Nutrition, Metabolism & Cardiovascular Diseases (2019) **29**, 887–905

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

REVIEW

Dietary fat intake and metabolic syndrome in adults: A systematic review

Alicia Julibert, Maria del Mar Bibiloni, Josep A. Tur*

Research Group on Community Nutrition and Oxidative Stress, University of Balearic Islands & CIBEROBN (Physiopathology of Obesity and Nutrition CB12/03/30038), E-07122, Palma de Mallorca, Spain

Received 25 February 2019; received in revised form 5 May 2019; accepted 6 May 2019
Handling Editor: A. Siani
Available online 17 May 2019

KEYWORDS
Metabolic syndrome;
Fatty acids;
Dietary fat;
Fat intake;
n-3 PUFA;
n-6 PUFA

Abstract *Background and aims:* The metabolic syndrome (MetS) is a cluster of coexisting cardiovascular risk factors. The role of specific dietary fats was reemphasized by dietary recommendations. This systematic review aims to assess evidence for the effect of dietary fat intake on MetS occurrence and reversion in adults.
Methods and Results: The MEDLINE database was used to search the existing literature. We included observational studies that analyzed dietary fat intake in adults with MetS and clinical trials that compared the effects of different dietary fat diets on MetS and/or its components. Thirty articles were selected (14 observational and 16 clinical trials), and we included information of dietary fat and fatty acids as well as MetS, body mass index, cholesterol, hypertension, and diabetes in adults. SFA intake was found to be positively associated with MetS components. Most of the observational reviewed studies found beneficial associations between MUFA and PUFA (including n-3 and n-6 subtypes) intake and MetS components. Clinical trials also supported the benefits of MUFA- or PUFA-enriched diets (including low-fat diets) in reducing MetS.
Conclusions: The effects of dietary SFAs on MetS will be influenced by other specific nutrients. Replacement of SFA by MUFA and PUFA has been associated with a decrease in MetS. Dietary recommendations should emphasize on different qualities of fat intake, not only to reduce total fat intake, to obtain health benefits in adults.

Introduction

The metabolic syndrome (MetS) is a cluster of coexisting cardiovascular (CV) risk factors that include obesity, dyslipidemia, hypertension (HTN), and impaired glucose metabolism [1]. In developed countries, it is estimated that MetS affects approximately 25% of the population [2,3]. MetS prevalence substantially increases the risk of CV events, and it has become one of the major medical and public health problems worldwide during the last decades [4]. Previous studies have suggested that diet and lifestyle interventions may be more effective in preventing MetS development than pharmacological agents [5–8]. In fact, several studies have shown that lifestyle modifications such as increased physical activity, adherence to a healthy diet, and/or weight loss are associated with reversion of MetS and its components [9–14].

There is evidence that diet influences MetS incidence [15,16]. Several studies showed that metabolic stressors including an energy-dense high-saturated fat diet promote

* Corresponding author. Research Group on Community Nutrition and Oxidative Stress, Universitat de les Illes Balears & CIBEROBN, Guillem Colom Bldg, Campus, E-07122 Palma de Mallorca, Spain. Fax: +34 971 173184.
E-mail address: pep.tur@uib.es (J.A. Tur).

https://doi.org/10.1016/j.numecd.2019.05.055
0939-4753/

obesity, insulin resistance, and MetS [17–19]. However, in a recent meta-analysis, a higher dietary inflammatory index (DII) score, indicating a pro-inflammatory diet, was not associated with an increased risk of MetS, but it was substantially associated with 35% higher risk of CVD [20].

During the last decades, the "diet-heart hypothesis" has been promoted, which postulated that a higher total dietary fat and saturated fatty acid (SFA) intake leads to an increased incidence of cardiovascular diseases (CVD) by increasing plasma total cholesterol (TC) and low-density lipoprotein–cholesterol (LDL-c) [21–23]. Nevertheless, a meta-analysis of prospective epidemiologic studies showed that there is insufficient evidence yet to associate dietary SFA and an increased risk of CHD or CVD [24]. New evidence suggests that a high-dietary fat diet rich in unsaturated fatty acids (UFA), such as the Mediterranean dietary pattern, may prevent the development of metabolic diseases such as type 2 diabetes mellitus (T2DM), reducing MetS and CVD risk [25–28].

Lately, it has been recognized that the unwanted consequences of low-fat campaigns and several dietary guidelines have changed their dietary recommendations on dietary fats. For example, the 2015–2020 Dietary Guidelines for Americans essentially deleted the upper limit on total fat intake but retained the recommendations of $<$10% of calories from SFA and replacing SFA with UFA [29]. This recommendation would be practically accomplished by high consumption of vegetables, plant oil, nuts, and fatty fish and low consumption of red meat and processed foods [30]. However, developing countries are in a state of nutrition transition that is associated with increases in obesity, MetS, and T2DM[31].

Therefore, taking into consideration the totality of the scientific evidence for the association of dietary fat intake with CVD [32–34] and that dietary guidelines are changing their dietary fat recommendations [29], this systematic review aims to assess evidence for the effect of dietary fat intake on MetS occurrence and reversion in adults.

Methods

A systematic literature search was performed up to March 2019. Published studies have been retrieved from MEDLARS Online International Literature (MEDLINE), through PubMed, using the following combinations of terms: ((dietary fat [MeSH Major Topic]) AND (fatty acids [MeSH Term]) AND (metabolic syndrome [MeSH Term])). The search was limited to studies written in English and those conducted in adults (age $\geq$18 years). No publication date or status restrictions were applied. We included observational studies analyzing dietary fat intake in adults with MetS and clinical trials comparing the effects of different dietary fat diets on MetS and/or its components in adults. Despite that the Third Report of the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP III) [35] definition is the most widely used MetS criteria (hyperglycemia/insulin resistance, visceral obesity, atherogenic dyslipidemia, and HTN), no additional restriction was applied in this review. Then, 117 articles were selected.

The articles were reviewed by at least two reviewers and were taken into account for the selection criteria listed on the JADAD scale or Oxford Quality Scoring System, a procedure to independently assess the methodological quality of a clinical trial. They were excluded if they were (i) studies on population without MetS, (ii) review articles, (iii) records not related to the aim of this review, (iv) studies on plasma fatty acid composition, (v) studies related to other diseases, (vi) intervention with fatty acid and other nutrients/drugs, (vii) genetic studies, (viii) studies related to inflammatory or oxidative stress markers, and (ix) hypocaloric diets. Finally, 30 articles were included in this systematic review (Fig. 1).

The following information was extracted from each included study: (1) characteristics of the study design: type of study, sample size, age and sex of participants, inclusion and exclusion criteria, and duration of the study; (2) methods: type of dietary intervention, duration,

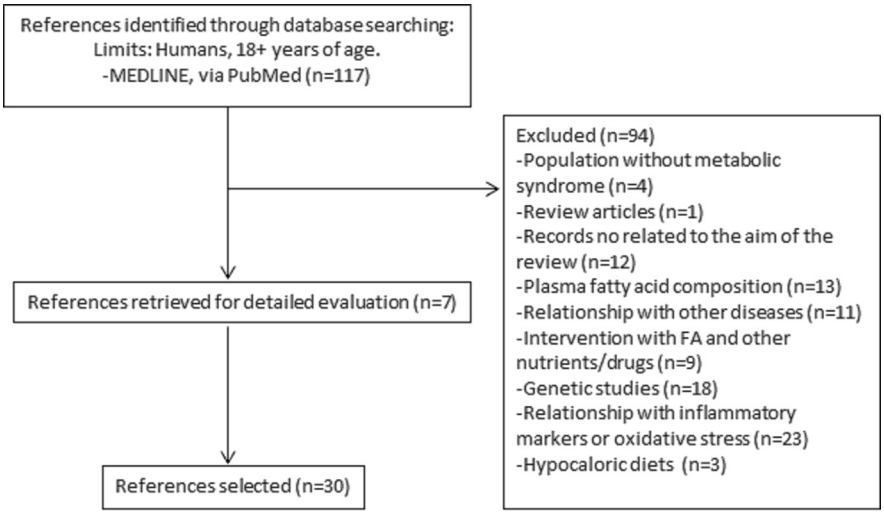

Figure 1 Flowchart of systematic reviews included in the final analysis.

Table 1 Observational studies.

Reference	Design	Methods	Outcomes	Limitations
Studies on ≥45 yo adults				
Cicero et al., 2010 [47]	Retrospective study n = 111 (60 ± 13.2 yo)	PUFA-treated patients with normal-high BP and with or without MetS. 12 months of treatment: daily 2 g esterified PUFAs containing at least 85% of EPA and DHA with 0.9:1.5 ratio.	- At the baseline, 52% of the selected subjects had the characteristics of MetS. - After 3 months of treatment: - Plasma lipids: TC and TG were significantly decreased; HDL-c was increased. - After 12 months of treatment*: - PUFA supplementation was associated with a significant reduction in SBP (−2.7 ± 2.5 mmHg), DBP (1.3 ± 3.3 mmHg), and PP (−1.4 ± 4.2 mmHg), independently from the hypotriglyceridemic effect and from a baseline diagnosis of MetS. - The basal heart rate also significantly decreased (4.0 ± 4.4 bpm) - Independently from the patient sex, DBP change is also inversely related to patient age. - Not observe any specific differences that could lead to the creation of sub-groups affected or not affected by MetS.	Retrospective design. Lack of a comparative group to validate PUFA effects.
Noel et al., 2010 [43]	Cross-sectional study n = 1207 (45 −75 yo)	Dietary intake was assessed using a FFQ. Principal component analysis revealed 4 FA patterns: F1. SFA/dairy pattern F2. n3FA/fish factor F3. (VLC) SFA and PUFA/oils F4. MUFA/trans	- F1 pattern: - The F1 was inversely associated with fasting serum glucose concentration*. - The F1 was associated with higher serum glucose concentration* but this association remained significant after adjustment for BMI. - F2 pattern: - Participants in Q5 were more likely to be older (59 vs. 56 yo) than those in Q1. - Participants in Q5 had higher BMI vs. those in Q1, but WC did not differ. - The F2 was associated with larger WC after adjustment for covariates and inversely with high BP after adjustment covariates and BMI*. - The F2 was associated with a lower of likelihood of MetS*. - F3 pattern: - The F3 was inversely associated with WC after adjustment for covariates, but was no longer significant after additional adjustment for BMI*. - The F4 was not significantly associated with MetS risk factors*.	Cross-sectional study Not representative of all Puerto Ricans living in the US
Cabello-Saavedra et al., 2010 [48]	Cross-sectional study n= (55−80 yo)	Dietary intake was assessed using a FFQ. Inclusion criteria: T2DM or ≥3 CV risk factors.	- Baseline characteristics: - MetS prevalence: 55.1% female; the mean age was 67.6 ± 6.2 yo. - MetS P: 42.4% men and 47.5% women (ATP-III criteria); 63.6% for both sexes (IDF criteria). - Components of MetS: Subjects with MetS showed higher values for WC, weight, BMI, TG, FBG, and BP. According to ATP-III and IDF criteria: higher values for HTN, central obesity, and FBG. - Dietary intake: Statistically significant differences were observed between subjects with and without MetS for: total energy and simple sugar intake, dietary glycemic load and % of dietary protein using both criteria. - According to ATP-III criteria: MetS was inversely associated with fiber (ORs of 0.55; 95% CI: 0.35−0.86) and PUFA (OR = 0.60; 95% CI: 0.39−0.94) intake*. - According IDF criteria: MetS was inversely associated with fiber and positively with CH intake (OR = 1.71; 95% CI: 1.05−2.79)*.	Cross-sectional study Sample is not representative of the general population. Use of FFQ. 2 types of MetS criteria

(*continued on next page*)

Table 1 (*continued*)

Reference	Design	Methods	Outcomes	Limitations
Studies on wide age range adults				

Ebbesson et al., 2007 [40]	Cross-sectional study n = 691 (325 men and 366 women; 34–75 yo)	Dietary intake was assessed using a FFQ.	- Baseline characteristics:
			  - Subjects were slightly overweight, had relatively low BP and TG levels, and had high HDL-C levels.
			- SFA intake*
			  - SFA consumption was associated with high TG levels and BP.
			- Trans FA consumption was associated with high BP.
			- n-3 FA intake*
			  - n-3 FA was associated with low BP, TG, and 2 h glucose test and high levels of HDL-c, FBG, and HOMA.
			  - EPA, DHA, DPA were positively associated with fasting insulin, HOMA, and stearic acid consumption and negatively associated with TG and DBP.
			  - DHA intake was positively associated with HDL-C level and inversely associated with 2-hour glucose levels.
			  - ALA consumption was not associated with MetS components.
			- FBG was not related to consumption of FA.
				Cross-sectional study.
				Other components of the Eskimo lifestyle.

Shin et al., 2009 [38]	Cross-sectional study n = 7081 men (>30 yo)	The association of MetS and sociodemographic characteristics, FFQ, and eating habits of Korean males with and without MetS.	- The P rate of MetS in participants aged 30 to 39, 40 to 49, 50 to 59, and 60 + yo was 18.2%, 19.8%, 21.9%, and 20.5%.
			- Participants with MetS (40–60 yo): BMI≥25 (87.4% case group vs. 31.1% controls), high family history of T2DM (27.6% vs. 21.6%), and smokers (50.1% vs. 45.3%) vs. not MetS.
			- Dietary intake and MetS*
			  - Participants with MetS significantly increase of seaweed and oily food intake, eat fast, and overeat frequently vs. not MetS.
			  - Participants with high fruits intake vs. low intake had a lower risk of MetS (OR did not show statistical significance).
				Cross-sectional study.
				Using self-administered FFQ.
				BMI, instead of WC, for obesity index.
				The P of the MetS could not be generalized into whole Korean population nor the results to the women.
				Potential selection bias.

Baik et al., 2010 [44]	Prospective cohort study n = 3504 (40–69 yo)
	Not MetS and CVD.
		Dietary intake was assessed using a FFQ.	- 4-year follow-up period, 602 cases (345 men and 257 women) of MetS were newly identified.
			- Baseline characteristics: Men and women who frequently ate fish. They had heavier weight, high fat intake, and alcohol drinking.
			- Fish and n-3 FA intake and MetS*
			  - The adjusted risk of MetS was decreased to less than half for men who ate fish daily vs. those eating fish < 1 day/week.
			  - Fish intake and n-3 PUFA were inversely associated with MetS risk (except in women), and TG and HDL-C. OR for: high TG levels 0.54 (95% CI 0.34 to 0.86) in men; low HDL-C 0.61 (95% CI 0.38 to 0.98) in men.
			- No significant associations were observed between fish intake and MetS other components	

Hekmatdoost et al., 2011 [41]	Cross-sectional study n = 822 (354 men and 468 women; 18–74 yo)	Assessment of FFQ, Height, BMI, WC, BP, age, physical activity, smoking habits, blood samples	- SFA intake
			  - Significant correlation of SFA intake vs. MetS.
			  - MetS components: SFA and total fat associated with higher SBP and TG levels and lower HDL-c levels.
			  - Dietary intake: Participants in Q1 (low SFA intake) consumed more grains, dairy products, fruits, and vegetables and less meat than those in Q4 (high SFA intake)*.
			  - SFA intake was not associated with age*.
			- No relation exists between LA and oleic acid and components of the MetS.	

Mirmiran et al., 2012 [45]	Cross-sectional study n = 2451 (19−84 yo TLGS; 54% men)	FFQ to determine the intake of n-3 and n-6 PUFAs.	- Baseline characteristics:
			  - Participants in Q4 of n-6/n-3 ratio (mainly young) consumed less protein, SFA, ALA, and cholesterol and more CH, LA, dietary fiber, vegetable oil, and fish.
			- n-6/n-3 PUFA ratio*: High dietary ratio of n-6 to n-3 PUFA was associated with an enlarged WC but not associated with MetS.
			- n-3 PUFA intake*:
			  - Intakes of n-3 PUFA and EPA + DHA were inversely associated with high WC and/or serum TG.
			  - P of obesity was lower in high intake of EPA + DHA (>intakes of fish) vs. in other intake patterns.
			  - ALA was inversely associated with MetS.
			  - Higher EPA + DHA intake was associated with 34% lower high serum TG in subjects with lower n-6 PUFA intake, and 28% lower concentration in subjects with higher n-6 PUFA intake vs. subjects with lower intakes of both.
			- n-6 PUFA intake*:
			  - n-6 FA Intake was associated with high TG component with a trend toward a lower P.
			  - P of obesity was lower in n-6 PUFA high intake (vegetable oil) vs. other intake patterns.
				Cross-sectional design.
				Use of FFQ to determine n-3 and n-6 PUFA intake.
				Only healthy adults

Lai et al., 2013 [46]	Cross-sectional study n = 4941 NHLBI (52.1 ± 13.9 yo)	Dietary intake was assessed using a FFQ.	- Baseline characteristics:
			  - Mean age: 52.1 yo; P of MetS: 21.0%.
			  - Higher n-3 FA was associated with older age, HTN, and history of CHD.
			- n-3 PUFA intake*:
			  - Dietary n-3 FA was not associated with P MetS.
			  - Neither fish consumption nor dietary ALA was associated with P MetS.
				Cross-sectional design.
				Information of n-3FA was based on a self-reported questionnaire.
				Single FFQ does not fully capture dietary habits over time.
				Single assessment of physical activity.
				Subject: Hispanic whites.

Shab-Bidar et al., 2014 [31]	Cross-sectional study n = 2750 (44% men and 56% women; 20−74 yo)	Compare the serum lipids of each type of dietary intake fat:total fat, total PUFA, total MUFA intake, total SFA (% E), and Ratio P/S. Dietary intake was assessed using a FFQ, 24-h Recall, and physical activity questionnaire. Anthropometric and BP measurements	- Baseline characteristics:
			  - Mean age: 40.8 (14.6) yo. (men) and 38.6 (12.9) yo (women)
			  - Mean fat intake: 34.2% of total E in men and women.
			- SFA intake*:
			  - SFA intake was associated with high TG levels and low HDL-C levels.
			- MUFA intake*:
			  - MUFA was associated with HDL-C levels.
			- PUFA intake*:
			  - PUFA intake was inversely associated with HDL-C.
			  - P/S ratio was positively associated with HDL-c levels and negatively associated with LDL:HDL-C ratio.
			- Significant association between FA and MetS risk, except for total PUFA intake*.	

(*continued on next page*)

Table 1 (*continued*)

Reference	Design	Methods	Outcomes	Limitations
Hosseinpour-Niazi et al., 2015 [42]	Cross-sectional study n = 4677 (2075 men and 2602 women; 19−84 yo) 3 years	Usual dietary intake was assessed using a FFQ.	- Baseline characteristics: - Mean age: 41.7 (13.9) yo; BMI: 27.2 (4.7) kg/m^2 - Mean daily intakes: Total fat 29.9%; SFA 10.2%; MUFA 10.2%, PUFA 6.1%. - Subjects with high intakes of SFA and total fat consumed less CH, fiber, fruit, vegetable, whole grain, legume, and hydrogenated and nonhydrogenated vegetable oils. - SFA and total fat intake*: - High SFA intake (≥9.5% of total E) was associated with 39% higher P of MetS, among subjects with lower total fat intake, and 22% higher among subjects with higher total fat intake. - High SFA + total fat/MUFA/PUFA intakes were associated with abnormal glucose homeostasis, elevated BP, and/or TG.	Cross-sectional study Use of UASD FCT to determine PUFA, MUFA, and SFA intakes, in absence of a complete Iranian FCT. Only healthy adults and findings. It cannot be extrapolated to other populations.
Lee et al., 2016 [37]	Cross-sectional study n = 3212 (30 −74 yo)	Intake of macronutrients was calculated based on 24-hour recall.	- Baseline characteristics: - Subjects with MetS were older, higher BMI, HTN, DM, dyslipidemia, and more active vs. not MetS and young. - Biochemical measurements: Subjects with MetS showed higher FBG, TG, TC, HDL-C, LDL-C, AST, ALT, and BP than among non-MetS participants. - Dietary fat intake: Subjects with MetS consumed less total fat, SFA, and MUFA. - Total fat*: - E from total fat, and when it is substituted by CH, was associated with lower P of MetS in total and in male subjects before and after adjustment (middle-aged subjects). - SFA and MUFA*: - SFA, MUFA, and SFA for CHO were negatively associated with risk of MetS (middle-aged men). No significant association was found in older subjects and women.	One-day 24-hour recall method. Types of CH were not available in the KNHANES data.
Park et al., 2016 [39]	Cross-sectional study n = 38.766 (≥19 yo) 8 years	Daily food intake was calculated based 24-hour recall. Anthropometric data and blood samples were collected	- Baseline characteristics: - MetS Incidence: 18.7% (19.8% men and 18.2% women). - Age and BMI were higher in the MetS group than in the non-MetS group. - Dietary fat intake: Daily intake of total fat, SFA, MUFA, and PUFA was higher in the non-MetS group than in the MetS group. - Total fat*: - Fat intake was inversely associated with MetS prevalence. - The OR for having moderate- and high-fat intake was lower than that for low-fat intake. -SFA and MUFA and PUFA*: - The OR for MetS was significantly lower in the moderate and high tertiles of SFA, MUFA, and PUFA intake than that in the low tertile. - All individual components of MetS were significantly and inversely associated with SFA and MUFA intake (except for BP). - PUFA intake was inversely associated with WC, TG, and HDL levels. - n-3 and n-6 PUFA*: - WC, TG, and HDL-C were inversely associated with both. - The risk of MetS was inversely associated with both.	Cross-sectional study The 24-h recall method Trans FA was not included as an independent variable

Ahola et al., 2017 [36]	Cross-sectional study n = 791 without diabetic nephropathy, and who had completed a minimum of 3-d diet record. (n = 136 men No MetS: 41.2 ± 13.8 yo; n = 192 men MetS: 50.5 ± 12.8 yo; n = 203 women No MetS: 40 ± 12.4 yo; n = 260 women MetS: 47.2 ± 12.8 yo)	Subjects' dietary intake was evaluated using 2 methods: 1. Self-administered dietary questionnaire (typical food in Finland) 2. 3-d exercise and diet record. Another 3-d exercise and food record was completed after 10 wk.	- Baseline characteristics: - Subjects with MetS were significantly older, had longer DB duration, and worse glycemic control. - They reported lower energy intake but proportions of dietary macronutrients or FA were not associated with MetS. - Macronutrient distribution did not differ between participants with and without the MetS. - Macronutrient substitution*: - Proportions of dietary macronutrients were not associated with MetS in either men or women. - Favoring CH over fats was associated with lower P of WC. - Favoring CH or fats over proteins was associated with lower P BP.	Methods to evaluate dietary intake. Potential selection bias. Possibility of residual confounding. The intake of items such as fiber, vitamins, and minerals from different food sources is not taken into account.

Abbreviations. *Results adjusted for age; ALA: α-linolenic acid; AST: aspartate transaminase; ALT: alanine transaminase; ATP III: Adult Treatment Panel III; BMI: Body Mass Index; BP: Blood Pressure; CH: carbohydrate; CHD: coronary heart disease; CV: cardiovascular; DBP: diastolic blood pressure; DHA: docosahexaenoic acid; DPA: docosapentaenoic acid; E: energy; EPA: eicosapentaenoic acid; F1: Factor 1; FA: fatty acid; F2: Factor 2; F3: Factor 3; F4: Factor 4; FFQ: food frequency questionnaire; FBG: fasting blood glucose; HDL-C: high-density lipoprotein−cholesterol; HOMA-IR index: homeostasis model assessment-insulin resistance; HTN: hypertension; IDF: International Diabetes Foundation; KNHANES: Korea National Health and Nutrition Examination Survey; LA: linoleic acid; LDL-C: low-density lipoprotein−cholesterol; MetS: Metabolic Syndrome; MUFA: monounsaturated fatty acids; NHLBI: National Heart, Lung, and Blood Institute; n-3 LC-PUFAs: omega-3 long-chain polyunsaturated fatty acids; n-6 PUFA: omega 6 polyunsaturated fatty acids; OR: Odds Ratio; P: Prevalence; PP: pulse pressure; PUFA: polyunsaturated fatty acids; Ratio P/S: ratio of polyunsaturated fat to saturated fat; Q: quartile; SBP: systolic blood pressure; SFA: saturated fatty acids; TC: total cholesterol; TG: triacylglycerides; T2DM: Type 2 diabetes mellitus; TLGS: Tehran Lipid and Glucose Study; UASD FCT: United States Department of Agriculture Food Composition Table; US: United States; VLC SFA: very long-chain saturated fatty acids; WC: waist circumference; wk: week; yo: years old.

Table 2 Main results of observational studies.

Fatty acid intake	Reference	Age	BMI	TG	Glucose	WC	BP	HDL-c	TC	HOMA-IR	Insulin	MetS
SFA	Shab-Bidar et al., 2014 [31]	B		↑				↓*				
	Ebbesson et al., 2007 [40]	B		↑*			↑*					
	Hekmatdoost et al., 2011 [41]	B		↑			↑SBP	↓				↑
	Hosseinpour-Niazi et al., 2015 [42]	B		↑*	↑*		↑*					↑*
	Lee et al., 2016 [37]	B										↓*
	Noel et al., 2010 [43]	A			↓FBG* ↑* = **	↓↓* = **						
	Ahola et al., 2017 [36]	B		↓*	↓*	↓*	↓*	↑*				=*
	Park et al., 2016 [39]	B										↓*
Trans FA	Ebbesson et al., 2007 [40]	B					↑*	↑*				
	Noel et al., 2010 [43]	A		=*	=*	=*	=*	=*				
MUFA	Shab-Bidar et al., 2014 [31]	B						↑*				
	Ahola et al., 2017 [36]	B										=*
	Noel et al., 2010 [43]	A		=*	=*	=*	=*	=*				
	Hekmatdoost et al., 2011 [41]	B		=	=	=	=	=				
	Lee et al., 2016 [37]	B		↓*	↓*	↓*		↑*				↓*
	Park et al., 2016 [39]	B										↓*
PUFA	Shab-Bidar et al., 2014 [31]	B						↓*				=*
	Noel et al., 2010 [43]	A				↓↓* = **						
	Ahola et al., 2017 [36]	B										=*
	Cabello_Saavedra et al., 2010 [48]	A		↓*		↓*		↑*				↓*
	Park et al., 2016 [39]	B										↓*
PUFA n-3	Ebbesson et al., 2007 [40]	B		↓*	↓2GT* ↑FBG*		↓*	↑*		↑*		↓
	Noel et al., 2010 [43]	A	↑			=↑* = **	↓*					↓*
	Baik et al., 2010 [44]	B		↓*	=*	=*	=*	↑*				↓*
	Mirmiran et al., 2012 [45]	B	↓*	↓*		↓*						↓*
	Lai et al., 2013 [46]	B										=*
	Shin et al., 2009 [38]	B		↓*	=*	↓*	=*	↑*				↑*
	Park et al., 2016 [39]	B										↓*
ALA	Mirmiran et al., 2012 [45]	B		↓*		↓*						↓*
	Ebbesson et al., 2007 [40]	B		=*	=*	=*	=*	=*				
	Lai et al., 2013 [46]	B										=*
DHA	Mirmiran et al., 2012 [45]	B		↓*								
	Ebbesson et al., 2007 [40]	B	↓*	↓*	↓GT*		↓DBP*	↑*		↑*	↑*	
	Cicero et al., 2010 [47]	A		↓			↓*	↑	↓			
DPA	Ebbesson et al., 2007 [40]	B		↓*			↓DBP*			↑*	↑*	
EPA	Mirmiran et al., 2012 [45]	B	↓*	↓*								
	Cicero et al., 2010 [47]	A		↓			↓*	↑				
	Ebbesson et al., 2007 [40]	B		↓*			↓DBP*			↑*	↑*	
PUFA n-6	Mirmiran et al., 2012 [45]	B	↓*	↓*								↓*
	Hekmatdoost et al., 2011 [41]	B		=	=	=	=	=				↓*
	Park et al., 2016 [39]	B		↓*	= *	↓*	= *	↑*				

Abbreviations. ↑: increased values; ↓: decreased values; = : no changes; studies done on A: ≥45 years old and B: Wide age range; *: Results adjusted for age and **: Results adjusted for age and BMI; ALA: α-linolenic acid; BMI: Body Mass Index; BP: Blood Pressure;;CH: carbohydrate; DBP: diastolic blood pressure; DHA: docosahexaenoic acid; DPA: docosapentaenoic acid; EPA: eicosapentaenoicacid; FA: fatty acid; FBG: fasting blood glucose; HDL-C: high-density lipoprotein–cholesterol; HOMA-IR index: homeostasis model assessment-insulin resistance; LDL-C: low-density lipoprotein–cholesterol; MetS: Metabolic Syndrome; MUFA: monounsaturated fatty acids; n-3 PUFAs: omega-3 polyunsaturated fatty acids; n-6 PUFA: omega 6 polyunsaturated fatty acids; PUFA: polyunsaturated fatty acids; SBP: systolic blood pressure; SFA: saturated fatty acids; TC: total cholesterol; TG: triacylglycerides; WC: waist circumference; 2GT: 2-hour glucose test.

characteristics of participants included, and data collection; (3) results: type of outcome measure/intervention; and (4) study limitations. On tables, reviewed studies were classified as studies done on ≥45-year-old adults and those done on adults with a wide age range.

Results

Observational studies

Fourteen articles assessed the association between fatty acid intake and MetS (Tables 1 and 2). Some of observational studies done on a wide age range adult people assessed the prevalence of MetS according to age and showed higher MetS prevalence among older subjects than among younger peers [36–39]. Although not all the studies were adjusted according to age, the results overall reflected a homogeneous pattern.

SFA and MetS

SFA intake was associated with high blood pressure (BP), and/or triglyceride (TG), low high-density lipoprotein–cholesterol (HDL-c), and/or fasting serum glucose levels [31,37,40–43], but it was also pointed out that MetS components were inversely associated with SFA

[39]. SFA was inversely associated with waist circumference (WC) after adjustment for age, but this association was no longer significant after additional adjustment for BMI [43].

Trans-fatty acids and MetS

Trans-fatty acid consumption was associated with higher BP and HDL-c [40]. Nevertheless, no significant associations between trans-FA and MetS components were reported [43].

MUFA and MetS

Monounsaturated fatty acids (MUFA) were positively associated with HDL-c levels [31]. However, other studies either did not show this significant association with MetS components [41,43] or showed an inverse association with them [39].

PUFA and MetS

The polyunsaturated fat-to-saturated fat ratio (P/S ratio) was positively associated with HDL-c levels [31], but polyunsaturated fatty acid (PUFA) intake was inversely associated with HDL-c and WC [31,43]. Another study showed an inverse association of PUFA intake with WC and TG but a positive association with HDL-c [39].

PUFA n-3 intake was associated with low levels of BP, TG, and 2-hour glucose test and high levels of HDL-c, fasting glucose, HOMA, WC, and/or obesity prevalence [40,43–45]. Despite that another study found that PUFA n-3 was inversely associated with WC after adjustment for age, this association was no longer significant after additional adjustment for BMI [43]. These results suggested that the association between fish intake and MetS is largely driven by associations with TG and HDL-c levels. In fact, an inverse association between frequency of fish intake and MetS risk was reported [39,43,44]. Nevertheless, seaweed and oily food intake were also higher in Korean men with MetS than in their healthy peers [38]. It was also pointed out that there was no significant association between PUFA n-3 and MetS prevalence [46].

α-Linolenic acid (ALA) intake was not associated with MetS prevalence [40,46] and, independently of n-6 PUFA intakes, higher ALA intake was associated with 28% lower risk of MetS [45].

EPA and DHA intakes were inversely associated with TG and TC levels, prevalence of obesity, and/or BP [40,45,47] and positively associated with HDL-c levels [40,47].

PUFA n-6 intake was inversely associated with MetS, obesity prevalence, and TG levels and/or positively associated with HDL-c levels [39,45]. PUFA intake was also inversely associated with MetS [48]. However, the n-6/n-3 PUFA ratio was not associated with a decrease in MetS prevalence [45]. In this line, there was also no relationship between LA and MetS components [41].

Clinical trials

Sixteen reviewed articles were clinical trials, and they evaluated dietary fat effects on MetS and/or their components (Tables 3 and 4). All studies were adjusted for age, reflecting a homogeneous pattern.

Dietary fat intake and MetS

MetS prevalence was reduced with a long-chain n-3 polyunsaturated fatty acid (LFHCC n-3: 20.5%) diet, high-SFA (HSFA: 10.6%) diet, high-MUFA (HMUFA: 12%) diet, and low-fat high-complex carbohydrate (LFHCC: 10.4%) diet [49]. MetS prevalence also decreased following consumption of calorie-restricted moderately restricted carbohydrate (MRC) diet vs. calorie-restricted high-carbohydrate (HCHO) diet [50]. However, Mediterranean diets supplemented with olive oil or nuts were not associated with reduced incidence of MetS compared with low-fat diets; however, both diets were associated with significant MetS reversion (28.2% of participants) [51].

Dietary fat and obesity in individuals with MetS

Enriched diets (including low-fat diets) decreased body weight (BW) and/or WC independently of fatty acid intake [49,52–56]. Moreover, Mediterranean diets supplemented with olive oil significantly reduced BW; individuals on the Mediterranean diet with nuts maintained stable BW, but both Mediterranean diet groups showed lower WC increases than the low-fat diet [57]. Accordingly, the n-3 PUFA-enriched diet showed decrease in BMI [58]. MRC diet vs. HCHO diet also led to significant reductions in BW, BMI, and WC [50].

Dietary fat and plasma lipids in individuals with MetS

Increased dietary n-3 PUFA and/or extra virgin olive oil showed beneficial synergistic effects on lipid metabolism, hence decreasing TG [49,55,58,59], TC [59], TC/HDL-c, and LDL-c/HDL-c [60] and/or increasing HDL-c [55,59–61]. Moreover, a daily supplement of long-chain (LC) n-3 PUFA (4.0 g fish oil (FO):2.5 g EPA + DHA) in combination with either a moderate- or a high-n-6 PUFA diet showed a reduction in fasting plasma TG [62]. The effect of FO supplementation on levels of serum lipids also increased HDL-c and TG levels [63]. Otherwise, low-fat diets containing simple carbohydrates (CH) increased the TG level [52], but the TG level decreased when complex CH were included [52,59]. However, moderate replacement of CH by dietary fats between MRC and HC diets did not show significant difference in terms of their effect on serum HDL-c and TC [50].

Dietary fat and hypertension in individuals with MetS

Diets enriched with PUFA or MUFA (including low-fat diets) or after the FO supplementation period were associated with significant reductions in systolic blood pressure (SPB) and DBP [49,54,55,58,64]. An MRC diet also showed a 33% significant reduction in HTN prevalence [50]. Nevertheless, there were no significant differences in SBP, DBP, or PP levels when four isoenergetic diets distinct in fat quantity and quality (LFHCC n-3, HSFA, HMUFA, and LFHCC) were compared [53,59].

Dietary fat and hyperglycemia in individuals with MetS

LFHCC (n-3) diet and MUFA or n-3-enriched diets decreased fasting blood glucose, insulin, and/or HOMA-IR [45,51,55,58,61]. FO supplementation reduced glycosylated hemoglobin A1C (HbA1c) [63] but elevated glycemia. The

Table 3 Clinical trials.

Reference	Design	Methods	Outcomes	Limitations
Studies on ≥45 yo adults				

Poppitt et al., 2002 [52]	Randomized controlled trial n = 39 (12 men and 27 women; CG: 48.6 ± 4.4 yo; LF-CC: 44.2 ± 5.5 yo; LF-SC: 45.9 ± 5.0 yo)
	≥3 MetS risk factors
	6 months
		Intervention diets:
		1. CG
		2. LF-CC group
		3. LF-SC group BW, BMI, BP, and blood lipids were measured at 0, 2, 4, and 6 months.
		Total dietary intake was estimated from 7-d and 3-d weighed-food records (collected in 5 occasions).
			- Baseline characteristics:
			  - There were no significant differences in age, BW, BMI, WC, BP, FBG, or lipid profile between the 3 diet groups.
			- Anthropometric measurements:
			  - Weight loss was greatest with the LF-CC diet but with no changes in abdominal obesity. LF-CC group showed BMI decrease over the 6 months.
			  - There were no significant changes in WC over time among diet groups.
			- Biochemical parameters:
			  - TC and HDL-C decreased in all 3 groups.
			  - TG was higher in the LF-SC group vs. in the other 2 groups.
			  - There was no significant between groups for SBP and DBP.
				There were no significant changes in WC over time among diet groups.

Brady et al., 2004 [62]	Randomized double-blinded parallel-design study (n = 29 men; 48 ± 2 yo)
	12 wk
		Intervention groups:
		1. Consume moderate (olive oil)
		2. Consume high (maize oil).
		6-week run-in period: Moderate- or high-n-6 PUFA diet.
		Second 6 weeks: + 4.0 g FO (2.5 g EPA + DHA/d).
		Experimental cooking oils and spreads formulated (moderate/high n-6PUFA content).
			- Biochemical parameters:
			  - Fasting plasma TG showed significant reduction in the two types of n-6 PUFA diets after supplementation with FO.
			  - Postprandial plasma TG was higher in high n-6 PUFA diet after supplementation with FO.
			  - TC, LDL-C, and HDL-C showed no significant differences between groups.
			- IS and IR
			  - Supplementation with LC n-3 PUFA showed no impact on insulin action in those subjects consuming either the moderate or high n-6 PUFA diet.	

Babio et al., 2014 [51]	Randomized controlled trial n = 7447 (men: 55−80 yo; women: 60−80 yo)
	6 y (median follow-up of 4.8 y)
		Intervention groups:
		1.MedDiet + EVOO
		2.MedDiet + nuts
		3.Low-fat diet (CG)
		14-item validated questionnaire to assess adherence to the MedDiet.
		Usual dietary intake was assessed using a FFQ.
		Anthropometric data and blood samples were collected
			- Comparison between groups:
			  - The P of high FBG was significantly higher in the CG at the end of follow-up than in MedDiet groups.
			  - There was a significantly smaller increase in P of MetS in the MedDiet groups than in CG.
			  - Not found between-group differences in incidence of MetS or its components.
			- Reversion of MetS*:
			  - During a median of follow-up of 4.8 y, reversion occurred in 28.2% of participants. Both MedDiet groups were more likely to MetS reversion.
			  - Reversion of central obesity and high FBG was higher in both MedDiet groups than CG.
				Results cannot be generalized to the general population because the sample comprised older participants with high risk of CVD.

Tardivo et al., 2015 [58]	Randomized controlled trial n = 49 postmenopausal women (45−70 yo)
	≥3 MetS risk factors
	6 months with assessments at 0, 2, 4, and 6 months
		3-day food record
		Women were randomly assigned into two groups:
		1. Diet alone (control, n = 43)
		2. Diet + 900 mg/day n-3 supplementation (n = 44)
		Each capsule of 1 g marine PUFA extract: approximately 180 mg EPA, 120 mg DHA and 2 mg antioxidant tocopherol (3 gel capsules/day orally and during meals)
		Anthropometric data and blood samples were collected (at baseline and at 6 months).
			- Laboratory and dietary characteristics of both groups:
			  - Obese with abdominal fat deposition and lower HDL-C levels.
			  - TG and glucose levels were above desirable values.
			  - Lower average daily caloric intake with higher quantities of n-6 than n-3.
			- Comparison between groups and between time periods:
			  - BMI (−5.5% vs. −0.9%-control) and WC (−4.3% vs. −3.3%) were reduced between time periods at 2 groups
			  - BP: SBP was reduced in both groups; DBP decreased only in the n3 + diet group.
			  - Food intake: total calories decreased according to total fat and PUFA intake in both groups.
			  - Biochemical assessment: TG, insulin, and HOMA-IR decreased only in the diet + n-3 group.	

Ortega et al., 2016 [61]	Randomized controlled trial n = 36 (PLAC 53 ± 2 yo, OLE 54 ± 2 yo)
	≥3 MetS risk factors
	Physically inactive
	24 wks
		Each subject underwent 24 wk of high-intensity interval training (HIIT) was double-blinded randomized to one of the 2 intervention groups:
		1. Placebo (PLAC) milk: 500 mL/d of semi-skim milk (8 g of fat)
		2. n-3 + OLE supplemented milk: 500 mL/d of semi-skim milk enriched with n-3 PUFA (275 mg) and oleate (7.5 g)
			Compared to the PLAC group, HIIT accompanied by n-3 + OLE supplemented affected:
			- Biochemical parameters:
			  - Increased HDL-c.
			  - Improved insulin concentrations during IVGTT.
			
			HIIT and n-3 + OLE supplemented did not affected:
			- Anthropometric variables and blood pressure.
			- Cardiometabolic variables
				The data are limited to FFA concentrations in blood and did not evaluate membrane phospholipid composition.

Estruch et al., 2016 [57]	Randomized controlled trial n = 7447 (men: 55−80 yo; women: 60−80 yo)
	6 y (median follow-up of 4.8 y)
		Intervention groups:
		1.MedDiet + EVOO
		2.MedDiet + nuts
		3.Low-fat diet (CG)
		14-item validated questionnaire to assess adherence to the MedDiet.
		Usual dietary intake was assessed using a FFQ and urinary hydroxytyrosol (a biomarker of EVOO consumption) and plasma ALA (a FA characteristic of walnuts) in random subsamples of participants at 1, 3, and 5 years.
		Anthropometric data and blood samples were collected.
			Comparison between groups:
			- Dietary fat intake:
			  - Median total fat intake (%E) after 5 y decreased from 40·0%−37.4% (CG) and increased from 40.0% to 41.8% (MedDiet + EVOO) and from 40.4% to 42.2% (MedDiet + nuts) ($p < 0·0001$ for all).
			  - MUFA and PUFA
			  %E from MUFA and PUFA were higher in MedDiet + EVOO and MedDiet + nuts than in CG ($p < 0.0001$).
			- BW
			  - Participants in the MedDiet + EVOO showed BW decrease but changes were only significant at 3 and 5 years.
			  - Participants in the MedDiet + nuts showed nonsignificant decrease in BW at 3 y and significant decrease at 5 y but did not differ from the CG.
			- WC
			  ◦ After 3 and 5 years, WC increased slightly in all three groups.
				Methods to evaluate dietary intake (FFQ). There were difficulties in ensuring compliance with dietary instructions. There were no changes in fat intake as percentage of total energy intake. It was small.

(*continued on next page*)

Table 3 (*continued*)

Reference	Design	Methods	Outcomes	Limitations
Studies on wide age range				
Shaw et al., 2009 [56]	Randomized controlled trial n = 486 (220 men and 266 women; 35–70 yo; BMI 20–40 kg/m^2) ≥3 MetS risk factors 12 weeks	Pre- and post- intervention dietary composition of subjects allocated to the 4 isoenergetic diets distinct in fat quantity and quality: 1. HSFA 2. HMUFA 3. LFHCC with LC n-3 PUFAs (1.2 g/d) 4. LFHCC with placebo Dietary intake was assessed by FFQ and 24-h Recall at 3 nonconsecutive days. 24-h recall every fortnight.	Dietary fat intake: - Total fat: - %E from fat was greater in HSFA and HMUFA vs. LF and LFn-3 diets. - SFA and MUFA: - The %E from SFA and MUFA was significantly higher in the HSFA and HMUFA diet groups. - CH: - %E from CH was consistently greater in diets LF and LFn-3 vs. diets HSFA and HMUFA. - EPA and DHA: - Intake of EPA and DHA was significantly greater on the LFn-3 diet vs. other diets. - BW was significantly reduced in LF and LFn-3 diets ($P < 0.0005$).	
Ebrahimi et al., 2009 [64]	Randomized controlled trial n = 120 (40–70 yo) 6 months	Two groups: 1. IG: 1 g of FO (1 capsule: 180 mg EPA and 120 mg DHA) 2. GC Anthropometric measurements and serum plasma were collected.	Dietary fat modification affected - Anthropometric measurements: - IG was associated with BW decrease. - BP: IG was associated with BP decrease. - Biochemical parameters: - IG was associated with TC and TG decrease ($p < 0.05$). - No significant changes were observed in the control group.	Controlled trial design with no double-blinded placebo
Gulseth et al., 2010 [53]	Randomized controlled trial n = 428 (196 men and 232 women; 35–70 yo; BMI 20–40 kg/m2) ≥3 MetS risk factors 12 wk	Pre- and post-intervention dietary composition of subjects allocated to the 4 isoenergetic diets distinct in fat quantity and quality: 1. HSFA 2. HMUFA 3. LFHCC with LC n-3 PUFAs (1.2 g/d) 4. LFHCC with placebo Dietary intake was assessed using a FFQ and 24-h Recall at 3 nonconsecutive days.	Dietary fat modification affected: - BP: No differences in SBP, DBP, or PP between all dietary groups. - Anthropometric measurements: - BW remained unchanged in HSFA and HMUFA groups but lightly reduced in LFHCC and LFHCC-n3 groups.	
Tierney et al., 2011 [59]	Single-blinded dietary intervention study n = 417 (185 men; 35–70 yo) 12 wk	Pre- and post-intervention dietary composition of subjects allocated to the 4 isoenergetic diets distinct in fat quantity and quality: 1. HSFA 2. HMUFA 3. LFHCC with LC n-3 PUFAs (1.2 g/d) 4. LFHCC with placebo 24-h Recall at 3 nonconsecutive days	Dietary fat modification affected: - Anthropometric measurements: - LFHCC and LFHCC n-3 diets showed BW reduction (<0.84 kg or 1% BW). - BMI, WC, and BP did not change. - Markers of SI: - Reducing dietary SFA intake (HMUFA and LFHCC diets) showed no effect on SI, fasting insulin, glucose concentrations, or HOMA-IR. - Biochemical parameters: - LFHCCn-3 and HSFA diets decreased TG and/or TRL TG in men. - HSFA and HMUFA diets increased HDL-C, improved total to HDL-C ratio and showed no effect in TC.	

Paniagua et al., 2011 [49]	Clinical intervention study n = 337 (149 females; 35−70 yo; BMI 20−40 kg/m^2) ≥3 MetS risk factors 12 wks	Pre- and postintervention dietary composition of subjects allocated to the 4 isoenergetic diets distinct in fat quantity and quality: 1. HSFA 2. HMUFA 3. LFHCC with LC n-3 PUFAs (1.2 g/d) 4. LFHCC with placebo Dietary intake was assessed using 24-h Recall at 3 nonconsecutive days.	- Baseline characteristics: – 37.9% of subjects with 3 MetS criteria, 40.3% with 4 MetS criteria, and 21.8% with 5 MetS criteria. Dietary fat modification affected: - Anthropometric measurements: - P of WC decreased with HSFA and LFHCC n-3 diets. - BP: P of elevated BP was reduced with LFHCC and LFHCC n-3 diets. - Biochemical parameters: - P of HTG decreased after LFHCC n-3 diet. - P of MetS decreased in HSFA (10.6%), HMUFA (12%), LFHCC (10.4%), and LFHCC n3 (20.5%). 11% P of MetS at postintervention assessment was reduced in the compiled group (HSFA + HMUFA + LFHCC) vs. 20.5 in LFHCC-n3 ($p < 0.028$)	Lack of follow-up assessment of the subjects' nutritional risk over time.
Pałkowska et al., 2012 [54]	Randomized controlled trial n = 23 (22−65 yo; 14 men) with MetS. 12 wk	Subjects were randomly divided into 2 groups: 1. CG: PUFA n3/n6 ratio 1:10 2. IG: PUFA n3/n6 ratio 1:5 Fiber intake: 29 g/day; 28% fat; 53% CH; 18% prot; <200 mg CT/day.	Dietary fat modification affected: - Anthropometric measurements: Body mass and WC decrease. - BP: SBP and DBP decreased.	
Rajaie et al., 2014 [50]	Randomized crossover clinical trial; n = 30 women (20−65 yo); BMI >25 kg/m^2 with MetS	2-week run-in period 2 diets: 1. CH diet (60−65% CH; 20−25% FA; 15−17% PROT.) 2. MRC diet: 43−47% CH; 36−40% FA; 15−17% PROT.) 3-d food record and 2-d physical activity record were obtained from each participant.	- Anthropometric measurements and BP: - Both diets led to reductions in BW, BMI, and WC. - P of central obesity was not altered by either diet. - BP: P of HTN was 33% reduced in MRC diet. - Biochemical parameters: - FBG, serum HDL-C, TC, insulin, HOMA-IR, TG to HDL-C ratio, HTG and low HDL-C were not affected by diets. - Consumption of CH diet increased P of hyperglycemia. - P of MetS decreased following consumption of MRC diet.	
Lee et al., 2014 [63]	Randomized single-blinded controlled trial n = 71 (≥21yo) T2DM (n = 56) MetS (n = 15) 8 wk	Individuals received either PUFA-containing oils: 1. CO (n = 25) 2. BO (n = 26) 3. FO (n = 20) Serum FA, TG, CT, HDL-C, LDLC, leptin, CRP, glucose, and HbA1c were assessed from fasting participants at baseline and after intervention	- Fasting PUFA levels were stable in 4 weeks and did not change between 4 and 8 weeks. - Biochemical parameters: - After BO supplementation: TC decrease. - After FO supplementation: Lower levels of TG and HbA1c and higher HDL-C and insulin levels. - No changes in fasting glucose levels.	8-week trial. Placebo oil (CO). Population with early-stage T2DM and MetS. GI symptoms.
Venturini et al., 2015 [60]	Controlled intervention study n = 102 with MetS (21 men and 81 women; 38−76 yo) 90 days	Patients were randomly assigned to one of 4 groups: 1. GC 2. FO (3 g/day 10 caps) 3. OO (10 ml/day) FOO (3 g/d + 10 ml/d)	- Anthropometric measurements: - WC reduction in OO vs. FO. - Biochemical parameters: - TC, TC/HDL-C, and LDL-C/HDL-C decrease in FOO vs. CG and OO	Small number of participants. Other lifestyle factors were not measured.

(*continued on next page*)

Table 3 (*continued*)

Reference	Design	Methods	Outcomes	Limitations
Yubero-Serrano et al., 2015 [55]	Randomized controlled trial n = 486 (220 men and 266 women; 35–70 yo; BMI 20–40 kg/m^2) ≥3 MetS risk factors 12 wk	Each subject was randomly stratified to one of 4 isoenergetic diets distinct in fat quantity and quality: 1. HSFA 2. HMUFA 3. LFHCC n-3 diet 4. LFHCC control diet Dietary intake was assessed using two 3-d weighted food dietary records (2 weekdays and 1 weekend) that were completed pre- and post-intervention	Dietary fat modification affected: - Markers of IS: - HMUFA and LFHCC n-3 diets decreased fasting insulin and HOMA-IR concentrations in the IR group (tertile 3). - HSFA diet increased fasting insulin and HOMA-IR concentrations in the IR group (tertile 1). - Anthropometric measurements: - LFHCC n-3 and LFHCC control diets reduced BMI and WC in the IR groups (tertiles 1 and 2). - BP: LFHCC n-3 diet decreased DBP and SBP in the IR group (tertile 1). - Biochemical parameters: - LFHCC n-3 diet decreased TG concentrations in the IR group (tertile 1). - HMUFA and HSFA diets increased HDL-c in the IR group (tertile 1).	Ensuring complete adherence to dietary instructions. The study represents a secondary analysis of the LIPGENE study.

Abbreviations. ALA: α-linolenic acid; AUC: Under the curve; BMI: Body Mass Index; BO: botanical oil; BP: Blood Pressure; BW: body weight; CG: Control Group; CH: carbohydrate; CO: corn oil; CRP: C-reactive protein; DBP: diastolic blood pressure; DHA: docosahexaenoic acid; DPA: docosapentaenoic acid; E: energy; EPA: eicosapentaenoic acid; EVOO: Extra virgin olive oil; FA: fatty acid; FBG: fasting blood glucose; FFQ: food frequency questionnaire; FO: fish oil; FOO: fish oil and extra virgin olive oil group; GLA: gamma-linolenic acid; GI: gastrointestinal; HC: hip circumference; HDL-C: high-density lipoprotein cholesterol; HIIT: high-intensity interval training; HMUFA: high monounsaturated fatty acids; HOMA-IR index: homeostasis model assessment-insulin resistance; HSFA, high-saturated fatty acid; HTN: hypertension; IG: intervention group; IR: insulin resistance; IS: insulin Sensitivity; IVGTT: intravenous glucose tolerance test; LA: linoleic acid; LDL-C: low-density lipoprotein–cholesterol; LF: Low fat; LF-CC: low-fat complex carbohydrate diet; LFHCC, low-fat, high complex carbohydrate; LF-SC: low-fat, simple carbohydrate diet; MedDiet: Mediterranean diet; MRC: moderately restricted carbohydrate MUFA: monounsaturated fatty acids; MetS: Metabolic Syndrome; n-3 LC-PUFAs: omega-3 long-chain polyunsaturated fatty acids; n-6 PUFA: omega 6 polyunsaturated fatty acids; OFTT: oral fat tolerance test; OLE: oleate; OO: olive oil; P: Prevalence; PLAC: placebo; PUFA: polyunsaturated fatty acids; PP: pulse pressure; PROT: Protein; SBP: systolic blood pressure; SFA: saturated fatty acids; TC: total cholesterol; TG: triacylglycerides; T2DM: Type 2 diabetes mellitus; TRL: TG-rich lipoproteins; WC: waist circumference; wk: week; yo: years old.

Table 4 Main results of clinical trials.

Types of diet	Reference	Age	BMI	TG	Glucose	WC	BP	HDL-c	TC	HOMA-IR	Insulin	HbA1c	MetS
LFHCC n-3	Paniagua et al., 2011 [49]	B		↓		↓	↓						↓
	Tierney et al., 2011 [59]	B	=	↓	=	=	=			=	=		
	Gulseth et al., 2010 [53]	B	↓				=						
	Yubero-Serrano et al., 2015 [55]	B	↓	↓		↓	↓			↓	↓		
	Shaw et al., 2009 [56]	B	↓										
LFHCC	Paniagua et al., 2011 [49]	B					↓				=		↓
	Poppit et al., 2002 [52]	A	=	↓	=FBG	=	=	↓	↓				
	Tierney et al., 2011 [59]	B	=			=	=						
	Gulseth et al., 2010 [53]	B	↓				=						
	Yubero-Serrano et al., 2015 [55]	B	↓			↓							
	Shaw et al., 2009 [56]	B	↓				=						
LFSC	Poppit et al., 2002 [52]	A		↑	=FBG	=	=	↓	↓				
HSFA	Paniagua et al., 2011 [49]	B				↓							↓
	Gulseth et al., 2010 [53]	B					=						
	Yubero-Serrano et al., 2015 [57]	B						↑		↑	↑		
	Tierney et al., 2011 [60]	B	=	↓		=	=	↑	=				
HMUFA	Paniagua et al., 2011 [49]	B											↓
	Venturini et al., 2015 [60]	B				↓		↑					
	Gulseth et al., 2010 [53]	B					=						
	Yubero-Serrano et al., 2015 [55]	B						↑		↓	↓		
	Tierney et al., 2011 [59]	B	=		↓	=	=	↑	=				↓
	Babio et al., 2014 [51]	A											↓
	Estruch et al., 2016 [57]	A				↓							
MRC	Relaje et al., 2014 [50]	B	↓	=	=FBG	↓	↓	=	=	=	=		
HCHO	Relaje et al., 2014 [50]	B	↓	=	↑	↓		=	=	=	=		
n-3 PUFA-enriched diet	Venturini et al., 2015 [60]	B				↓		↑	↓				
	Badry et al., 2004 [62]	A		↓				=	=		=		
	Lee et al., 2014 [63]	B		↓	=FBG			↑	↓		↑	↓	
	Ortega et al., 2016 [61]	A	=				=	↑			↓		
	Ebrahimi et al., 2009 [64]	B	↓	↓			↓		↓				
	Tardivo et al., 2015 [58]	A	↓	↓		↓	↓						

Abbreviations↑: increased values; ↓: decreased values; = : no changes; studies done on A: ≥45 years old; and B: Wide age range; BMI: Body Mass Index; BP: Blood Pressure; FBG: fasting blood glucose; HbA1c: glycated hemoglobin; HCHO: high-complex carbohydrate; HDL-C: high-density lipoprotein−cholesterol; HMUFA: high monounsaturated fatty acids; HOMA-IR index: homeostasis model assessment-insulin resistance; HSFA, high-saturated fatty acid; LDL-C: low-density lipoprotein−cholesterol; LFHCC, low-fat, high-complex carbohydrate; LFHCC n-3: low-fat, high-complex carbohydrate omega-3 long-chain polyunsaturated fatty acids; LF-SC: low-fat, simple carbohydrate diet; MRC: moderately restricted carbohydrate; MUFA: monounsaturated fatty acids; MetS: Metabolic Syndrome; OFTT: oral fat tolerance test; TC: total cholesterol; TG: triacylglycerides; WC: waist circumference.

HSFA diet also increased fasting insulin and HOMA-IR [55]. Moderate replacement of CH by dietary fats was not associated with significant changes in fasting plasma glucose, insulin, and HOMA-IR levels [50].

Discussion

The present systematic review provides a complete summary of the findings evaluating the association between dietary fat and MetS (including all its components) reported in the included studies [36,37,39,41–44,46,48,49,51,54].

First, according to the main recommendations in dietary guidelines to decrease the SFA intake, a positive association between SFA intake and MetS components was observed in most studies [31,40–43,55]. However, it was also pointed out that total fat and SFA intake did not differ between subjects with and without MetS [36]. Moreover, a meta-analysis revealed the lack of association between the harmful role of dietary SFA per se and CVD [24]. In this line, several studies showed that neither eggs nor dairies (rich in cholesterol and SFA) or coconut oil (rich in vegetable SFA) showed a beneficial influence on lipid profile and CV health [65–68] or MetS [69]. On the other hand, despite not finding a significant association between intake of trans FA and MetS [43], plasma TFA concentrations were significantly associated with MetS prevalence and its individual components except for BP [70]. Therefore, it is necessary to consider alternative macronutrients to replace trans-fats and saturated fat in the context of a dietary pattern that emphasizes vegetables, fish, nuts, and whole grains versus processed ones as the basis of a heart-healthy diet [32,34].

Second, despite that reductions in SFA intake are usually accompanied by increased proportion of CHO intake [37], scarce or null CV benefits were reported when SFA was replaced by total CH [30,32,49]. On the contrary, significant reductions in CVD and/or MetS risk were achieved only when SFA was replaced by MUFA and/or PUFA [30,32,49]. Nevertheless, the findings of Prospective Urban Rural Epidemiological (PURE) showed that total fat and individual types of fat (SFA, MUFA, and PUFA) were not associated with CVD or CVD mortality, whereas SFA was

inversely associated with stroke [71]. A cross-sectional analysis of the PURE study also demonstrated that replacement of SFA with MUFA or PUFA improved the risk of several markers (LDL-c and BP) but seemed to worsen others (HDL-c and TG). The observed association between SFA and CVD events was explained by the association of SFA with the apolipoprotein B (ApoB)-to-apolipoprotein A1 (ApoA1) ratio but not by associations with other lipid markers including LDL-c [72]. On the other hand, evidence from observational and interventional studies supports the benefits of both n-3 and n-6 PUFA in reducing MetS [31,44,51], although other studies pointed out otherwise [36,40,46].

Third, enriched diets (including low-fat diets) decreased BW and/or WC independently of fatty acid intake [49,52–55]. A Cochrane meta-analysis comparing the weight loss effects of a low-fat diet vs. those of a usual diet showed a BW decrease of −1.5 kg [73]. Otherwise, the Prevención con Dieta Mediterránea (PREDIMED) trial [57] showed that a Mediterranean diet containing MUFA- and PUFA-rich foods, such as extra-virgin olive oil (EVOO) or nuts did not increase BW, but both groups showed a lower WC increase. Accordingly, this diet enriched with healthy fatty foods also found a protective effect of EVOO against weight gain, central adiposity, oxidation of LDL-c, and increase in HDL-c [74]. Moreover, low-fat diets enriched with PUFA or replaced by healthy sources of fats (fish, avocado, nuts, broccoli, thistle, olives, linseed and canola oil, etc.) or healthy sources of CH (whole grains, legumes, vegetables, and fruits) decreased TG levels [30,49,55,59]. Then, consumption of “low-fat” or “non-fat” products with high amounts of refined grains and added sugars may be discouraged. Rather than substitute unhealthy saturated fats, such as palm oil or that of sausages or meats from industrial-bred animals with CH, or reduce their presence in the diet, the advice would be to replace them with other healthy fats [29].

Finally, MetS is apparently more prevalent in adults aged ≥40 years, with a risk threefold higher than that in adults aged from 20 to 39 years [75]. However, only few studies exclusively included a population older than 45 years, and most of them considered a wider age range. Among these latter studies, three studies looked at the prevalence of MetS according to age and confirmed higher prevalence among older subjects [36–38]. Furthermore, intervention diets including healthy fats improved the lipid profile and other metabolic risk factors before and after age adjustment, as shown in most of the reviewed studies. Moreover, other authors specifically demonstrated that a reduction in CT, LDL-c, insulin, and/or TG could occur in younger healthy adults, as well as in older ones with MetS independently of age, sex, and BMI [76].

Strengths and limitations of the study

This study has several strengths. In the current study, relationships between total fat, PUFA, MUFA, and SFA dietary intake and occurrence and reversion of MetS and its components in adults were assessed. The relevance of both the quality and quantity of dietary fat and their relationship with MetS and cardiometabolic risk factors were also demonstrated.

Several limitations should be also considered. First, results were obtained by using differently designed studies and MetS definition. Then, studies were included using the NCEP-ATP III (2001) [48], (2002) [40,41,54], (2004) [46,47,56,63], and (2005) [39,42,43,60,64] MetS definition and also their variations [37,38,44,45,53,55,59] and other definitions [31,36,48–52,57,61,62]. Second, the studies’ heterogeneity in altering dietary fat intake resulted in difficulties in fully explaining the effects of different dietary changes. Moreover, the FFQ or some method of dietary recall could overestimate the intake of certain food groups even after they were validated. Third, there have been lacks of follow-up assessment of the subjects’ nutritional risk over time or they have been done on small sample size population. Next, it is hard to differentiate between the effect of calorie restriction and changes in dietary fat composition, as well as catabolic metabolism during weight reduction could have effects. Finally, the consistency and precision of the studies could determinate bias on obtained results.

Conclusions

A significant association between fatty acid intake and risk of MetS has been revealed. The effects of dietary SFAs on MetS will be influenced by other specific nutrients. Replacement of SFA by MUFA and/or PUFA has been associated with a decrease in MetS. Dietary recommendations should emphasize on different qualities of fat intake, not only to reduce total fat intake to obtain health benefits in interventional dietary programs of adults. Dietary advice should not be to "avoid fats", but it should be necessary to qualify what kind of fat is preferable to consume through a healthy diet and lifestyle.

Funding

This study was supported by the Official Funding Agency for biomedical research of the Spanish government, Institute of Health Carlos III (ISCIII), through the Fondo de Investigación para la Salud (FIS), which is co-funded by the European Regional Development Fund (Projects 11/01791, 14/00636, and 17/01827, Red Predimed-RETIC RD06/0045/1004, and CIBEROBN CB12/03/30038), Grant of support to research groups no. 35/2011 and Grant no. AAEE097/2017 (Balearic Islands Gov.), and EU Cost ACTION CA16112. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors’ contribution

AJ provided previous literature searches and analysis and prepared the main outline of the manuscript. All authors

contributed to the preparation of the manuscript. All read and approved the final manuscript.

Declaration of conflicts of interest

The authors declare that they have no conflict of interest.

References

[1] Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al., International Diabetes Federation Task Force on Epidemiology and Prevention, National Heart, Lung, and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society, International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International diabetes Federation task force on epidemiology and prevention; National heart, Lung, and blood Institute; American heart association; World heart Federation; International atherosclerosis society; and International association for the study of obesity. Circulation 2009;120(16):1640–5.

[2] Athyros VG, Ganotakis ES, Elisaf M, Mikhailidis DP. The prevalence of the metabolic syndrome using the National cholesterol educational program and International diabetes Federation definitions. Curr Med Res Opin 2005;21(8):1157–9.

[3] Ford ES, Li C, Zhao G. Prevalence and correlates of metabolic syndrome based on a harmonious definition among adults in the US. J Diabetes 2010;2(3):180–93.

[4] Zimmet P, Magliano D, Matsuzawa Y, Alberti G, Shaw J. The metabolic syndrome: a global public healthproblem and a new definition. J Atheroscler Thromb 2005;12:295–300.

[5] Orchar TJ, Temprosa M, Goldberg R, Haffner S, Ratner R, Marcovina S, et al., Diabetes Prevention Program Research Group. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. Ann Intern Med 2005;142(8):611–9.

[6] Mensink M, Blaak EE, Corpeleijn E, Saris WH, de Bruin TW, Feskens EJ. Lifestyle intervention according to general recommendations improves glucose tolerance. Obes Res 2003;11(12):1588–96.

[7] Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al., Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346(6):393–403.

[8] Yamaoka K, Tango T. Effects of lifestyle modification on metabolic syndrome: a systematic review and meta-analysis. BMC Med 2012; 10:138.

[9] Earnest CP, Johannsen NM, Swift DL, Lavie CJ, Blair SN, Church TS. Dose effect of cardiorespiratory exercise on metabolic syndrome in postmenopausal women. Am J Cardiol 2013;111:1805–11.

[10] Azadbakht L, Mirmiran P, Esmaillzadeh A, Azizi T, Azizi F. Beneficial effects of a dietary approaches to stop hypertension eating plan on features of the metabolic syndrome. Diabetes Care 2005; 28:2823–31.

[11] Akbaraly TN, Singh-Manoux A, Tabak AG, Jokela M, Virtanen M, Ferrie JE, et al. Overall diet history and reversibility of the metabolic syndrome over 5 years: the Whitehall II prospective cohort study. Diabetes Care 2010;33:2339–41.

[12] Case CC, Jones PH, Nelson K, O'Brian Smith E, Ballantyne CM. Impact of weight loss on the metabolic syndrome. Diabetes Obes Metab 2002;4:407–14.

[13] Lofgren IE, Herron KL, West KL, Zern TL, Brownbill RA, Ilich JZ, et al. Weight loss favourably modifies anthropometrics and reverses the metabolic syndrome in premenopausal women. J Am Coll Nutr 2005;24:486–93.

[14] de la Iglesia R, Lopez-Legarrea P, Abete I, Bondia-Pons I, Navas-Carretero S, Forga L, et al. A new dietary strategy for long-term treatment of the metabolic syndrome is compared with the American Heart Association (AHA) guidelines: the MEtabolic Syndrome REduction in NAvarra (RESMENA) project. Br J Nutr 2014;111:643–52.

[15] Marventano S, Salomone F, Godos J, Pluchinotta F, Del Rio D, Mistretta A, et al. Coffee and tea consumption in relation with non-alcoholic fatty liver and metabolic syndrome: a systematic review and meta-analysis of observational studies. Clin Nutr 2016 Dec;35(6):1269–81.

[16] Schwingshackl L, Bogensberger B, Benčič A, Knüppel S, Boeing H, Hoffmann G. Effects of oils and solid fats on blood lipids: a systematic review and network meta-analysis. J Lipid Res 2018 Sep; 59(9):1771–82.

[17] Storlien LH, Baur LA, Kriketos AD, Pan DA, Cooney GJ, Jenkins AB, et al. Dietary fats and insulin action. Diabetologia 1996;39(6): 621–31.

[18] Feskens EJ, Virtanen SM, Räsänen L, Tuomilehto J, Stengård J, Pekkanen J, et al. Dietary factors determining diabetes and impaired glucose tolerance. A 20-year follow-up of the Finnish and Dutch cohorts of the Seven Countries Study. Diabetes Care 1995;18(8):1104–12.

[19] Melanson EL, Astrup A, Donahoo WT. The relationship between dietary fat and fatty acid intake and body weight, diabetes, and the metabolic syndrome. Ann Nutr Metab 2009;55(1–3):229–43.

[20] Namazi N, Larijani B, Azadbakht L. Dietary inflammatory index and its association with the risk of cardiovascular diseases, metabolic syndrome, and mortality: a systematic review and meta-analysis. Horm Metab Res 2018;50(5):345–58.

[21] Hu FB, Willett WC. Optimal diets for prevention of coronary heart disease. JAMA 2002 Nov;288(20):2569–78.

[22] Keys A, Menotti A, Aravanis C, Blackburn H, Djordevic BS, Buzina R, et al. The seven countries study: 2,289 deaths in 15 years. Prev Med 1984 Mar;13(2):141–54.

[23] Kato H, Tillotson J, Nichaman MZ, Rhoads GG, Hamilton HB. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California. Am J Epidemiol 1973 Jun;97(6):372–85.

[24] Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. Am J Clin Nutr 2010;91(3):535–46.

[25] Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al., PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. N Engl J Med 2018 Jun 21;378(25):e34.

[26] Godos J, Zappalà G, Bernardini S, Giambini I, Bes-Rastrollo M, Martinez-Gonzalez M. Adherence to the Mediterranean diet is inversely associated with metabolic syndrome occurrence: a meta-analysis of observational studies. Int J Food Sci Nutr 2017; 68(2):138–48.

[27] Salas-Salvadó J, Díaz-López A, Ruiz-Canela M, Basora J, Fitó M, Corella D, et al., PREDIMED-Plus investigators. Effect of a lifestyle intervention program with energy-restricted Mediterranean diet and exercise on weight loss and cardiovascular risk factors: one-year results of the PREDIMED-Plus Trial. Diabetes Care 2018. pii: dc180836.

[28] Salas-Salvadó J, Bulló M, Babio N, Martínez-González MÁ, Ibarrola-Jurado N, Basora J, et al., PREDIMED Study Investigators. Reduction in the incidence of type 2 diabetes with the Mediterranean diet: results of the PREDIMED-Reus nutrition intervention randomized trial. Diabetes Care 2011;34(1):14–9.

[29] US Dep. Health Hum. Serv, US Dep. Agric. 2015–2020 dietary guidelines for Americans. 2015. https://health.gov/dietaryguidelines/2015/guidelines/. [Accessed 31 October 2018].

[30] Wang DD, Hu FB. Dietary fat and risk of cardiovascular disease: recent controversies and advances. Annu Rev Nutr 2017;37:423–46.

[31] Shab-Bidar S, Hosseini-Esfahani F, Mirmiran P, Hosseinpour-Niazi S, Azizi F. Metabolic syndrome profiles, obesity measures and intake of dietary fatty acids in adults: Tehran lipid and glucose study. J Hum Nutr Diet 2014;27(Suppl 2):98–108.

[32] Siri-Tarino PW, Chiu S, Bergeron N, Krauss RM. Saturated fats versus polyunsaturated fats versus carbohydrates for cardiovascular disease prevention and treatment. Annu Rev Nutr 2015;35: 517–43.

[33] Sacks FM, Lichtenstein AH, Wu JHY, Appel LJ, Creager MA, Kris-Etherton PM, et al., American Heart Association. Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association. Circulation 2017;136(3):e1–23.

[34] de Souza RJ, Mente A, Maroleanu A, Cozma AI, Ha V, Kishibe T, et al. Intake of saturated and trans unsaturated fatty acids and risk of all-cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. BMJ 2015;351:h3978.

[35] Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American heart association/National heart, Lung, and blood Institute scientific statement. Circulation 2005;112: 2735–52.
[36] Ahola AJ, Harjutsalo V, Thorn LM, Freese R, Forsblom C, Mäkimattila S, et al. The association between macronutrient intake and the metabolic syndrome and its components in type 1 diabetes. Br J Nutr 2017;117(3):450–6.
[37] Lee KW, Cho Y, Jo G, Park YK, Shin MJ. Association of dietary intakes of total and subtypes of fat substituted for carbohydrate with metabolic syndrome in Koreans. Endocr J 2016;63(11):991–9.
[38] Shin A, Lim SY, Sung J, Shin HR, Kim J. Dietary intake, eating habits, and metabolic syndrome in Korean men. J Am Diet Assoc 2009; 109(4):633–40.
[39] Park S, Ahn J, Kim NS, Lee BK. High carbohydrate diets are positively associated with the risk of metabolic syndrome irrespective to fatty acid composition in women: the KNHANES 2007-2014. Int J Food Sci Nutr 2017;68(4):479–87.
[40] Ebbesson SO, Tejero ME, Nobmann ED, Lopez-Alvarenga JC, Ebbesson L, Romenesko T, et al. Fatty acid consumption and metabolic syndrome components: the GOCADAN study. J Cardiometab Syndr 2007;2(4):244–9.
[41] Hekmatdoost A, Mirmiran P, Hosseini-Esfahani F, Azizi F. Dietary fatty acid composition and metabolic syndrome in Tehranian adults. Nutrition 2011;27(10):1002–7.
[42] Hosseinpour-Niazi S, Mirmiran P, Fallah-ghohroudi A, Azizi F. Combined effect of unsaturated fatty acids and saturated fatty acids on the metabolic syndrome: Tehran lipid and glucose study. J Health Popul Nutr 2015;33:5.
[43] Noel SE, Newby PK, Ordovas JM, Tucker KL. Adherence to an (n-3) fatty acid/fish intake pattern is inversely associated with metabolic syndrome among Puerto Rican adults in the Greater Boston area. J Nutr 2010;14(10):1846–54.
[44] Baik I, Abbott RD, Curb JD, Shin C. Intake of fish and n-3 fatty acids and future risk of metabolic syndrome. J Am Diet Assoc 2010; 110(7):1018–26.
[45] Mirmiran P, Hosseinpour-Niazi S, Naderi Z, Bahadoran Z, Sadeghi M, Azizi F. Association between interaction and ratio of ω-3 and ω-6 polyunsaturated fatty acid and the metabolic syndrome in adults. Nutrition 2012;28(9):856–63.
[46] Lai YH, Petrone AB, Pankow JS, Arnett DK, North KE, Ellison RC, et al. Association of dietary omega-3 fatty acids with prevalence of metabolic syndrome: the National heart, Lung, and blood Institute family heart study. Clin Nutr 2013;32(6):966–9.
[47] Cicero AF, Derosa G, Di Gregori V, Bove M, Gaddi AV, Borghi C. Omega 3 polyunsaturated fatty acids supplementation and blood pressure levels in hypertriglyceridemic patients with untreated normal-high blood pressure and with or without metabolic syndrome: a retrospective study. Clin Exp Hypertens 2010;32(2):137–44.
[48] Cabello-Saavedra E, Bes-Rastrollo M, Martinez JA, Diez-Espino J, Buil-Cosiales P, Serrano-Martinez M, et al. Macronutrient intake and metabolic syndrome in subjects at high cardiovascular risk. Ann Nutr Metab 2010;56(2):152–9.
[49] Paniagua JA, Pérez-Martinez P, Gjelstad IM, Tierney AC, Delgado-Lista J, Defoort C, et al. A low-fat high-carbohydrate diet supplemented with long-chain n-3 PUFA reduces the risk of the metabolic syndrome. Atherosclerosis 2011;218(2):443–50.
[50] Rajaie S, Azadbakht L, Khazaei M, Sherbafchi M, Esmaillzadeh A. Moderate replacement of carbohydrates by dietary fats affects features of metabolic syndrome: a randomized crossover clinical trial. Nutrition 2014;30(1):61–8.
[51] Babio N, Toledo E, Estruch R, Ros E, Martínez-González MA, Castañer O, et al., PREDIMED Study Investigators. Mediterranean diets and metabolic syndrome status in the PREDIMED randomized trial. CMAJ 2014;186(17):E649–57.
[52] Poppitt SD, Keogh GF, Prentice AM, Williams DE, Sonnemans HM, Valk EE, et al. Long-term effects of ad libitum low-fat, high-carbohydrate diets on body weight and serum lipids in overweight subjects with metabolic syndrome. Am J Clin Nutr 2002;75(1): 11–20.
[53] Gulseth HL, Gjelstad IM, Tierney AC, Shaw DI, Helal O, Hees AM, et al. Dietary fat modifications and blood pressure in subjects with the metabolic syndrome in the LIPGENE dietary intervention study. Br J Nutr 2010;104(2):160–3.
[54] Pałkowska E, Bartnikowska E, Owsiak D. The use of low-caloric diet with modified fatty acids pool in the therapy of the metabolic syndrome. Rocz Panstw Zakl Hig 2012;63(2):163–9.
[55] Yubero-Serrano EM, Delgado-Lista J, Tierney AC, Perez-Martinez P, Garcia-Rios A, Alcala-Diaz JF, et al. Insulin resistence determines a differential response to changes in dietary fat modification on metabolic syndrome risk factors: the LIPGENE study. Am J Clin Nutr 2015;102(6):1509–17.
[56] Shaw DI, Tierney AC, McCarthy S, Upritchard J, Vermunt S, Gulseth HL, et al. LIPGENE food-exchange model for alteration of dietary fat quantity and quality in free-living participants from eight European countries. Br J Nutr 2009;101(5):750–9.
[57] Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, Fitó M, Chiva-Blanch G, et al., PREDIMED Study Investigators. Effect of a high-fat Mediterranean diet on body weight and waist circumference: a prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial. Lancet Diabetes Endocrinol 2016;4(8):666–76.
[58] Tardivo AP, Nahas-Neto J, Orsatti CL, Dias FB, Poloni PF, Schmitt EB, et al. Effects of omega-3 on metabolic markers in postmenopausal women with metabolic syndrome. Climacteric 2015;18(2):290–8.
[59] Tierney AC, McMonagle J, Shaw DI, Gulseth HL, Helal O, Saris WHM, et al. Effects of dietary fat modification on insulin sensitivity and on other risk factors of the metabolic syndrome FLIPGENE: a European randomized dietary intervention study. Int J Obes 2011;35(6):800–9.
[60] Venturini D, Simão AN, Urbano MR, Dichi I. Effects of extra virgin olive oil and fish oil on lipid profile and oxidative stress in patients with metabolic syndrome. Nutrition 2015;31(6):834–40.
[61] Ortega JF, Morales-Palomo F, Fernandez-Elias V, Hamouti N, Bernardo FJ, Martin-Doimeadios RC, et al. Dietary supplementation with omega-3 fatty acids and oleate enhances exercise training effects in patients with metabolic syndrome. Obesity (Silver Spring) 2016;24(8):1704–11.
[62] Brady LM, Williams CM, Lovegrove JA. Dietary PUFA and the metabolic syndrome in Indian Asians living in the UK. Proc Nutr Soc 2004;63(1):115–25.
[63] Lee TC, Ivester P, Hester AG, Sergeant S, Case LD, Morgan T, et al. The impact of polyunsaturated fatty acid-based dietary supplements on disease biomarkers in a metabolic syndrome/diabetes population. Lipids Health Dis 2014;16(13):196.
[64] Ebrahimi M, Ghayour-Mobarhan M, Rezaiean S, Hoseini M, Parizade SM, Farhoudi F, et al. Omega-3 fatty acid supplements improve the cardiovascular risk profile of subjects with metabolic syndrome, including markers of inflammation and auto-immunity. Acta Cardiol 2009;64(3):321–7.
[65] Kratz M, Baars T, Guyenet S. The relationship between high-fat dairy consumption and obesity, cardiovascular, and metabolic disease. Eur J Nutr 2013;52(1):1–24.
[66] Kurotani K, Nanri A, Goto A, Mizoue T, Noda M, Oba S, et al., Japan Public Health Center-based Prospective Study Group. Cholesterol and egg intakes and the risk of type 2 diabetes: the Japan public health center-based prospective study. Br J Nutr 2014;112(10): 1636–43.
[67] Alexander DD, Miller PE, Vargas AJ, Weed DL, Cohen SS. Meta-analysis of egg consumption and risk of coronary heart disease and stroke. J Am Coll Nutr 2016;35(8):704–16.
[68] Dehghan M, Mente A, Rangarajan S, Sheridan P, Mohan V, Iqbal R, et al. Prospective Urban Rural Epidemiology (PURE) study investigators. Association of dairy intake with cardiovascular disease and mortality in 21 countries from five continents (PURE): a prospective cohort study. Lancet 2018;392(10161):2288–97.
[69] Drehmer M, Pereira MA, Schmidt MI, Alvim S, Lotufo PA, Luft VC, et al. Total and full-fat, but not low-fat, dairy product intakes are inversely associated with metabolic syndrome in adults. J Nutr 2016;146(1):81–9.
[70] Zhang Z, Gillespie C, Yang Q. Plasma trans-fatty acid concentrations continue to be associated with metabolic syndrome among US adults after reductions in trans-fatty acid intake. Nutr Res 2017;43:51–9.
[71] Dehghan M, Mente A, Zhang X, Swaminathan S, Li W, Mohan V, et al., Prospective Urban Rural Epidemiology (PURE) study investigators. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five

continents (PURE): a prospective cohort study. Lancet 2017; 390(10107):2050–62.
[72] Mente A, Dehghan M, Rangarajan S, McQueen M, Dagenais G, Wielgosz A, et al., Prospective Urban Rural Epidemiology (PURE) study investigators. Association of dietary nutrients with blood lipids and blood pressure in 18 countries: a cross-sectional analysis from the PURE study. Lancet Diabetes Endocrinol 2017;5(10):774–87.
[73] Hooper L, Abdelhamid A, Bunn D, Brown T, Summerbell CD, Skeaff CM. Effects of total fat intake on body weight. Cochrane Database Syst Rev 2015:CD011834.
[74] Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al., PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. N Engl J Med 2018 Jun 21; 378(25):e34.
[75] Ervin RB. Prevalence of metabolic syndrome among adults 20 years of age and over, by sex, age, race and ethnicity, and body mass index: United States, 2003-2006. Natl Health Stat Report 2009;5(13):1–7.
[76] Kuhnt K, Fuhrmann C, Köhler M, Kiehntopf M, Jahreis G. Dietary echium oil increases long-chain n-3 PUFAs, including docosapentaenoic acid, in blood fractions and alters biochemical markers for cardiovascular disease independently of age, sex, and metabolic syndrome. J Nutr 2014;144(4):447–60.