cholesterol" OR "triglycerides" OR "Cholesterol, HDL" OR "High Density Lipoprotein Cholesterol" OR "Cholesterol, LDL" OR "Low Density Lipoprotein Cholesterol" OR "Cholesterol, VLDL" OR "Very Low Density Lipoprotein Cholesterol" OR "Diabetes Mellitus" OR "Diabetes" OR Hyperglycemia OR "insulin resistance"). For the other databases, the necessary adaptations were made, according to their specificities.

The reference lists of the selected articles were also examined, as well as the review articles found when applying the search strategy. Additionally, the BVS database was consulted, which contains works from postgraduate programs (theses and dissertations) and other types of productions classified within the scope of grey literature.

Eligibility criteria

Observational study; having analyzed women (>18 years); studies that included Afro-descendant individuals, studies that identified dietary patterns associated with risk factors for MetS or itself, and articles which defined dietary patterns using statistical techniques a posteriori, such as a factor analysis (FA), principal component analysis (PCA) and cluster analysis.

Selection of articles

Duplicate articles were checked and, subsequently, two evaluators (LBB and IRSG) conducted the selection of publications recovered through the initial search strategy. This selection was based on the reading of the titles and abstracts, and it was conducted independently, by applying the pre-defined eligibility criteria. The selected articles at this stage were assessed by reading the full text, also independently by the two authors. In case of disagreements in any selection stage, these were solved by consensus after the discussion between the peers. When no agreement was reached, the divergences were solved by two other researchers (HSF and TAS).

The Rayyan application (Rayyan QCRI: https://www.rayyan.ai/) was used for duplicate articles by title and abstract.

Data extraction

The results of data extraction, performed independently by two reviewers (LBB and IRSG), were compared and discrepancies were resolved by consensus. When this did not happen, a third researcher (EAS) was called to decide. The following information was extracted in Excel spreadsheet: publication year; study location; period of realization; methodological design; target-public characteristics (age, women percentage, afro-descendants percentage); sample size; exposures and outcomes assessed; MetS risk factors; assessment methods of food consumption; the statistical method used in the definition of food consumption pattern; the name given to dietary patterns and their characteristics; adherence categories to the dietary pattern (dichotomous, tertile, Quartile or Quintile); risk estimates with 95%CI for different adherence categories to the dietary patterns and significance level of the associations (p-value). Additionally, the necessary information was extracted to assess the quality of the articles.

Methodological quality assessment of the articles

The quality of the selected studies was assessed independently by three researchers (LBB, IRSG, and NBRV) by using the Quality Assessment Tool for Quantitative Studies of the Effective Public Health Practice Project (EPHPP)[24]. In case of divergences, a fourth reviewer was consulted (EAS).

The EPHPP comprises 22 different items divided into eight blocks: selection bias, study design, confounding factors, blinding, data collection method, dropouts, and withdrawals, the integrity of intervention, and analysis. Nevertheless, for this study, two blocks were not considered: the integrity of intervention, and analysis. For some of these blocks, the classification criteria were adjusted based on the study types included in this review[25,26]. As to study design, as cross-sectional studies were included, which by nature, do not have a control or intervention group, to not classify them as weak in this block, the assessment was designated as "not applicable". At the "blinding" criterion, all studies were classified as moderate.

Each one of the blocks was assessed and classified as strong, moderate, or weak, and, in the end, the studies were designated as high/strong quality when no assessment item of the study was categorized as of low/weak evidence; moderate when only one of the criteria was defined as low/weak and; weak when it was attributed low/weak pattern to two or more items of the analyzed criteria.

Evidence quality assessment

The evidence quality of the present MA was assessed by using the NutriGrade scoring system[27]. The assessment was conducted based on 8 criteria: 1) risk of bias, 2) precision, 3) heterogeneity, 4) directness, 5) publication bias, 6) funding bias, 7) effect size, and 8) dose-response. The maximum scoring for the MA is 10 points being the evidence quality classified as follows: a) very low evidence (scoring<4), b) low evidence (from 4 to 5.99 points), c) moderate quality (from 6 to 7.99 points), and d) high evidence quality (scoring≥8).

Statistical analysis

The MA was conducted to combine the results and compare the odds ratio (OR) for MetS-RF

according to the higher categories of consumption of healthy or unhealthy dietary patterns, in comparison to the lower categories of consumption of these patterns. As a result of the dietary patterns being specific for each population and, thus, having distinct nomenclatures, only patterns that shared the majority of food and with similar factorial charges were considered.

The generic inverse variance method was used. Relative risk (RR) or hazard ratio (HR) were considered directly as OR estimates[7,8]. Random effect models were used to calculate ORs grouped with their respective 95%CI. Heterogeneity was assessed by using the Q test at a significance level of 10% and I^2 statistics, which produces results ranging from 0% to 100%: I^2=0% to <25%, no/low heterogeneity; I^2 from ≥25% to <50%, moderate heterogeneity; I^2>50%, high heterogeneity[28].

The analyses were pre-stratified based on the characteristics of the respective samples and, in this study, were identified as follows:

a) *Women Public* - Studies whose samples were composed only of women and without definition of race/skin color, that is, all ethnicities;

b) *Afro-descendant Population* - Studies which approached participants of both genders, being the Afro-descendant the inclusion criterion and;

c) *General Population* - All studies that met the inclusion criteria of the present article and that analyzed the samples constituted without distinction of ethnicity and with the inclusion of both genders. The studies could include data of Afro-descendant individuals and women; however, the data were analyzed on a consolidated and not discriminated basis regarding these categories.

The sensitivity analysis by excluding one study at a time was performed to assess the influence of one single study on the estimate and its contribution as a source of heterogeneity. Analyses of sub-groups were also performed to verify the contribution in the heterogeneity of the following factors: design, study location, and percentage of women or Afro-descendant individuals in the sample.

The publication bias was assessed by visual analysis of funnel plots. All analyses were performed using the software Revman version 5.4.

Results

A total of 8,496 articles were identified. Of these, 83 were submitted to full-text assessment; 67 were considered non-adherent to the inclusion criteria. Thus, 16 studies were selected. After exploring the reference lists in these articles, other six studies were included. Therefore, 22 publications were included in this SR (Figure 1).

Characteristics of the studies and quality assessment

The publications of manuscripts that involved the researched theme began in 2004, being 2009 the year presenting the greatest number (n=4) of publications (Chart 1).

The period of collection of the analyzed data in the selected studies varied between the years 1992[29] and 2019[30-35] and the difference between the data collection year and the publication of results varied from one[36] to 13 years[37] (Chart 1).

The cross-sectional design was the most frequent one (n=13; 59.1%)[6,12,29,31,33,35,38-44] and only eight studies included only women in their samples[30,32,33,35,39,42,45,46]. Amongst the other research that assessed both genders, the percentage contribution of women to the samples ranged from 47%[36] to 76%[47] (Chart 1). Of these, only four presented data on food consumption stratified by gender[31,32,48,49].

Regarding ethnicity, 10 studies (45.4%) were carried out only on Afro-descendant population[31-33,35,38,41,43,45-47] (Chart 1).

All studies analyzed at least one risk factor for MetS or this condition itself. The conditions most frequently studied were DM and factors related to it (n=5)[29,36,37,44,47]; obesity/overweight and abdominal obesity (n=9)[30-33,35,39,43,45,46] and MetS (n=3)[6,12,38] (Chart 1).

Almost all studies (n=19) used only the food frequency questionnaire (FFQ) as an assessment method of food consumption[6,12,29-33,35-45,48,49] (Chart 2).

As to the definition of dietary patterns, 18 studies derived the dietary patterns through the PCA or FA methods[6,12,30-33,35-37,39,40,43-49] and the number of patterns established in each study ranged from two to six. Seven studies[6,31,32,41,43,45,47] assessed the association of the outcome with two distinct dietary patterns and only one assessed six distinct dietary patterns[29] (Chart 2).

The healthy dietary pattern included in the MA was characterized by the presence of the following food groups: vegetables, whole grains, low-fat dairy products, legumes, soup, fish, nuts, and oils (olive oil and other vegetable oils). The food groups included in the unhealthy dietary pattern were sauces, eggs (without specification

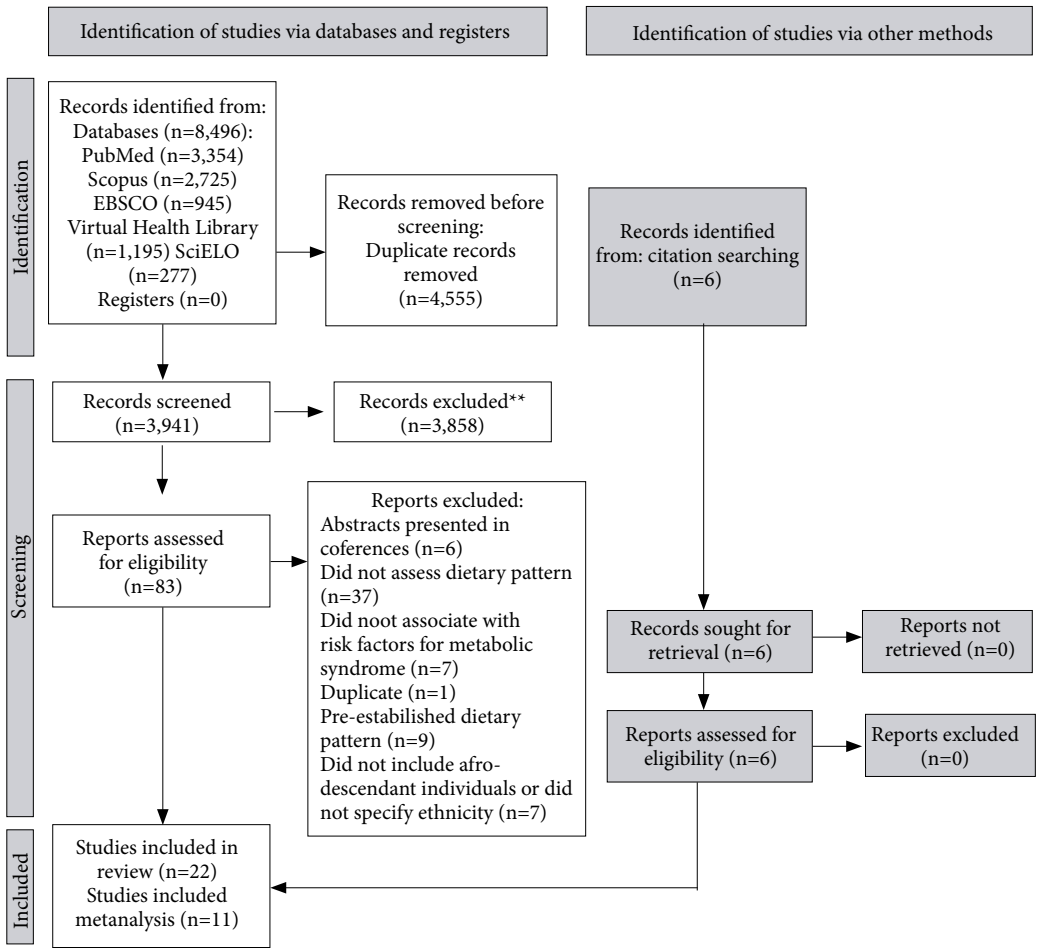

Figure 1. Flow diagram of the study selection process.

Source: Authors.

of cooking method and based on the recommendations of a food pattern with characteristics of the Mediterranean diet) tomato sauce, pasta, ready-made salad dressing, refined grains, fries, high-fat dairy products, red meat, processed meat, sweets and desserts, sugar-sweetened drinks, condiments, margarine, canned fish, coffee, fried food, and fast food. It is important to highlight that each study named the dietary patterns distinctively (Chart 2).

The methodological quality of the articles was classified as strong for 14 studies, moderate for six, and weak for two works (Chart 1).

Dietary pattern MA and its association with MetS or its risk factors

Healthy dietary pattern

Eleven studies met the MA inclusion criteria. Four articles were analyzed as to the healthy dietary pattern in the Women Population group, not evidencing the relation with the occurrence of MetS-RF (Figure 2.1 A). In the Afro-descendant Population group (5 studies), results were like those of the Women Population (Figure 2.1 B). As to the General Population (9 research), in contrast to the other two groups, there was a significant association (OR=0.77; 95%CI: 0.61-0.98), despite the high (I^2=79%) heterogeneity (Figure 2.1 C).

Chart 1. Main characteristics of the studies included in the systematic review.

Author, year of publication and country	Periodical	Data collection year	Study design	Target-public	Sample size; age range	% Women/ % afro-descendant	Assessed outcome	Assessed risk factors for MetS	Methodological quality
Frank et al., 2014[47] Ghana	Br J Nutr	Between August 2007 and June 2008	Case-control	Men and women	1,221 participants: 679 controls and 542 cases; Average age of 50.4 years	76.0/100	T2DM	WC, WHR, fasting glycemia	Strong
Nettleton et al., 2009[48] USA	Am J Clin Nutr	2002-2003	Cohort	Men and women	5,316 participants; 45-84 years	53.0/24.28	CVD	WC, HDL cholesterol, blood pressure	Strong
Lara et al., 2019[49] USA	J Am Coll Cardiol	2003-2007	Cohort	Men and women	16,068 participants; ≥45 years	59.0/33.6	CI	WC, HDL cholesterol, blood pressure, SAH, LDL cholesterol, high fasting glucose, T2DM	Strong
Nettleton et al., 2008[36] USA	Diabetes Care	2002-2003, 2004-2005 and 2005-2007	Cohort	Men and women	5,011 participants; 45-84 years	47.0/24.04	T2DM	CC, HDL cholesterol, blood pressure, triglyceride, LDL cholesterol, fasting glucose	Strong
Liu et al., 2009[12] USA	Am J Clin Nutr	Between July 2000 and August 2002	Cross-sectional	Men and women	4,601 participants; 45-84 years	53.0/24	MetS	WC, HDL cholesterol, blood pressure, triglyceride, LDL cholesterol, high fasting glucose	Strong
Liu et al., 2013[38] USA	Obesity	September 2000 and March 2004	Cross-sectional	Men and women	1,775 participants; 21-94 years	>50.0/100	MetS	WC, HDL cholesterol, blood pressure, triglyceride, LDL cholesterol, high fasting glucose	Strong
Deshmukh-Taskar et al., 2009[6] USA	Public Health Nutr	1995-1996	Cross-sectional	Men and women	995 participants; 19-39 years	61.0/20	MetS	WC, blood pressure arterial, T2DM (insulin and glucose), HDL cholesterol, triglyceride	Strong
Nettleton et al., 2006[40] USA	Am J Clin Nutr	-	Cross-sectional	Men and women	5,089 participants; 45-84 years	53.0/24	Endothelial inflammation	WC, blood pressure, high serum insulin and glucose, HDL cholesterol, LDL cholesterol	Strong
Davis et al., 2013[44] USA	Am J Clin Nutr	-	Cross-sectional	Men and women	235 participants; Average age of 56.5 years	71.0/27.2	T2DM	T2DM	Moderate

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Delisle et al., 2009[41] Spain	Nutr J	2001	Cross-sectional	Men and women	213 participants; Average age of 36.5 years	61.0/100	Conditions of self-reported CVD	T2DM, SAH, cholesterol, obesity	Moderate
Keding et al., 2011[46] Tanzanian	Food Nutr Bull	2006-2007	Cohort	Women	252 participants; 16-45 years	100.0/100	Obesity and anemia	Overweight (BMI)	Moderate
Boggs et al., 2015[32] USA	J Nutr	1995 and 2011	Cohort	Women	37,001 participants; 21-69 years	100.0/100	Mortality by all causes according to BMI	Overweight (BMI)	Strong
Holmes et al., 2018[31] Nigerian, Tanzanian, South Africa and Uganda	Public Health Nutr	2011	Cross-sectional	Men and women	738 participants; Average age of 38.8 years	60.0/100	Obesity/ overweight	Overweight [BMI)	Weak
Becquey et al., 2010[43] Burkina Faso	Nutr J	April/May 2005	Cross-sectional	Men and women	1,072 participants; 15-65 years	52.0/100	Overweight	Overweight (BMI)	Strong
Boggs et al., 2011[45] USA	Am J Clin Nutr	1995 and 2001	Cohort	Women	41,351 participants; 21-54 years	100.0/100	Weight gain	Overweight (BMI)	Strong
Liese et al., 2004[29] USA	Br J Nutr	1992 and 1994	Cross-sectional	Men and women	980 participants; 40-69 years	55.0/26	Sensitivity to insulin and adiposity	BMI, WC, high glucose and insulin	Strong
Fröhlich et al., 2019[30] Brazil	Ciência & Saúde Coletiva	Between January and April, 2011	Case-control	Women	541 participants: 215 cases and 326 Controls; 18 to 53 years	100/ not white 10.7 (cases) and 13.2 (controls)	Abdominal obesity	WC	Moderate
Silva et al., 2014[42] Brazil	Cad Saúde Pública	2003	Cross-sectional	Women	1,026 participants; 20-60 years	100/ 16.2	SAH	BMI, Blood pressure	Strong
Perozzo et al., 2008[39] Brazil	Cad Saúde Pública	2003	Cross-sectional	Women	1,026 participants; 20-60 years	100/ 16,2	Abdominal obesity	BMI, WC	Moderate
Gower et al., 2021[37] USA	Eur J Clin Nutr	Between 2003 and 2007	Cohort	Men and women	13,528 participants; ≥45 years.	57/ 30	High fasting insulin	High fasting insulin, BMI	Strong
Sarfo et al., 2021[33] East Africa	Nutrients	2019	Cross-sectional	Women	1,152 participants; 15-49 years	100/100	Overweight/ obesity	BMI	Moderate
Mukoma et al., 2022[35] South Africa	SAJCN	2019	Cross-sectional	Women	160 participants; Between 8 and 24 years	100/100	Body adiposity	BMI	Weak

USA: United States of America; MetS: metabolic syndrome; T2DM: Type 2 diabetes mellitus; BMI: body mass index; WC: waist circumference; WHR: waist-to-hip ratio; SAH: systemic arterial hypertension; CVD: cardiovascular disease; CI: cardiac insufficiency; LDL: low density lipoprotein; HDL: high density lipoprotein.

Source: Authors.

Chart 2. Characteristics of the studies included in the systematic review related to food consumption.

Source	Assessment method of food consumption	Statistical method to identify dietary patterns	Dietary patterns and characteristics	Category/ pattern scoring	HR/ OR/RR[6]	CI95%[7]	p for the trend
Nettleton et al., 2009[48]	FFQ[1]	PCA[2] (with varimax orthogonal rotation)	1-Dietary pattern fat and processed meat: added fat, processed meat, French fries, and desserts;	Quintile 1 Quintile 5	1.00 1.82	Reference 0.99-3.35	0.100
			2-Dietary pattern vegetables and fish: vegetables, fish, soup, Chinese food, red meat, poultry, and soya;	Quintile 1 Quintile 5	1.00 0.98	Reference 0.54-1.79	0.380
			3-Dietary pattern beans, tomatoes and refined grains: Beans, tomato, refined grains, high-fat dairy products, avocado/guacamole and red meat;	Quintile 1 Quintile 5	1.00 0.8	Reference 0.45-1.42	0.790
			4-Dietary pattern whole grains and fruit: whole grains, fruit, nuts and seeds, green leafy vegetables, and low-fat dairy products.	Quintile 1 Quintile 5	1.00 0.54	Reference 0.33-0.91	0.007
Nettleton et al., 2008[36]	FFQ	PCA (with varimax orthogonal rotation)	1-Dietary pattern fat and processed meat: added fat, processed meat, French fries and desserts;				
			2-Dietary pattern vegetables and fish: vegetables, fish, soup, Chinese food, red meat, poultry and soya;				
			3-Dietary pattern beans, tomatoes and refined grains: Beans, tomato, refined grains, high-fat dairy products, avocado / guacamole and red meat;	Quintile 1 Quintile 5	1.00 1.23	Reference 0.85-1.78	0.004
			4-Dietary pattern whole grains and fruit: whole grains, fruit, nuts and seeds, green leafy vegetables and low-fat dairy products.	Quintile 1 Quintile 5	1.00 0.66	Reference 0.47-0.93	0.005
Liu et al., 2009[12]	FFQ	Reduced classification regression	RRR[3] dietary pattern: food with high glycemic index (bread / refined grain noodles, white potato and sweet bread), meat with high content of fat, cheese and processed food (French fries, snack food, pizza, ice cream).				<0.001
Liu et al., 2013[38]	FFQ	PCA	1-"South" pattern: beans and legumes, corn products, fried fish and chicken, margarine and butter, rice and noodles;	Tertile 1 Tertile 3	1.00 2.16	Reference 1.30-3.60	0.004
			2-"Fast food" pattern: sugars and sweetened juices, fast food and snack food;	Tertile 1 Tertile 3	1,00 2.40	Reference 1.40-4.20	0.002
			3-"Prudent" pattern: fruit and vegetables, cold and hot cereals, nuts and seeds.	Tertile 1 Tertile 3	1.00 0.75	Reference 0.50-1.10	0.120
Lara et al., 2019[49]	FFQ	PCA and Factor analysis	1-Convenience pattern: meat, pasta, Mexican dishes, pizza, French fries, Chinese dishes and fast food;	Quartile 1 Quartile 4	1.00 1.21	Reference 0.83-1.77	0.17
			2-Plant-based pattern: cruciferous vegetables and other vegetables, fruit, beans and fish;	Quartile 1 Quartile 4	1.00 0.59	Reference 0.41-0.86	0.004
			3-Sweets/Fat pattern: desserts, bread for breakfast, chocolate, sweets, solid fats and oils and diverse sugar;	Quartile 1 Quartile 4	1.00 0.76	Reference 0.51-1.11	0.240
			4-South pattern: fried food, organ meat, processed meat, eggs, added fat and sugar-sweetened drinks;	Quartile 1 Quartile 4	1.00 1.32	Reference 0.90-1.93	0.240
			5-Alcohol/ salad pattern: wine, liqueur, bear, vegetables and salad dressing.	Quartile 1 Quartile 4	1.00 0.83	Reference 0.59-1.16	0.450

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Chart 2. Characteristics of the studies included in the systematic review related to food consumption.

Source	Assessment method of food consumption	Statistical method to identify dietary patterns	Dietary patterns and characteristics	Category/ pattern scoring	HR/ OR/RR[6]	CI95%[7]	p for the trend
Keding et al., 2011[46]	24HR[4] (applied for 3 non-consecutive days)	PCA	1-"Traditional coast" pattern: fruit, nuts, starchy plants and fish;				
			2-"Purchase " pattern: bread or cakes, sugar and tea;				0.005
			3-"Traditional-countryside" pattern: cereals, vegetables and the food group oil or fat;				
			4-"Pulses" pattern: dried and cooked common red beans, chickpeas, cowpeas, green beans, green peas (dried), pigeon peas and soya;				
			5-"Animal products" pattern: products of animal origin, excluding fish.				0.003
Deshmukh-Taskar et al., 2009[6]	YFQ[5]	PCA and Factor analysis	1-Western dietary pattern: refined grains, French fries, dairy products rich in fat, dishes with cheese, red meat, processed meat, eggs, snack food, sweets and desserts, sugar-sweetened drinks and condiments;		0.93	0.80-1.07	0.070
			2-Prudent dietary pattern: whole grains, legumes, vegetables, tomatoes, 100%-fruit juice, low-fat dairy products, poultry, soups and salad dressing with low-fat content.		0.93	0.80-1.07	0,350
Davis et al., 2013[44]	FFQ	Factor analysis through PCA	1-Pizza and sweets pattern: pizza, sweets, bread, pasta and fried chicken;				
			2-Meat pattern: eggs, processed meat and cultural meat (for instance, goat and oxtail);				
			3-Fried food pattern: French fries and fried chicken;				
			4-Fruit and vegetable pattern: fresh fruit, non-aquatic vegetables and fish; 5-Caribbean starch pattern: vegetables rich in starch, rice and beans.				
Boggs et al., 2015[32]	FFQ	Factor analysis	1-Prudent dietary pattern: vegetables and fruit;				
			2-Western pattern: red and processed meat, fried food8.	Quintile 1 Quintile 5	1.00 1.10	Reference 0.82-1.46	0.74
Holmes et al., 2018[31]	FFQ	PCA	1-Mixed-diet pattern: non-processed food, such as legumes, fresh fish, cereals, fruit and beans, and, processed food, such as cold meat, salad dressing and canned fish;	Tertile 1 Tertile 3	1.00 0.81	Reference 0.46-1.44	0.950
			2-Processed diet pattern: salad dressing, margarine, French fries, coffee, canned fish, butter, sweets and refined grains.	Tertile 1 Tertile 3	1.00 3.00	Reference 1.66-5.45	<0.0001
Nettleton et al., 2006[40]	FFQ	PCA	-Fat and processed meat pattern: fats and oils, meat with high content of fat and processed meat, French fries, snack food and desserts;				
			2-Vegetables and fish pattern: vegetables, fish and soup;				
			3-Beans, tomato and refined grains pattern: legumes, tomato, refined bread, rice, noodles, cheese with high content of fat, cheese and cream sauce, avocado and guacamole;				
			4-Whole grains and fruit pattern: whole-grain bread, rice and noodles, fruit, seeds, nuts and peanut butter				

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Chart 2. Characteristics of the studies included in the systematic review related to food consumption.

Source	Assessment method of food consumption	Statistical method to identify dietary patterns	Dietary patterns and characteristics	Category/ pattern scoring	HR/ OR/RR[6]	CI95%[7]	p for the trend
Becquey et al., 2010[43]	Qualitative FFQ	PCA	1-Snack food pattern: food usually consumed between the main meals (déguè, milk, sugar-sweetened drinks, yogurt, bread, fruit…);		1.04	0.95-1.13	0.424
			2-Modernity pattern: opposite to traditional dishes and sauces (sauces of tô, okra and Sumaúma) and local snack food (peanut, cakes and local drinks) to more modern-type food or preparations (scrambled eggs, chicken, tomato sauce, pasta, cheese, meat, soft drinks, soup, French sauce, hamburger).		1.19	1.03-1.36	0.018
Boggs et al., 2011[45]	FFQ	PCA and Factor Analysis	1-Vegetables/fruit pattern: vegetables, fruit, legumes, fish and whole grain;				0.820
			2-Meat/fried food pattern: red meat, processed meat, French fries, fried chicken and added fat.				0.080
Frank et al., 2014[47]	FFQ and 24HR	Factor analysis through PCA.	1-Shopping dietary pattern sweets and sugar-sweetened drinks, rice, food rich in protein (red meat, poultry, eggs and milk), vegetable oils (vegetable oil and margarine) fruit and vegetables (carrot, lettuce and cucumber);	Quintile 1 Quintile 5	1.00 0.11	Reference 0.06-0.21	<0.001
			2-Traditional dietary pattern: banana, green leafy vegetables, beans, Garden egg, fish, corn (banku), palm oil, okra and fruit.	Quintile 1 Quintile 5	1.00 3.2	Reference 1.96-5.22	<0.001
Liese et al., 2004[29]	FFQ	Cluster grouping	1-French fries pattern: whole milk, soft drinks, pastry, cakes, sweets;				0.161
			2-White bread pattern: White bread, tomato, cheese, dried beans, eggs, fats and oils and beer;				0.000
			3-Low-frequency eater pattern: distinguished by the lower daily average intake of food of several groups, which reflected in lesser intake of general energy;				0.003
			4-Fruit and poultry pattern: fruit and fruit juice, poultry, in addition to ice cream and meal substitutes;				
			5-Wine pattern: denoted the intake of food groups of mean levels, except wine and mixed drinks, of which a total of 2,3 portions per day were consumed;				
			6-Brown bread pattern: brown bread and cereals or rich in fibers, rice, noodles, legumes and also cooked or baked potatoes, low-fat dairy products, fish diet soft drinks and tofu.				

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Chart 2. Characteristics of the studies included in the systematic review related to food consumption.

Source	Assessment method of food consumption	Statistical method to identify dietary patterns	Dietary patterns and characteristics	Category/ pattern scoring	HR/ OR/RR[6]	CI95%[7]	p for the trend
Delisle et al., 2009[1]	FFQ	Cluster analysis	1-Western pattern: sweet food and drinks, animal fat and diverse/mixed dishes (this food group includes composed dishes as croquettes, soups and sauces);				
			2-Healthier dietary pattern: consumption of milk and dairy products, fish, legumes, fruit and bread.		1.51	0.56-3.48	0.480
Fröhlich et al., 2019[30]	FFQ	Factor analysis through PCA	1-Animal fat/calorie pattern: consumption of animal fat, jam, bread, potatoes/manioc, coffee, eggs, red meat and sweets;	Quartile 1 Quartile 4	1.00 0.86	Reference 0.49-1.51	
			2-Snack food/fast food pattern: consumption of salty and sweet biscuits, cold meats, snack food, soft drinks, fast food, vegetable oil and dairy products;	Quartile 1 Quartile 4	1.00 0.61	Reference 0.36-1.01	
			3-Fruit/vegetable pattern: consumption of green vegetables, yellow vegetables, banana, citric fruit, whole cereals, other vegetables, other fruit.	Quartile 1 Quartile 4	1.00 2.26	Reference 1.30-3.93	
Silva et al., 2014[42]	FFQ	RRR	1-Factor 1: cheese, cream, processed meat;	Tertile 1 Tertile 2 Tertile 3	1.30 1.23 1.00	0.89-1.90 0.83-1.81 Reference	0.376
			2-Factor 2: condensed milk, papaya, apple, banana, Orange, pumpkin, leafy vegetables, other vegetables and in natura fruit juice and lesser consumption of processed meat;	Tertile 1 Tertile 2 Tertile 3	0.83 0.62 1.00	0.59-1.19 0.42-0.90 Reference	0.046
			3-Factor 3: whole milk, creams, red meat, industrial mayonnaise and lesser consumption of processed meat.	Tertile 1 Tertile 2 Tertile 3	0.95 0.94 1.00	0.66-1.37 0.66-1.35 Reference	0.940
Perozzo et al., 2008[39]	FFQ	Factor analysis through PCA	1-Vegetables food pattern: cabbage, kale, cauliflower, Brussel sprout, pumpkin, carrot, orange, broccoli, beets, tomatoes, pods, bananas, papayas, apples, bergamots, and others. green vegetables and biscuits;	HC[8] LC[9]			
			2-Fruit dietary pattern: melon, watermelon, mango, pear, peach, persimmon, grape, lemon, passion fruit, pineapple, ice cream, avocado, guava, kiwi, natural juice and fish;	HC[8] LC[9]	1.00 1.05	Reference 0.99-1.11	0.070
			3-Nuts/oleaginous dietary pattern: almond, hazelnut, walnut, chestnut, prune, raisin, whole grain pasta, oatmeal, wheat bran, brown sugar, honey, rye bread, whole grain bread, soy, red wine and whole rice);	HC[8] LC[9]	1.00 0.93	Reference 0.89-0.98	0.088
			4-Bread/cassava/sweet potato dietary pattern: homemade bread, cassava, sweet potatoes, corn, beans, lentils, sugar, lard, whole milk, potatoes, cream, pasta and pork;	HC[8] LC[9]	1.00 0.98	Reference 0.92-1.03	0.460
			5-Chocolate/sweets dietary pattern: chocolate, candies, desserts, sweets, sour cream, ham, mortadella, salami, pantry, mayonnaise, processed cheese, fried foods, fast food, sweet biscuit, cuca and cake.	HC[8] LC[9]	1.00 1.03	Reference 0.97-1.09	0.323

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Chart 2. Characteristics of the studies included in the systematic review related to food consumption.

Source	Assessment method of food consumption	Statistical method to identify dietary patterns	Dietary patterns and characteristics	Category/ pattern scoring	HR/ OR/RR[6]	CI95%[7]	p for the trend
Gower et al., 2021[37]	FFQ	PCA	1-Convenience pattern: ready-made food/fast food;	Quintile 1 Quintile 5	1.00 0.99	Reference 0.82-1.19	0.810
			2-Plant-based pattern: poor in processed and prepared and sugar-sweetened food, and rich in fruit, legumes and cereals;	Quintile 1 Quintile 5	1.00 0.59	Reference 0.49-0.71	<0.0001
			3-Sweets/fat pattern: pastries and other sweets, fat snack food and fried food;	Quintile 1 Quintile 5	1.00 1.36	Reference 1.12-1.65	0.002
			4-Southern pattern: fried food, processed meat and sugar-sweetened drinks;	Quintile 1 Quintile 5	1.00 1.59	Reference 1.32-1.92	<0.0001
			5-Alcohol/salad pattern: alcohol (all types), green salad, and salad dressing.	Quintile 1 Quintile 5	1.00 0.74	Reference 0.62-0.87	<0.0001
Sarfo et al., 2021[33]	24HR	PCA	1-Vegetable-based pattern: intake of starchy plants, as cereals, roots and tubercles, as well as legumes and nuts, oils and fats;				
			2-Shopping pattern: Highly-processed food;				
			3-Mixed pattern: cereals, roots, tubercles, fruit, milk, sugar, sugar-sweetened drinks, legumes;				
			4-Vegetarian pattern: based on greenery (lettuce, tomato, cabbage, carrot, cassava leaves, black-eyed bean leaves, cucumber, eggplant, etc.);				
Mukoma et al., 2022[35]	Quantitative FFQ	PCA	1-Western pattern: sugar, tea and coffee, cooking fats, whole milk, breakfast cereals, red meat, vegetables, soup powder, condiments and sauces, processed meat, whole grain bread and fruit juice;				
			2-Mixed pattern: processed meat, red meat, fruits, vegetables, yogurt, rice and noodles, cakes and biscuits, soup powder, condiments and sauces and fruit juice.				

[1]FFQ: food frequency questionnaire; [2]PCA: Principal Component Analysis; [3]RRR: Reduced classification regression; [4]24HR: 24-hour food recall; [5]YFQ: food frequency questionnaire for youngsters/adolescents; [6]OR: odds ratio; RR: relative risk; HR: hazard ratio; [7]CI: confidence intervals; [8]High consumption; [9]Low consumption.

Source: Authors.

In the analysis of sub-groups (data not shown), regardless of gender or ethnicity, the stratification by study design pointed out reduced the chance for MetS-RF in cohort studies (n=4), being observed absence of heterogeneity (I^2=0%). The stratification by study conduction location pointed out that the healthy pattern reduced the chance of outcomes for studies conducted in the USA, although with elevated heterogeneity (I^2=74%). The studies with women percentage >50% in their samples denoted also that the healthy pattern did not lead to a decreased chance for the development of MetS risk factors. In the studies with a percentage sample lower than 50% of Afro-descendant individuals, the healthy dietary pattern reduced the chance for MetS-RF (OR=0.75; 95%CI: 0.57-0.98), although with high heterogeneity (I^2=83%). In the sensitivity analysis, the single exclusion of one of the studies did not reduce heterogeneity, however, the exclusion of two studies [6,30] caused more homogeneous results (OR=0,62; 95%CI: 0.55-0.71; I^2=0%).

The funnel plots of the MA on healthy dietary patterns presented asymmetry (Figure 3), revealing possible publication bias.

Figure 2.1 - Forest plot for the healthy dietary pattern

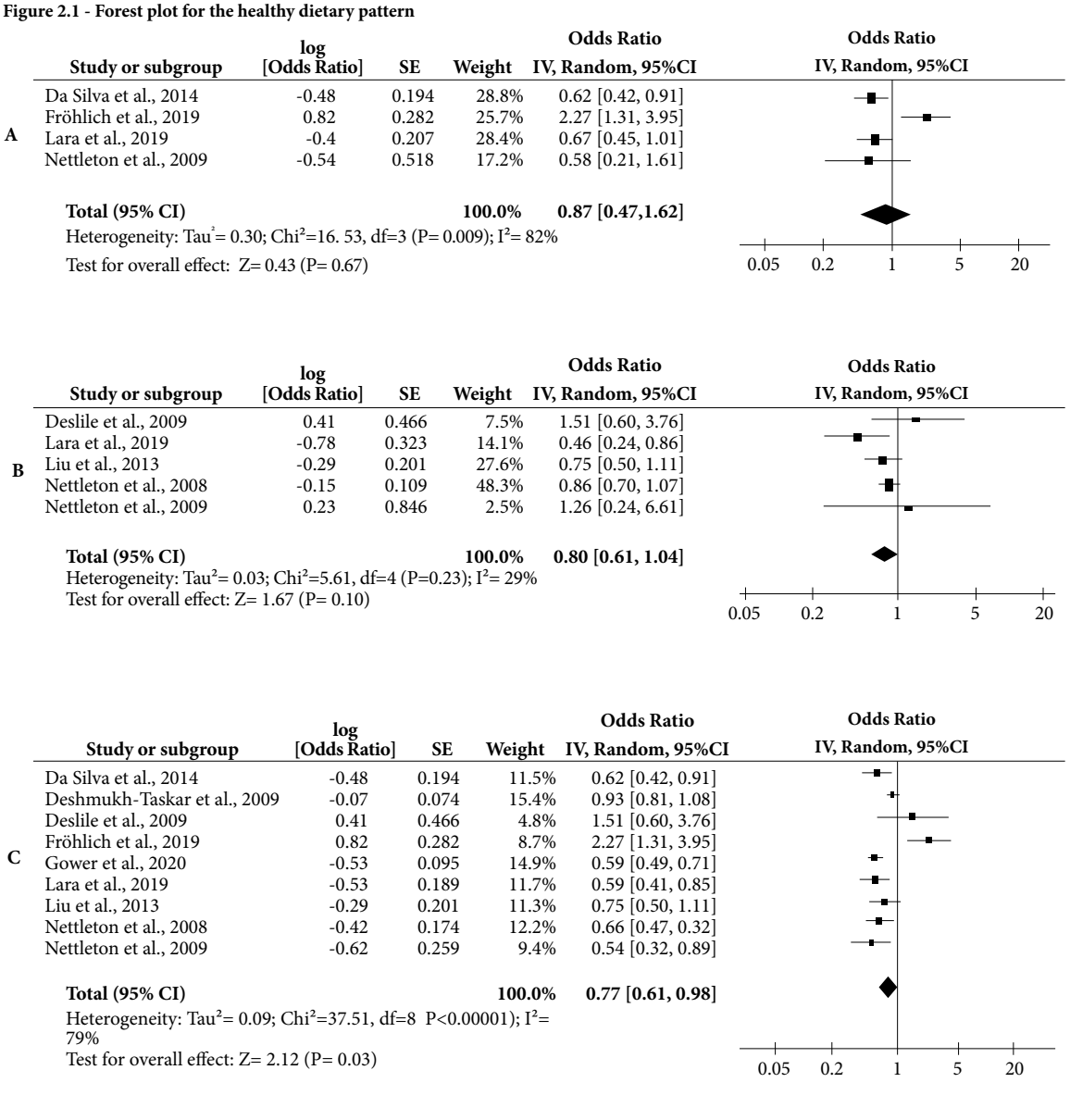

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Figure 2. Forest plot of the association between the highest category of a dietary pattern and the metabolic syndrome and its risk factors in women public (A), Afro-descendant population (B), and in the general population regardless of gender and ethnicity (C).

Unhealthy dietary pattern

Seven studies were included in the assessment of unhealthy dietary patterns for the Women Population, to which the results of the MA (OR=1.61; 95%CI: 1.35-1.91; I^2=14%) evidenced that greater consumption of food of such pattern increases the odds for MetS-RF (Figure 2.2 A). For the Afro-descendant Population (Figure 2.2 B), by the analysis of six studies, the unhealthy dietary pattern also indicated a greater risk for MetS-RF (OR=1.64; 95%CI: 1.15-2.32; I^2=71%).

Eleven studies were included in the MA on the unhealthy dietary pattern for the General

Figure 2.2 - Forest plot for the unhealthy dietary pattern

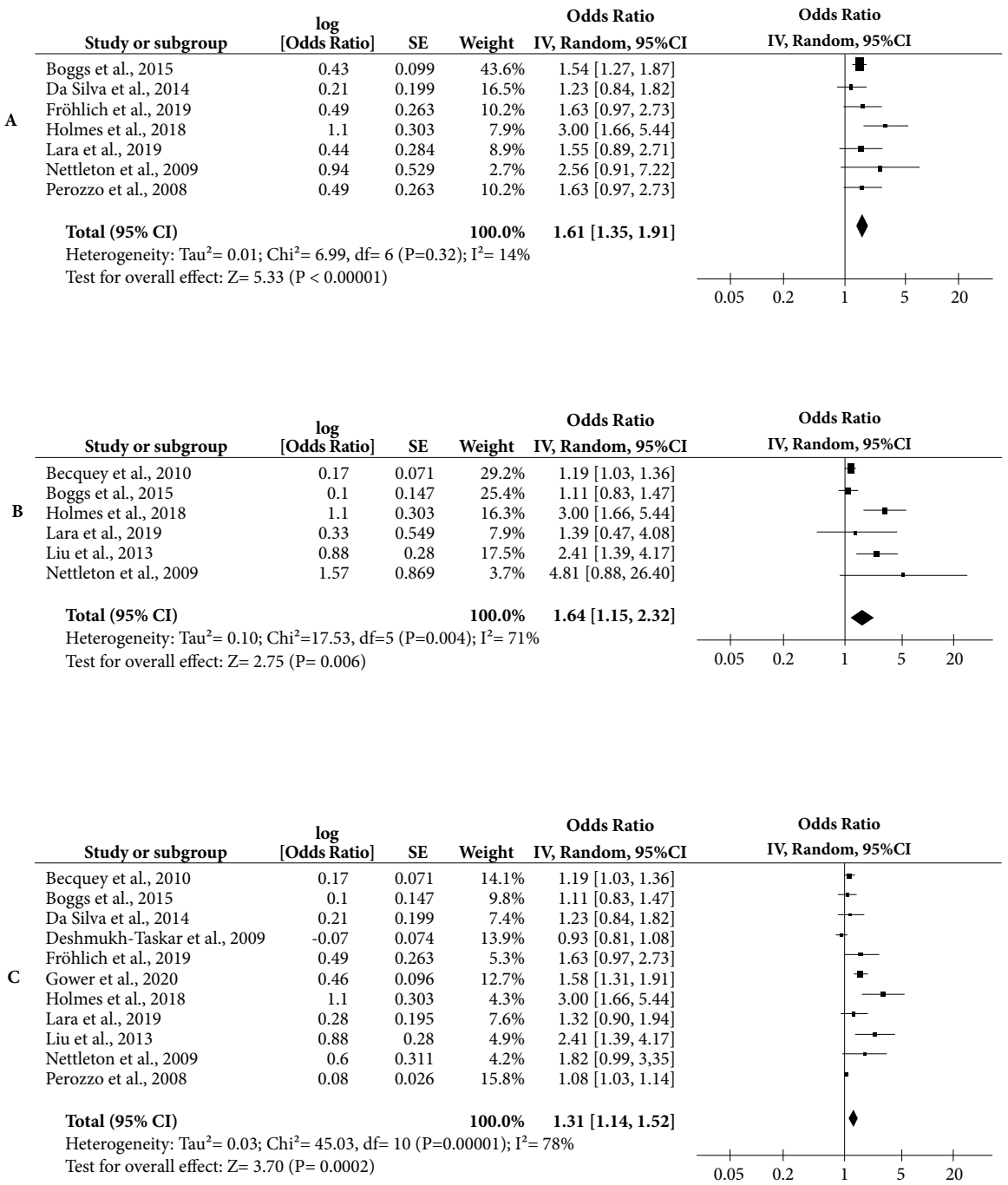

Figure 2. Forest plot of the association between the highest category of a dietary pattern and the metabolic syndrome and its risk factors in women public (A), Afro-descendant population (B), and in the general population regardless of gender and ethnicity (C).

Source: Authors.

Population. Grouped OR to different outcomes related to MetS in the comparison of the highest category about the lowest category of food consumption of unhealthy dietary patterns (Figure 2.2 C) was 1.31 (95%CI: 1.14-1.52; I^2=78%). In the sensitivity analysis, the exclusion of any one of the studies continued indicating that the unhealthy pattern was associated with higher odds for MetS-RF while keeping high heterogeneity (data not shown).

In the Analysis of sub-groups (data not shown), it was verified that the results involving cohort studies presented moderate heterogeneity (I^2=40%); the unhealthy dietary pattern did not increase the odds for the development of MetS-RF in the studies carried out outside the USA; a greater presence of Afro-descendant individuals in the samples elevated heterogeneity to 80%.

The funnel plots of the MA in the unhealthy dietary pattern presented asymmetry (Figure 3 B), suggesting the presence of publication bias.

Evidence quality

NutriGrade scoring obtained by the studies of the healthy dietary pattern was 3.75 for the MA involving Women and Afro-descendant Populations, indicating Very Low evidence quality. As to the metanalysis involving the General Population, the scoring was 7.05, indicating moderate evidence strength. In the MA for unhealthy dietary patterns, the scorings were: 6.15 for the Women Population; 6.05 for the Afro-descendant Population, and 6.35 for the General Population. All these scorings indicate moderate evidence quality. The main reasons that contributed to the observed decreased scorings were "precision", "heterogeneity", "dose-response" and "effect size", in addition to the presence of "publication bias".

Discussion

In this SR, the relation between "healthy" and "unhealthy" dietary patterns, and the MetS-RF was analyzed. The healthy eating pattern reduced the chances for such outcomes when the results obtained in the articles included individuals classified here as the General Population in their samples.

Regarding "unhealthy" dietary patterns, it was observed greater odds for the development of MetS-RF in the aggregated analysis involving all groups, regardless of the population involved.

In the studies related to the General Population, it was observed that the healthy pattern reduced in 13% the odds ratio for the development of MetS-RF. Such effect can be in part attributed to the characteristics of food consumption observed in this type of pattern, with high intake of

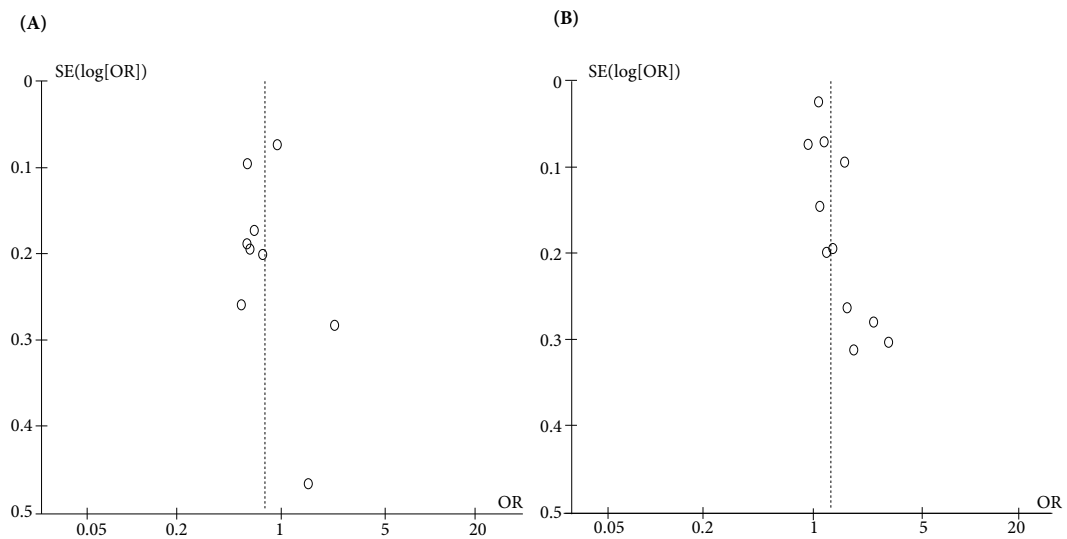

Figure 3. Funnel plots of studies that assessed the association between healthy (A) and unhealthy dietary patterns (B) and metabolic syndrome and its risk factors.

Source: Authors.

whole grains, fruit and vegetables, low-fat dairy products, foods rich in polyunsaturated fatty acids (which are related to multiple benefic effects to health[50]), and, in parallel, low intake of red or processed meat, refined grains and processed snack food[6,37,39,48,49]. These results corroborate those of other SR[5,8].

The healthy dietary pattern was not associated with MetS-RF in the studies that involved the Women Population or the Afro-descendant Population. One possible explanation would be the scarcity of studies with this approach. Other SR-MA studies that did not analyze the ethnicity issue, here classified in the General Population, verified the protective effect of healthy dietary patterns for MetS[5,8,51]. These studies were carried out with the inclusion of a greater quantity of publications (19 to 38), conferring them greater statistical power.

It is important to highlight that the different studies included in this SR-MA addressed different outcomes. Because there wasn't sufficient information in the primary studies to conduct a stratified analysis, all the data was analyzed in aggregate, with the MetS-RF as the outcome of interest. Furthermore, most studies used food frequency questionnaires to gather information on dietary patterns, which is a tool that's more susceptible to memory bias and overestimation of healthy food consumption[52].

When studying the effects of dietary patterns on health, it's important to consider how the results are categorized (tertile, quartile, or quintile) when comparing lower versus higher consumption. An MA examining the link between ultra-processed food consumption and the risk of noncommunicable diseases[53] found discrepancies in these categorizations, which can limit the conclusions drawn from the findings. To address this, the study recommends using standardized approaches to define the categories being compared. Additionally, factors such as geographic location and population characteristics should be considered, as they can explain much of the variability in results.

In the present MA, the studies with unhealthy patterns indicated an increment in the odds for MetS, being 31% for the General Population, 61% for the Afro-descendant Population, and 64% for the Women Population. These patterns are characterized by the presence of red meat, processed and ultra-processed food with high energy density, high content of saturated fats and trans fats, poor fibers, and micronutrients. Several biological mechanisms have been pointed out to explain the possible deleterious effects on health-related to unhealthy patterns. Among these, it is mentioned that foods that are sources of refined carbohydrates, red and processed/ultra-processed meat, fast food in general, and fried food have pro-inflammation properties, enabling the increased presence of certain cytokines that would be involved in the genesis of several chronic diseases[7,54].

Some studies have revealed that the consumption of foods with high energy density, high content of fats, and reduced fiber supply is related to a lower sensitivity to insulin and greater risk for the development of type 2 diabetes[55], accumulation of visceral fat[56], increased plasma lipids, MetS[6,12], and increased presence of inflammatory cytokines[57].

An MA[8] conducted with the inclusion of studies carried out in countries located in America, Asia and, Europe, assessed the relationship between gender, dietary pattern, and MetS, which did not verify the association of dietary pattern with MetS. However, it was observed that the "healthy" dietary pattern determined a stronger protective effect for women[8]. In the present MA, dietary patterns from two countries in the American continent (USA and Brazil), from one European country, and a set of countries in Asia were combined, each one of them with relative characteristics feeding behaviors very different from each other, originated from their distinct eating cultures. Nevertheless, the majority of the studies were concentrated in the USA, a fact that denotes insufficient scientific interest in the theme, mainly, when it refers to women and Afro-descendant populations.

In addition to the issue related to gender and ethnicity, another important aspect that needs to be better assessed by further studies and, which possibly influenced the results presented hereby, concerns the environmental and socio-economic factors, given that the regions of lower economic development, inserted in food deserts and scenarios of social vulnerability, are marked by restricted access to a healthy diet, with low intake of fruit, vegetables, legumes, and fish and, on the other hand, with high intake of processed meat[17,58,59]. Thus, more studies that approach socio-economic and environmental factors related to dietary patterns and MetS are necessary.

The analyses presented in this study denoted the existence of different levels of heterogeneity among the analyzed studies, which can be attributed to the peculiar characteristics (nutritional status, scholarship, socio-economic lev-

el) of the different populations investigated, to regional differences in the research due to the diverse locations where the studies were carried out, or to the different study designs, different food that composed the dietary patterns, and to the distinct statistical analyses conducted[60].

Regarding the association between healthy dietary patterns and MetS-RF, the analyses of this study based on NutriGrade indicated very low evidence strength for the Women Population and for the Afro-descendant Population, while there was moderate evidence strength for the General Population. In contrast, the evidence strength when assessing the associations with unhealthy dietary patterns was classified as moderate for all groups. An MA involving cohort studies found moderate evidence strength in the associations between diet quality (reflecting healthy dietary patterns) and multiple health outcomes[61]. Such a result is similar to the one found in this study for General Population as to the healthy dietary pattern.

It is highlighted that when this pattern was assessed for the Women Population and for the Afro-descendant population the number of manuscripts inserted in the MA was lesser, which may have led to very low evidence. In addition, other aspects that contributed to this were the high heterogeneity, presence of publication bias, and small effect sample. This discussion is important because in, MA studies, the assessment of evidence quality is an important factor for planning nutritional recommendations based on reliable evidence[61]. In this context, in a general way, evidence from moderate to high magnitude is considered acceptable to make recommendations in health promotion interventions[61,62]. Thus, the evidence found here for an unhealthy dietary pattern suggests that should be adopted at a strong recommendation level.

From the findings in the present SR-MA, it is identified the necessity of further studies on the Women Population and Afro-descendant Population to better elucidate the association between dietary patterns and MetS and its risk factors and, in addition, to assess which are the food that is part of the food culture of this public in the different regions worldwide, allowing health promotion interventions appropriate to different realities.

This study presents certain limitations, such as heterogeneity of the characteristic of the studies; the studies designs used to measure the exposure and dietary patterns; the scarcity of studies with the same dietary pattern and that presented data for the women and Afro-descendant populations; the presence of publication bias and; lastly, the grouped data used for the statistical analysis having already been calculated directly in the primary studies.

This study utilized different designs, including cross-sectional, case-control, and cohort studies, each with varying methods of data collection and analysis, resulting in different measures of association and frequency, which may constitute a limitation of the work. However, subgroups were analysed based on these designs to better understand the relationships between dietary patterns, ethnicities, gender, and MetS-RF. It should be emphasized that gender and ethnicity were not distinguished in the analysis, which is consistent with other meta-analyses[7,8]. Cross-sectional studies can establish statistical associations and provide an instant view of the situation, but there is weakness in establishing causal inference due to the possibility of temporality bias. Cohort studies, on the other hand, are more suitable for establishing causal relationships, as they are prospective in nature and measure incidence, with the outcome necessarily occurring after exposure.

The strengths of this work are the usage of validated research techniques and instruments, such as the EPHPP[24] used to assess the quality of the studies; the usage of PRISMA at the elaboration of the protocol of the present review and; the use of NutriGrade to assess the evidence quality. This one, despite its aims in the assessment of cohort studies and randomized clinical trials, has also been used in meta-analyses that include cross-sectional studies and case-control studies in parallel with cohort studies[63-65]. It is noteworthy the originality of the present study, which had as a focus and differential the inclusion of publications that had analyzed individuals of the women gender and of the Afro-descendant ethnicity.

It is concluded that a healthy dietary pattern decreases the odds of the development of MetS-RF, thus becoming an important protective factor against this aggravation in the general population. In contrast, an unhealthy dietary pattern is associated with higher odds for the development of outcomes related to such syndrome, both in the general population, regardless of sex and ethnicity, and in the women and Afro-descendant population, thus becoming a risk factor relevant. Such findings must be considered by public health professionals and managers to promote the adoption of healthy eating habits and life

quality of the population, especially those who live under greater social vulnerability.

To better demonstrate the relationships between dietary patterns and MetS-RF, it is recommended that further studies be carried out involving, particularly, women and the Afro-descendant public, and that, in addition, identify which foods most characterize the food culture of this public in the different regions of the world and how much they can mediate these relationships.

Collaborations

All authors contributed to the study's conception and design. The first draft of the manuscript was written by LB Barbosa, who was also responsible for defining the search strategy. Selection of articles, data collection and analysis were performed by LB Barbosa, IRS Gama, NBR Vasconcelos, EA Santos, T Ataide-Silva and HS Ferreira, and all authors commented on previous versions of the manuscript. All authors read and approved the final version of the manuscript.

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