*Feature Article*

# Lifestyle recommendations for the prevention and management of metabolic syndrome: an international panel recommendation

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*The importance of metabolic syndrome (MetS) lies in its associated risk of cardiovascular disease and type 2 diabetes, as well as other harmful conditions such as nonalcoholic fatty liver disease. In this report, the available scientific evidence on the associations between lifestyle changes and MetS and its components is reviewed to derive recommendations for MetS prevention and management. Weight loss through an energy-restricted diet together with increased energy expenditure*

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*through physical activity contribute to the prevention and treatment of MetS. A Mediterranean-type diet, with or without energy restriction, is an effective treatment component. This dietary pattern should be built upon an increased intake of unsaturated fat, primarily from olive oil, and emphasize the consumption of legumes, cereals (whole grains), fruits, vegetables, nuts, fish, and low-fat dairy products, as well as moderate consumption of alcohol. Other dietary patterns (Dietary Approaches to Stop Hypertension, new Nordic, and vegetarian diets) have also been proposed as alternatives for preventing MetS. Quitting smoking and reducing intake of sugar-sweetened beverages and meat and meat products are mandatory. Nevertheless, there are inconsistencies and gaps in the evidence, and additional research is needed to define the most appropriate therapies for MetS. In conclusion, a healthy lifestyle is critical to prevent or delay the onset of MetS in susceptible individuals and to prevent cardiovascular disease and type 2 diabetes in those with existing MetS. The recommendations provided in this article should help patients and clinicians understand and implement the most effective approaches for lifestyle change to prevent MetS and improve cardiometabolic health.*



## INTRODUCTION

The metabolic syndrome (MetS) involves diagnostic characteristics that vary according to the definition used. In addition, there is a constellation of associated factors that may be influenced by overnutrition and sedentary lifestyle. MetS represents a common clinical condition in countries where obesity and so-called Western (unhealthy) dietary patterns prevail. In close association with the rising obesity epidemic, the prevalence of MetS is also increasing to epidemic proportions, which entails substantial healthcare costs. The importance of MetS lays in its associated risk of cardiovascular (CV) disease (CVD) and type 2 diabetes (T2DM), as well as other harmful conditions such as nonalcoholic fatty liver disease. Currently, there is no effective preventive approach beyond lifestyle-based interventions aimed at normalizing body weight and achieving and maintaining cardio-metabolic control, including lipid levels, blood glucose, and blood pressure (BP). From a nutritional perspective, the available evidence suggests certain nutrients, foods, and dietary patterns have beneficial effects on MetS, and result in improved metabolic profiles both in the presence or absence of weight loss, but there is no definitive agreement on which nutritional approach is the best.[1–3] Thus, the aim of the present position statement is to update and focus current thinking on the role of lifestyle recommendations for the management of MetS.

In this article, the following levels of evidence (grades) are used to summarize the available scientific evidence and guide recommendations for the prevention and treatment of MetS: A: evidence from meta-analyses that incorporated quality ratings in the analysis or well-conducted randomized controlled trials (RCTs); B: evidence from prospective cohort studies or case–control studies; and C: expert consensus/opinion or clinical experience.

The information presented here is intended to provide a useful framework for patients, researchers, clinicians, policy makers, and other stakeholders to understand and implement the most effective approaches for lifestyle change to improve cardiometabolic health in individuals with MetS.

### Definition of metabolic syndrome

In the absence of a single definition, several closely related but individual definitions have been proposed for MetS. In 2001, the National Cholesterol Education Program Adult Treatment Panel III defined MetS as $\geq$3 of the following risk factors occurring together: abdominal obesity, atherogenic dyslipidemia, hypertension, and insulin resistance.[4] The International Diabetes Federation defined MetS as central obesity in addition to any 2 of the following: raised triglyceride (TG) levels, low high-density lipoprotein cholesterol (HDL-C) levels, hypertension, and elevated fasting plasma glucose.[5] The American Diabetes Association in conjunction with the European Association for the Study of Diabetes stated there was no need for the term MetS because all of its associated factors are treated individually once diagnosed.[6] The debate over the use of the term MetS continues, as noted by the World Health Organization[7]; what is not disputed, is that the factors underlying MetS are increasing worldwide. In 2005, the

American Heart Association/National Heart, Lung and Blood Institute also suggested criteria for the diagnosis of MetS.[8] Finally, in 2009, an attempt was made to reconcile existing definitions.[9] This integrated definition of MetS assigns equal levels of importance to all of its components; abdominal obesity as measured by waist circumference (WC), elevated TGs, low HDL-C, elevated BP, and elevated fasting glucose.[9] Despite the efforts by many organizations to provide a more unified definition, these conflicting definitions indicate that caution should be exercised when comparing studies.

The prevalence of MetS has increased over time and is now reaching epidemic proportions. In Western countries, the estimated prevalence of MetS is approximately one-fifth of the adult population, and this increases with age.[10] However, the prevalence of MetS is dependent on the population studied, age, sex, race, and ethnicity, as well as the definition used.

## WINE, ALCOHOL, AND METABOLIC SYNDROME

High alcohol consumption has been associated with an increased risk of death from several conditions, including liver cirrhosis, chronic pancreatitis, hypertension, cardiomyopathy, some cancers, injuries, and violence.[11] However, the results of several studies show a significant reduction in the risk of CVD events and all-cause mortality from light/moderate intake of alcoholic beverages: a J-shaped curve.[12] Regarding MetS, several studies have found an association between alcohol drinking and the prevalence of MetS and most of its components.[13] Although alcohol intake is positively correlated with plasma HDL-C concentration,[14] high alcohol intake has unfavorable effects on abdominal obesity, TG concentrations, BP, and, possibly, insulin sensitivity.[15–18] However, the effects differ when the daily dose of alcohol and the type of alcoholic beverage consumed are considered. A meta-analysis of observational studies[19] concluded that a favorable metabolic effect appeared to be restricted to moderate alcohol intake (<20 g/d for women and <40 g/d for men). With respect to the type of alcoholic beverages, some authors have not found differences in MetS rates among consumers of different alcoholic drinks, but others have reported lower rates among wine and beer drinkers.[20,21] In the PRevención con DIeta MEDiterránea (PREDIMED) trial, which included 7447 individuals at high CV risk, moderate wine drinkers (≥1 drink(s)/d) showed a reduced risk of prevalent MetS by 44%, compared with nondrinkers. In fact, moderate wine drinkers showed a lower risk of having abnormal WC, low HDL-C, high BP, and high fasting plasma glucose levels. This association was stronger for women, persons aged <70 years, and former or current smokers.[22] Similarly, in the Life Lines Cohort Study, which included 64 046 participants, the overall metabolic profile of wine drinkers was better than that of nondrinkers or drinkers of beer or spirits.[13] The protective effects of moderate beer intake seem to be lower than those of wine.[13] Besides containing alcohol, red wine is rich in polyphenols, which may beneficially influence carbohydrate metabolism[23] and BP.[24] Clinical studies have shown that other foods rich in polyphenols raise HDL-C concentrations.[25] Several studies,[26,27] but not all,[28] have found that wine drinkers had a significantly lower body mass index (BMI) and WC compared with nondrinkers. A long-term randomized intervention trial that included 224 patients with well-controlled T2DM demonstrated that moderate consumption of red wine reduced the number of MetS components by 65%. In addition, slow ethanol metabolizers significantly benefit from the effects of wine on glycemic control (fasting plasma glucose, homeostatic model assessment of insulin resistance, and hemoglobin $A_{1c}$) compared with fast ethanol metabolizers, suggesting that ethanol in wine plays a role in the protective effect.[29]

In summary, compared with abstainers and heavy drinkers, moderate wine drinkers have shown a lower prevalence of MetS and 4 of its 5 components—namely, increased WC, low HDL-C, high BP, and hyperglycemia. Moderate beer drinkers also exhibit a lower prevalence of MetS, but beer appears to be less effective than wine in protecting from MetS. Liquor and spirit intake increase the risk of MetS. The literature suggests that long-term moderate intake of red wine and beer may protect against developing MetS. It is also possible that confounding factors like more diseases among abstainers and heavy drinkers may influence the prevalence of MetS and alcohol exposure. Thus, intervention studies are needed to evaluate the potential benefit of moderate wine and beer intake in mitigating MetS and the associated increased risk of mortality, CVD, T2DM, and some types of cancer. Table 1 shows the grading of the evidence and recommendations regarding alcohol consumption and MetS.

## SMOKING AND METABOLIC SYNDROME

A meta-analysis of 13 prospective cohort studies with a combined total of 56 691 participants and 8688 MetS cases demonstrated that active smokers have a 26% increased risk of MetS compared with nonsmokers.[30] Slagter et al.[31] evaluated data from 24 389 men and 35 078 women participating in the Life Lines Cohort Study and found that this association applies to both sexes (odds ratio [OR], 1.7–2.4 for men and 1.8–2.3 for women; all $P < .001$) and different BMIs. Also, Hwang et al.[32] found a dose–response association between smoking and MetS in men. However, in the Multi-Ethnic Study of Atherosclerosis with 5913 participants, the prevalence of MetS was similar among 3 groups with

*Table 1* **Grading of the evidence and recommendations regarding alcohol consumption and metabolic syndrome**

| Evidence and recommendation | Grade |
|---|---|
| Evidence | |
| Compared with abstainers and heavy drinkers, moderate wine drinkers have a lower prevalence of metabolic syndrome[22–24] | B |
| Moderate beer drinkers exhibit a lower prevalence of metabolic syndrome, but beer appears to be less protective than wine[13] | B |
| Liquor and spirit intake increase the risk of metabolic syndrome[15–17] | B |
| Recommendation | |
| Long-term moderate intake of red wine and beer may protect against developing metabolic syndrome[13,22–24] | B |

differing smoking status.[33] The prevalence of MetS risk factors (except impaired fasting glucose) differs among current, former, and nonsmokers. The Coronary Artery Risk Development in Young Adults study with 4192 participants found that baseline smoking status was not predictive of the occurrence of MetS during 13.6 years of follow-up, although data on former smokers were lacking, which, may have influenced the risk of MetS.[34]

Smoking may increase MetS risk by several mechanisms. Nicotine released during smoking stimulates the release of several neurotransmitters and hormones (catecholamines, vasopressin, corticotropin-releasing hormone, adrenocorticotropic hormone, growth hormone, and others).[35] High levels of inflammatory biomarkers such as C-reactive protein have been shown to be elevated in smokers compared with nonsmokers.[36] Low HDL-C and increased TGs are frequently present due to an increased release of free fatty acids as a consequence of lower lipoprotein lipase activity, higher 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase activity, and higher glucose-6-phosphatase dehydrogenase activity, leading to increased hepatic very-low-density lipoprotein synthesis.[37] Also, in current smokers, the higher prevalence of increased WC despite lower BMI is attributable to increased cortisol production, which leads to accumulation of abdominal fat. Moreover, smokers tend to have insulin resistance due to the effects of cotinine (a metabolite of nicotine), carbon monoxide, cortisol, and growth hormone. The Multi-Ethnic Study of Atherosclerosis,[33] reported, however, that smokers had a lower prevalence of insulin resistance compared with nonsmokers, probably because of a lower BMI. Nevertheless, when adjustments were made for BMI, smokers were at a higher risk of MetS than nonsmokers.[33]

### Smoking cessation

Wada et al.[38] found that, after smoking cessation, the risk of MetS increased and remained high for at least 10 years in the individuals who smoked ≥20 cigarettes per day and for >20 years in those who smoked ≥40 cigarettes per day. In this context, in an adult Puerto Rican population, Calo et al.[39] found that MetS was more prevalent in former smokers (48.4%) compared with current (42.7%) and nonsmokers (40.0%). Another study that included 4542 men without MetS at baseline who were followed for an average of 3 years also showed this pattern (8.0% MetS incidence in nonsmokers, 7.1% in new smokers, 17.1% in ex-smokers, and 13.9% in current smokers).[40] In contrast, other researchers[41] found no differences between smokers and nonsmokers regarding total body fat and/or body fat distribution. Thus, smoking cessation programs should include lifestyle interventions to offset the MetS-augmenting side effect of smoking cessation.

Regarding smoking cessation and diabetes, in a meta-analysis of 88 studies that involved a combined total of 5 898 795 participants and 295 446 incident cases of T2DM, Pan et al.[42] found that the risk of developing T2DM increased in recent quitters but decreased noticeably as time passed after smoking cessation.

Regarding weight gain following smoking cessation, it needs to be emphasized that smoking, particularly in individuals with poor socioeconomic status, is associated with unhealthy diets, increased alcohol consumption, and limited physical activity, which are all behaviors that remain after quitting and may potentially enhance weight gain.[43–45] Table 2 shows the grading of the evidence and recommendations regarding smoking and MetS.

## PHYSICAL ACTIVITY AND METABOLIC SYNDROME

Physical inactivity is identified as the fourth leading risk factor for global mortality.[46] Regular physical activity leads to enhanced energy consumption and is associated with reduced risk of prevalent diseases such as obesity, MetS, T2DM, CVD, cognitive impairment, depression, and osteoporosis.[47] In MetS, the excess energy that is accumulated in adipose tissue and also stored ectopically in nonadipose tissues like the liver will cause metabolic disturbances that lead to increases in BP, blood glucose, TGs, and inflammation.[48] These metabolic alterations can be prevented or reduced if physical activity is performed daily, preferentially involving large muscle groups. Any type of physical activity is better than inactivity, and increasing physical activity may also have substantial beneficial effects on personal well-being.[49] Although there are gaps in the present knowledge of how long, what type, and during what periods of life people should exercise, the available scientific evidence can be summarized as outlined in Box 1:[50–54]

*Table 2* **Grading of the evidence and recommendations regarding smoking and metabolic syndrome**

| Evidence and recommendation | Grade |
|---|---|
| Evidence | |
| Smoking increases the risk of metabolic syndrome[30–32] | B |
| There is an increased risk of developing metabolic syndrome after quitting smoking[38–40] | B |
| Recommendation | |
| Stop smoking to prevent and treat metabolic syndrome. Smokers unable to quit smoking should be referred to a smoking cessation clinic[42] | A |
| Obese and overweight individuals should adopt a calorie-restricted diet after quitting smoking[44,45] | B |
| United States Food and Drug Administration–approved medications for smoking cessation may be considered to decrease postcessation weight gain | C |

*Box 1* **Summary of available evidence on physical activity**

- Observational studies of people with different levels of physical inactivity indicate that increasing physical activity is beneficial[55,56]
- Inactive people should start increasing physical activity slowly and gradually[57]
- Brisk walking is the preferred initial exercise modality[46,57]
- 30–60 min of daily physical activity is recommended, including aerobic exercise, work-related activity, and muscle strengthening[58]
- Physical activity can be accumulated throughout the day in blocks as short as 10 minutes
- A dose–response relationship exists between physical activity and health; the beneficial effects are greater when exceeding minimum recommendations
- Physical activity must be individualized based on fitness and comorbidities

It is very important to keep body weight as near to normal as possible for both prevention and treatment of MetS because its pathophysiology relates to a positive energy balance, with surplus fat stored in adipose tissue and ectopic tissues such as the liver, pancreas, skeletal muscle, and around upper airways and inner organs.[59] Life-style changes consisting of enhanced physical activity together with reduced energy intake (see below) are instrumental to both prevent and treat MetS. Table 3 shows the grading of the evidence and recommendations regarding physical activity and MetS.

## METABOLIC SYNDROME AND WEIGHT CONTROL

Obesity and MetS are intimately related. It is, therefore, difficult to separate their effects on the risk of vascular events or T2DM.[60] Nevertheless, weight loss will decrease the prevalence of MetS. Obesity is not necessarily always associated with MetS, but it will adversely affect the MetS diagnostic criteria, which include WC and BP, as well as HDL-C, TGs, and fasting blood glucose levels.[9,61] There are other characteristics that are shared between obesity and MetS—for example, elevated levels of serum uric acid, postprandial hypertriglyceridemia, dysfunctional HDL, increased small dense LDL, nonalcoholic fatty liver disease (the hepatic expression of MetS), insulin resistance, endothelial dysfunction, arterial stiffness, epicardial fat accumulation, prothrombotic state, abnormal adipokine levels, increased inflammation, and obstructive sleep apnea.[62,63]

*Table 3* **Grading of the evidence and recommendations regarding physical activity and metabolic syndrome**

| Evidence and recommendation | Grade |
|---|---|
| Evidence | |
| Physical activity has substantial beneficial effects on metabolic syndrome[50–54] | A |
| Recommendation | |
| Physical activity must be individualized based on fitness and comorbidities[57] | C |
| 30–60 min of daily physical activity is recommended, including aerobic and work-related activity and muscle strengthening[58] | B, C |

Obesity has traditionally been defined by the BMI, but cutoff values for BMI (and WC) vary by ethnicity. Therefore, it is probably more appropriate to use the Joint Interim Statement definition of MetS (October 2009), which includes WC definitions based on ethnicity.[9] Using uniform definitions of obesity and MetS will enable comparisons between studies because the various definitions of MetS result in significantly different assessments of vascular risk.[64,65]

Several diets were proposed in the past and will be promoted in the future to treat obesity. This in itself indicates there is no single perfect diet for weight loss. Calorie restriction plus exercise are time-honored criteria. Importantly, results from RCTs have shown that high-fat diets are equally effective or superior to low-fat diets for weight loss.[66] Regarding specific dietary patterns, probably the Mediterranean diet (MedDiet), a high–vegetable fat dietary pattern, is the best strategy to reduce incidence and lower the prevalence of MetS and its components.[67]

Insulin resistance is not a *sine qua* diagnostic component of MetS. Nevertheless, it is a common feature of both obesity and MetS. Improving insulin sensitivity will, in turn, result in beneficial effects on the MetS components BP, HDL-C, TGs, and blood glucose. Weight loss or medications (eg, metformin or pioglitazone) can increase insulin sensitivity. In turn, weight loss can be assisted by lifestyle measures and medication

*Table 4* **Grading of the evidence and recommendations regarding weight control and metabolic syndrome**

| Evidence and recommendation | Grade |
|---|---|
| Evidence | |
| There is no optimal diet for weight loss, but calorie restriction plus exercise are instrumental for losing weight[66] | B |
| Recommendation | |
| A healthy diet designed to achieve 5% weight loss should be prescribed for overweight and obese patients with metabolic syndrome[66,67] | A |

(eg, naltrexone + bupropion, liraglutide, orlistat, lorcaserin, and phentermine + topiramate).[68] Bariatric surgery can be used for the morbidly obese or for those with a lesser degree of obesity but with CVD risk factors.[69] Each abnormality associated with obesity and/or MetS can be addressed individually. Weight loss achieved by lifestyle or surgical interventions may also improve coronary circulatory dysfunction.[70] There is also a need to address modifiable risk factors if patients are judged to be at high risk of vascular events, even if their risk is not directly related to obesity or MetS. Options include smoking cessation, decreasing raised LDL-C levels, and prescribing antiplatelet agents.[71] Table 4 shows the grading of the evidence and recommendations regarding weight control and MetS.

## INFLUENCE OF DIET ON METABOLIC SYNDROME

### Mediterranean diet and metabolic syndrome

The term Mediterranean diet refers to the traditional dietary pattern of countries in the Mediterranean basin. It is a plant-based diet, including sizable quantities of fruits, vegetables, whole-grain cereals, legumes, nuts, and olive oil as the principal source of fat. It also includes fish and poultry in low to moderate amounts, a relatively low amount of red meat, and moderate daily consumption of alcohol, normally as red wine taken with meals.[72] The MedDiet is a high-fat dietary pattern because the total fat content ranges from 35% to 45% of energy, but most of that fat is unsaturated because olive oil is used abundantly in the kitchen and at the table. Because the MedDiet has been consistently shown to be cardioprotective,[73] it exemplifies the fact that high-fat diets can be beneficial for CV health if salutary vegetable fats are consumed.[74]

Regarding the MedDiet and CV health, both prospective cohort studies and RCTs have suggested that this dietary pattern is protective against the development of MetS and its individual components.[75–78] Based on the results of a meta-analysis of 50 independent studies and 534 906 individuals, adherence to the MedDiet was associated with 50% reduction in the prevalence of MetS compared with nonadherence.[79] Moreover, the MedDiet showed beneficial effects on the common MetS components of abdominal obesity, dyslipidemia, elevated fasting blood glucose, and high BP, which are also risk factors for the development of CVD and T2DM.[79,80] Finally, in both sexes, MetS has been associated with sexual dysfunction that can be improved by adoption of the MedDiet.[81] The antioxidant and anti-inflammatory effects of the MedDiet could offer a possible explanation for its beneficial effects on MetS.[75,82,83] Adoption of the MedDiet may, thus, be important for both prevention and resolution of MetS. It is not by chance that this dietary pattern was recognized as an Intangible Cultural Heritage of Humanity by (UNESCO) in 2010, emphasizing not only the food consumption aspects, but also its cultural roots, including conviviality, socialization, biodiversity and seasonality, culinary activities, physical activity, and adequate rest. Table 5 shows the grading of the evidence and recommendations regarding the MedDiet and MetS.

*Table 5* **Grading of the evidence and recommendations regarding the Mediterranean diet and metabolic syndrome**

| Evidence and recommendation | Grade |
|---|---|
| Evidence | |
| Mediterranean diet can be a useful strategy for preventing cardiovascular diseases and diabetes in individuals with metabolic syndrome[75–77,79] | B |
| Recommendation | |
| Mediterranean diet, with or without energy restriction, can be recommended for all people with metabolic syndrome as an effective component of the treatment strategy[76,77,79] | B |
| Minimally processed, seasonally fresh, and locally grown foods are preferred[73,74] | C |

### Olive oil and metabolic syndrome

Olive oil is probably the most representative component of the MedDiet. As discussed, the olive oil-rich MedDiet reversed MetS status in several RCTs[75,76,84] and reduced its incidence in observational studies.[79] This article focuses on the available evidence from RCTs concerning the benefits of olive oil at doses of 20–50 g/d, independent of the background diet, on MetS and its individual features. Virgin and extra-virgin olive oil have as a major component oleic acid, a monounsaturated fatty acid (MUFA), but they also contain minor components with bioactive properties.[85] Monounsaturated fatty acid consumption promotes beneficial blood lipid profiles, improves insulin sensitivity, and regulates blood glucose levels.[86–88] Dietary olive

oil and virgin olive oil, in contrast with other vegetable oils, reduced the risk of MetS,[25] the need for antihypertensive medication,[89] and systolic BP.[90] Recent evidence from the PREDIMED trial indicates that a MedDiet enriched with extra-virgin olive oil is not associated with weight gain in an older, mostly overweight or obese population at high CV risk.[91]

Oxidation and inflammation are mechanisms linked to MetS.[92,93] Oxidative stress is associated with the number of components of MetS.[93] Monounsaturated fatty acid–rich diets are more effective than those rich in polyunsaturated fatty acids (PUFAs) for reducing the resistance of LDL to oxidation.[94] Olive oil consumption has been found to decrease in vivo HDL oxidation, which would impair HDL function (ie, cholesterol efflux from cells).[95] The beneficial effect of olive oil on inflammation[96] could be conveyed through a transcriptomic effect by decreasing the expression of proinflammatory genes.[97,98]

Minor components of olive oil also play a beneficial role in MetS. For example, pomace olive oil, rich in triterpenes, was found to decrease postprandial TG-rich lipoproteins.[99] Compared with a low-phenolic olive oil, virgin olive oil, rich in phenolic compounds, was associated with an improved lipid profile, anti-inflammatory effect, lower systolic BP,[85,100,101] and improved expression of inflammatory and HDL-C efflux-related genes.[102,103]

These results indicate that olive oil as a dietary fat is a useful tool in the management of MetS. To achieve its benefits, a similar amount of consumed fat must be replaced by olive oil without increasing the total number of calories per day. On the basis of the health claims authorized by the United States Food and Drug Administration and the European Food Safety Authority, the recommended daily quantities are conservative: 23 g/d (2 tablespoons) for olive oil[104] and 20 g/d for phenolic-rich virgin olive oil,[105] respectively. In the PREDIMED study, daily consumption of 35–45 g/d of virgin olive oil for 5 years within the frame of a MedDiet pattern reversed MetS, mainly by reducing abdominal adiposity.[76] Low-density lipoprotein oxidation was also decreased by the MedDiet enriched with olive oil.[106] In the EUROLIVE study, conducted in different European countries, consumption of 25 mL/d (22 g/d) of any type of unheated olive oil in substitution of other fats during 3-week periods decreased TGs and systolic BP.[90] In the same study, an increase in HDL-C levels and function and a decrease in LDL oxidation and in the expression of inflammatory-related genes were directly related to the phenolic content of the olive oil administered.[102,107] Recommended daily doses of OO as the main source of dietary fat in American and European nutritional guidelines range 30–78 g/d depending on body weight.[108] Thus, olive oil doses around 40–45 g/d for culinary use and dressing vegetables and around 20–25 g/d for nonculinary use in replacement of other fats could be appropriate for MetS prevention and management. Table 6 shows the grading of the evidence and recommendations regarding olive oil consumption and MetS.

*Table 6* **Grading of the evidence and recommendations regarding olive oil and metabolic syndrome**

| Evidence and recommendation | Grade |
|---|---|
| Evidence | |
| Olive oil in replacement of other fats is useful for metabolic syndrome prevention and management[85–87] | B |
| Recommendation | |
| Daily consumption of olive oil at doses of 20–40 g/d in replacement for other fats is useful in the prevention and treatment of metabolic syndrome[76,104,105,108] | A |

## Dietary patterns and metabolic syndrome: beyond the Mediterranean diet

The importance of individual dietary components was assessed in several studies. However, because nutrients may have a synergistic effect on disease, it is more realistic to study dietary patterns. Reviewed here is the current evidence from prospective studies and RCTs on well-recognized dietary patterns other than the MedDiet.

*Western-type diets.* Consumption of Western diets, which are characterized by high intakes of red meat, processed foods, refined grain, sugars, and saturated fatty acids, has been associated with a higher prevalence of MetS in women[109] but not in elderly adults.[110] A prospective analysis conducted within the Atherosclerosis Risk in Communities study indicated an 18% greater risk of incident MetS for individuals with the highest Western dietary pattern score.[111]

*The Dietary Approaches to Stop Hypertension diet.* The Dietary Approaches to Stop Hypertension (DASH) diet proved to be effective for controlling BP and improving the lipid profile, glucose metabolism, and other CV risk factors.[112] However, observational data on the association between the DASH diet and MetS are scarce. An initial approach using the OmniHeart database revealed fewer MetS components in individuals following a DASH diet.[113] More recently, a cross-sectional analysis conducted in Iranian women suggested that individuals with a greater adherence to the DASH diet had a lower prevalence of MetS and most of its features after

controlling for potential confounders.[114] Likewise, findings from RCTs also suggested that the DASH diet has beneficial effects on MetS in both adults and children.[112,115]

*The new Nordic diet.* The Nordic diet is based on foods from Nordic countries. It contains increased amounts of plant foods, fish, and fish products (mainly fatty fish) from the sea and lakes, and mushrooms, berries, and other traditional fruits. A RCT has investigated the impact of the Nordic diet on MetS components. A total of 200 adults with MetS were randomized to a Nordic diet or a control diet for 18–24-week periods. The participants' lipid profiles improved significantly after the intervention diet, whereas changes in body weight, insulin sensitivity, and BP were not statistically significant.[116]

*Vegetarian diets.* The health benefits of strictly plant-based or vegetarian diets have mainly been assessed in the Seventh-day Adventist prospective cohorts and in studies of British vegetarians. In a cross-sectional analysis of 773 participants from the Adventist Health Study-2, a vegetarian dietary pattern was associated with a significantly lower risk of prevalent MetS than a nonvegetarian diet.[117] The protective effect of vegetarian diets on MetS has also been observed in other epidemiological studies conducted mostly in Asian populations, but the finding is not consistent.[118] No RCTs testing the effect of vegetarian diets on MetS or its components could be located in the existing literature.

*Other dietary patterns.* Other dietary patterns that have a high carbohydrate content and are rich in whole grains or high in protein have shown beneficial effects on MetS components in several trials.[119] However, the proportions of each macronutrient have not been well defined, and little information is available from large-scale observational studies.

Table 7 shows the grading of the evidence and recommendations regarding dietary patterns and MetS.

*Table 7* **Grading of the evidence and recommendations regarding particular diets and metabolic syndrome**

| Evidence and recommendation | Grade |
|---|---|
| Evidence | |
| Western dietary patterns are detrimental for metabolic syndrome and its components[109,111] | B |
| The Dietary Approaches to Stop Hypertension diet improves several components of metabolic syndrome [112–115] | A |
| Other dietary approaches such as the new Nordic diet or vegetarian diets are potentially effective to modulate metabolic syndrome components[116] | B |
| Recommendation | |
| The Dietary Approaches to Stop Hypertension diet, new Nordic diet, and plant-based/vegetarian diets can be recommended for people with metabolic syndrome as an effective component of the treatment strategy[109,111–116] | B |

## Legumes and metabolic syndrome

Legumes are seeds that are rich in protein, complex carbohydrates, fiber, and various bioactive micronutrients.; their effects on blood glucose regulation have been tested in several RCTs and. they were found to reduce postprandial blood glucose and insulin excursions. This effect is mediated by slow carbohydrate absorption that results in improved glycemic control.[120] To date, few studies have examined the association of legume consumption with MetS.[121] The Isfahan Healthy Heart Program reported that all components of MetS were less prevalent among individuals with regular legume consumption.[121] Other studies have related bean consumption to lower systolic BP, smaller WC, and lower body weight.[122,123] Furthermore, a population-based, cross-sectional study showed a substantial reduction in the risk of MetS with increased legume fiber intake.[124] Moreover, studies performed in diabetic patients revealed that higher consumption of legumes improved glycemic control and insulin resistance.[125–127] Finally, RCTs have shown beneficial effects of legumes on CV risk factors, such as lipids (TG) and BP.[128,129] In this regard, a recent meta-analysis of RCTs suggested a slight BP-lowering effect of legumes, but marked heterogeneity among studies precludes drawing firm conclusions.[130] In summary, the evidence suggests that eating a variety of legumes is beneficial in the prevention and management of MetS, T2DM, and CVD.[131] Table 8 shows the grading of the evidence and recommendations regarding legume consumption and MetS.

## Cereals and metabolic syndrome

Cereals and cereal-derived products are a staple for many world populations and an important component of a healthy dietary pattern. They have relatively low calorie density and may contribute to maintaining energy balance. Several epidemiologic studies have assessed the association of MetS with dietary fiber, mainly fiber derived from cereal consumption, and concluded that there is an inverse association.[132,133] A population-based, cross-sectional study evaluated the association between total dietary fiber and its types and sources with the risk of MetS. Those in the highest tertile of cereal fiber intake had lower odds of MetS compared with those in the lowest tertile (OR = 0.73; 95% confidence interval = .52–.97), but the association was no longer

*Table 8* **Grading of the evidence and recommendations regarding legumes and metabolic syndrome**

| Evidence and recommendation | Grade |
|---|---|
| Evidence | |
| Eating a variety of legumes is beneficial in the prevention and management of metabolic syndrome[124–129] | B |
| Recommendation | |
| Daily consumption of legumes is recommended to improve cardio-metabolic risk factors[128,129,131] | A |
| Legumes can be recommended for people with metabolic syndrome as an effective component in prevention and management of diabetes and cardiovascular disease[121–124,131] | A |

*Table 9* **Grading of the evidence and recommendations regarding cereals and metabolic syndrome**

| Evidence and recommendation | Grade |
|---|---|
| Evidence | |
| Eating a variety of cereals (whole grains) is beneficial in the prevention and management of metabolic syndrome[133] | B |
| Recommendation | |
| Daily consumption of cereals (whole grains) is recommended for cardiometabolic health[132–135] | A |
| Cereals can be recommended for people with metabolic syndrome[133,134] | B |

significant after adjusting for confounders.[124] Few long-term studies have examined the relation between breakfast cereal consumption and diabetes risk. There is some evidence supporting the role of breakfast cereals, especially those high in fiber, in the management of T2DM, but the evidence is not strong.[134] Evidence for the relation between breakfast cereals and hypertension is limited. The most convincing evidence comes from the Physicians' Health Study,[135] which found a 19% reduction in hypertension risk with daily breakfast cereal consumption and a stronger relation with whole-grain than with refined-grain cereals. The authors suggested a number of components in cereals, including folate, magnesium, potassium, and fiber, may be responsible for this effect. However, these results were obtained from physicians who are likely to have generally healthy lifestyles, and the results do not provide any data on hypertension risk in women. Table 9 shows the grading of the evidence and recommendations regarding cereals and MetS.

## Fruits, vegetables, and metabolic syndrome

Consumption of fruits and vegetables has been shown to have favorable effects on a wide spectrum of clinical outcomes, and, to that extent, most dietary guidelines emphasize their importance. Indeed, the cardiometabolic benefit ascribed to plant-based dietary patterns such as the MedDiet, DASH diet, and vegetarian diets can be ascribed, to a large extent, to their richness in fruits and vegetables. However, because they are complex food patterns, the specific contribution of the fruits and vegetables component to attenuating the risk of MetS cannot be determined, and the epidemiological evidence relating their intake to incident MetS is relatively scarce. Epidemiological studies conducted mostly in Asian populations have reported a more favorable cardiometabolic risk profile and reduced risk of MetS among individuals following plant-based diets (vegan and vegetarian) compared with omnivores.[118] Again, favorable impacts of such complex diets cannot be ascribed only to intake of fruits and vegetables. However, a meta-analysis of 5 prospective studies showed that total fruits and vegetables intake, but not intake of specific subtypes of fruits or vegetables, was associated with a lower relative risk of T2DM.[136] Green leafy vegetables showed the strongest protective association with incident T2DM.[136,137]

A meta-analysis of RCTs suggested that intake of fruits and vegetables reduces diastolic BP but has no impact on other features of MetS such as WC, systolic BP, fasting glucose, HDL-C, or TG levels in patients with MetS.[138] This analysis is based, however, on only 8 RCTs, so the data must be interpreted with caution. Increasing consumption of fruits and vegetables from 1 serving per day to 6–7 servings per day for 12 weeks also had no effect on insulin resistance in overweight individuals[139] or on a wide spectrum of inflammatory and oxidative stress markers in hypertensive individuals.[140]

In summary, data from epidemiological studies suggest that consumption of fruits and vegetables may reduce the risk of MetS. Beyond differences in study designs, factors such as duration of intervention and the "doses" of fruits and vegetables investigated need to be considered when trying to reconcile data from epidemiological studies and clinical trials. Displacing potentially unhealthy foods with fruits and vegetables in the diet also needs consideration when assessing the potential effect of fruit and vegetable intake on MetS and health in general. Although increased consumption of fruits and vegetables appears to be a justifiable and logical recommendation to manage the risk of MetS, further investigations are warranted to establish the extent to which such intake specifically contributes to the favorable health effects of dietary patterns such as the MedDiet or the DASH diet on MetS. Table 10 shows the grading of the evidence and recommendations regarding fruit and vegetable consumption and MetS.

*Table 10* **Grading of the evidence and recommendations regarding fruit/vegetable intake and metabolic syndrome**

| Evidence and recommendation | Grade |
|---|---|
| Evidence | |
| Eating a variety of fruits and vegetables is beneficial in the prevention and management of metabolic syndrome[138] | C |
| Recommendation | |
| Although the association between intake of fruits and vegetables and features of metabolic syndrome remains unclear, consumption of fruits and vegetables should be an integral part of a healthy and balanced diet[136–138] | A |

## Fish and metabolic syndrome

Consistent evidence from epidemiological studies indicates that consumption of fish (especially fatty fish) or intake of fish oil supplements rich in n-3 fatty acids relates to CV protection, especially coronary heart disease mortality.[141] Evidence from RCTs, however, is controversial.[142] Several studies have also shown beneficial effects of fish consumption on CV risk factors such as body weight, the lipid profile, BP, and insulin levels.[143] In cross-sectional analyses, a dietary pattern including frequent consumption of fish, cereals, legumes, vegetables, and fruits resulted in a lower likelihood of having MetS compared with dietary patterns in which consumption of potatoes, meat, and alcohol predominated in a Greek population sample[144]; in a Korean population, this dietary pattern was also inversely associated with the risk of hypertriglyceridemia and MetS.[145] Moreover, an inverse relationship has been found between central adiposity and fish consumption.[146] Evidence suggests that the beneficial effect of fish oil (long-chain n-3 PUFA) on MetS is mediated by improving dyslipidemia and adipose tissue storage and secretory functions, as well as reducing inflammation.[147] Also, a combination of fatty fish with bilberries and whole-grain products improved endothelial dysfunction and inflammation in overweight and obese individuals[147] and decreased MetS risk.[148] In a 4-year prospective Korean study, high consumption of fish and n-3 fatty acids resulted in lower MetS risk among men but not among women.[149] Adherence to an n-3 fatty acid/fish dietary pattern showed a significant inverse association with MetS among Puerto Ricans living in the United States,[150] but other nutrients in fish might have influenced this effect. Also, consumption of lean fish at least 4 times per week reduced BP in coronary heart disease patients in a small 8-week RCT.[151] In The WISH-CARE RCT, which included 273 individuals with MetS, an 8-week dietary intervention (with 100 g/d of white fish compared with no fish or seafood) resulted in a reduction of LDL-C, WC, and BP.[152] An 8-week pilot study in which fatty fish was consumed 4–5 times/week found decreases in potential mediators of lipid-induced insulin resistance and inflammation,[153] and it has been reported that fatty fish meals may be associated with improved glucose metabolism.[154] Moreover, fish oil consumption for 4 weeks improved lipid metabolism in individuals with MetS.[155] However, incorporating sardines daily in the diet of drug-naive diabetic patients had no effect on glycemic control in a recent RCT.[156] Of interest, the protective effects of fish consumption against atherosclerosis might be partly explained by changes in HDL particles shifting their subclass distribution toward larger particles.[157] Fish oil was found to reduce blood glucose, insulinemia, and insulin resistance in women with MetS,[158] and such benefits may be seen even with short-term dietary supplementation.[159] Also, serum adiponectin levels increased after a sardine diet in patients with T2DM[156] and following fish oil supplementation in individuals with MetS,[160] although null findings on metabolic variables have also been reported.[161,162] On the other hand, results of the National Heart, Lung, and Blood Institute Family Heart Study do not support an association between dietary n-3 fatty acids and MetS.[163] A recent review[164] concludes that long-chain n-3 PUFAs play a role in limiting visceral adiposity and dyslipidemia, and possibly hypertension and inflammation, but the evidence on glucose homeostasis and insulin resistance is inconsistent.

Further studies are warranted to establish the ability of fish and long-chain n-3 fatty acid consumption to improve MetS and its components. Nevertheless, as reviewed,[165] there is little evidence that consumption of fish of any type or of long-chain n-3 PUFAs has a protective effect on the incidence of T2DM, which is a MetS component in lieu of hyperglycemia. Table 11 shows the grading of the evidence and recommendations regarding fish and n-3 fish oil consumption and MetS.

## Other dietary features that can influence metabolic syndrome

*Nuts and metabolic syndrome.* Nuts (tree nuts and peanuts) are high-energy, nutrient-dense seeds made of complex matrices that are rich in unsaturated fatty acids, fiber, nonsodium minerals, tocopherols, and bioactive phytochemicals such as polyphenols and phytosterols. Most of these components are bioavailable after consumption by humans and synergize to beneficially affect metabolic pathways, leading to protection from CVD and T2D.[166] Indeed, nut consumption has been consistently related to protection from fatal and nonfatal coronary heart disease, as shown in a recent meta-

*Table 11* **Grading of the evidence and recommendations regarding intake of fish and n-3 fish oils and metabolic syndrome**

| Evidence and recommendation | Grade |
|---|---|
| Evidence | |
| Fish or n-3 fatty acid intake may reduce the risk of metabolic syndrome[148–150,152] | C |
| Recommendation | |
| Eating a variety of fish at least twice a week, especially fish containing n-3, may be useful in preventing metabolic syndrome[148–150,152] | C |

analysis of 6 prospective studies.[167] The same meta-analysis showed an inverse association between nut consumption and risk of incident T2DM, as derived from findings in 6 prospective studies.[167] The meta-analysis of 4 observational studies also showed a protective effect of nuts on hypertension.[168] Many RCTs have compared the effects of nut-enriched diets versus nut-free diets on the lipid profile. A pooled analysis of 25 clinical trials indicated a consistent cholesterol-lowering effect of nut-enriched diets, which was related to both nut dose and initial lipid levels, and nut diets also reduced TGs in individuals whose TG levels were elevated at baseline.[169] Although nuts are energy-dense foods, a previous meta-analysis of 31 RCTs showed small, nonsignificant associations of nut consumption with reduced, not increased, adiposity measures (body weight, BMI, and WC).[170] The fact that, besides reducing coronary heart disease risk, nut consumption has a favorable effect on T2DM, BP, and TGs and tends to be associated with reduced visceral adiposity, which are all MetS criteria, suggests that nuts might have a beneficial impact on MetS itself.

A recent meta-analysis of 49 RCTs examining nut consumption, which included a combined total of 2226 participants, reported beneficial effects on at least 1 criterion of MetS in the examined studies; the reported benefits included modest but significant decreases in TGs and fasting blood glucose and a tendency to lower WC, with no adverse effects on other criteria.[171] When evaluating the effect of nut consumption on MetS, data from 3 large epidemiologic studies were found that suggested a beneficial effect.[172–174] One cross-sectional assessment of the PREDIMED cohort of older persons at high CV risk showed that frequent nut eaters had a lower risk of MetS, as well as reduced risk of T2DM and abdominal obesity.[172] Similarly, nut consumption was related to a lower incidence of MetS in the prospective Seguimiento Universidad de Navarra cohort of Spanish university graduates[173] and to a lower prevalence of MetS in a cross-sectional report from the US National Health and Nutrition Examination Survey for 2001–2004.[174] One of the intervention arms in the PREDIMED trial was given advice on a MedDiet supplemented with 1 daily serving of mixed nuts. In a preliminary report of the PREDIMED cohort after 1 year of intervention, the prevalence of MetS was reduced by 14% in the group receiving supplementary nuts, compared with 2% in the control diet group.[84] The recently published results of the full PREDIMED cohort after 4.8 years of follow-up show that participants with MetS at baseline (n = 3392) who were allocated to the MedDiet with nuts intervention arm had a 28% higher rate of MetS reversion compared with those in the control diet group, and this beneficial effect was driven mainly by reduced WC.[76] Of note, a similar beneficial effect was observed in the MedDiet enriched with extra-virgin olive oil intervention arm.

In summary, there is both epidemiological and RCT evidence of a salutary effect of nut consumption on MetS components and on the full syndrome. There is probably an added benefit if nuts are incorporated into a MedDiet. Table 12 shows the grading of the evidence and recommendations regarding nut consumption and MetS.

*Table 12* **Grading of the evidence and recommendations regarding nut intake and metabolic syndrome**

| Evidence and recommendation | Grade |
|---|---|
| Evidence | |
| There is epidemiological and clinical trial evidence of a salutary effect of nut consumption on metabolic syndrome components and on the full syndrome itself[76,172–174] | B |
| There is an added cardio-metabolic benefit from incorporating nuts into a Mediterranean-type dietary pattern[166–169] | A |
| Recommendation | |
| Consume 1 to 1.5 servings of nuts daily to reduce low-density lipoprotein cholesterol and cardiometabolic risk[76,84,166–169,172–174] | A |

*Dairy products, eggs, and metabolic syndrome.* Several epidemiological studies have investigated the association between dairy product consumption and the risk of cardio-metabolic disease; however, little is known about the possible effects of eggs. Regarding dairy products, a review of 10 cross-sectional and 3 prospective studies suggested a protective effect of dairy product consumption on MetS, but the evidence was inconclusive.[175] Five other prospective studies published after this review have also demonstrated an inverse association between total dairy,[176–178] regular or reduced-fat dairy,[179,180] and MetS incidence. Only 1 prospective study has analyzed the associations between the type of dairy products consumed and MetS incidence in young adults,[181] showing an inverse association between an increased consumption of high-fat dairy products, reduced-fat dairy products, milk, or cheese and MetS

incidence. Similarly, in senior adults at high CV risk, higher consumption of low-fat dairy products, yogurt (total, low-fat, and whole-fat yogurt), and low-fat milk was associated with reduced risk of MetS; conversely, higher consumption of cheese was related to a higher risk of MetS.[179] The most recent meta-analysis on dairy consumption and MetS was published in 2016.[182] This meta-analysis, based on 9 prospective cohort studies, found that high dairy consumption was associated with a 15% reduction in MetS risk, as well as a reduction of 12% in MetS risk per 1-serving/day increment of dairy consumption. Overall, the majority of the literature suggests a benefit of dairy consumption on the risk of MetS, although the data remain somewhat inconclusive. Limitations of the epidemiologic studies that compound the results include the following: biases that were introduced from the failure to suitably control for confounding variables; limited information regarding dairy intake (including type of dairy product, quantity and fat content, synergistic effects with other foods, substituting effects, and whether it is fermented); and the use of different MetS diagnostic criteria.

Several studies have also explored the associations between dairy product consumption and MetS components. To date, 6 meta-analyses of observational studies have been published showing inverse associations between total or low-fat dairy consumption and diabetes incidence.[183–188] In 2 of these meta-analyses, an inverse association was also reported for yogurt and cheese consumption.[184,185] In a recent meta-analysis of prospective studies that included 3 large cohorts (Nurses Health Study I and II and Health Professionals Follow-up Study), yogurt consumption related inversely to diabetes incidence (18% lower risk of T2DM per 1 serving of yogurt).[186] After this meta-analysis, 2 other prospective studies have been published with similar results.[189,190] Finally, a more recent (2016) dose–response meta-analysis combined the results of 22 prospective studies, with a combined total of 579 832 individuals including 43 118 with T2DM, and showed a 3% and 4% lower risk of diabetes per 200 g/d of total and low-fat dairy products consumed, respectively.[188] This meta-analysis also showed a nonlinear inverse relationship between yogurt consumption and risk of T2DM, revealing a 14% lower risk when yogurt consumption was 80–125 g/d, compared with no intake of yogurt. However, cheese intake was not associated with the risk of T2DM. Only a few RCTs have examined the effect of dairy products on insulin resistance or pancreatic insulin secretion, and the results are contradictory.[191]

Regarding eggs and cardio-metabolic risk, a recent meta-analysis of prospective studies suggests that egg consumption is associated with an increased incidence of T2DM among the general population and of CVD comorbidity among diabetic patients.[192] On the other hand, the results of 2 large prospective studies that examined the risk of T2DM derived from egg consumption suggest a neutral or even protective effect, particularly in men.[193,194] Thus, the role of eggs in the development of T2DM remains unclear.

Results of a systematic review of prospective studies suggested a protective effect of dairy product consumption on obesity; however, the effect was small.[195] In addition, an inverse association between the risk of overweight/obesity or weight gain and yogurt consumption was recently reported in 2 large cohort studies.[196,197] The effect of dairy consumption on weight and body composition was further investigated in 2 meta-analyses of RCTs. The first meta-analysis of 14 RCTs found that increasing dairy consumption to recommended daily intakes in adults who do not follow any calorie-restricted diet had a small effect on weight loss but also resulted in decreased fat mass and WC.[198] The second meta-analysis of 29 RCTs found that overall consumption of dairy products did not result in a significant reduction in weight; however, a subgroup analysis showed that consumption of dairy products in the context of energy restriction did reduce body weight.[199] Regarding the BP component of MetS, consumption of milk and dairy products has been inversely related to the risk of hypertension,[200] and some intervention studies have shown a BP-lowering effect of milk-derived peptides.[201,202] Contradictory results of prospective studies or RCTs have been reported in relation to the other components of MetS (ie, TGs or HDL-C levels).

Although more studies are warranted to clarify the metabolic effects of dairy consumption, some evidence suggests that many dairy components may contribute to beneficial effects on MetS.[191,203] For example, some studies have demonstrated that dairy calcium reduces gut fatty acid bioavailability,[204] increases lipogenesis through effects on intracellular calcium,[205] decreases BP, and increases insulin sensitivity. Besides a BP-lowering effect,[202] some peptides present in dairy products have also been shown to increase satiety through the modulation of gastrointestinal hormones.[206,207] Medium-chain fatty acids from milk improve insulin sensitivity and potentially have beneficial effects on weight.[208] The possibility that dairy-derived trans-palmitoleic acid has metabolic bioactivities has also been proposed.[191] Fermented products and some probiotic bacteria have also improved MetS components through different mechanisms.[191,203]

In summary, there is no evidence to support the existing public health advice to limit consumption of dairy products to prevent MetS. Cheese and other dairy products are, in fact, nutrient-dense foods that can give pleasure in daily meals. More high-quality research is needed to identify the role of eggs in the development

*Table 13* **Grading of the evidence and recommendations regarding dairy product and egg intake and metabolic syndrome**

| Evidence and recommendation | Grade |
|---|---|
| Evidence | |
| There is no evidence to support the existing public health advice to limit consumption of dairy products to prevent metabolic syndrome[182] | B |
| There is no evidence to limit eggs intake to prevent metabolic syndrome[193,194] | C |
| Recommendation | |
| Dairy products and particularly yogurt consumption may be useful in preventing metabolic syndrome[179,182,188] | B |

of T2DM. Table 13 shows the grading of the evidence and recommendations regarding dairy product and egg consumption and MetS.

## SWEETS, SUGAR-SWEETENED BEVERAGES, AND ARTIFICIAL SWEETENERS

Sugars, including disaccharides (sucrose) and monosaccharides (glucose, fructose), are major ingredients of processed foods.[209] Global intake of sugars is increasing as traditional diets are being replaced by Western diets high in processed foods.[210] Sugars provide energy that, if not balanced by energy expenditure from physical activity, will lead to weight gain. Adiposity is causally linked to insulin resistance, T2DM, dyslipidemia, and high BP, which are components of MetS.[211] A high intake of sugars will also increase blood glucose and insulin secretion independent of total energy intake. In this situation, insulin hypersecretion may lead to insulin resistance, T2DM, and diabetic dyslipidemia (high TGs, low HDL-C).[211]

Sugar-sweetened beverages (SSBs) are responsible for a large proportion of total sugar and energy intake in both developed and developing countries.[212] Sugar-sweetened beverages are also unique in that they are not as satiating as solid foods, which could lead to overconsumption of energy.[213,214] In meta-analyses of long-term prospective cohort studies and short-term RCTs, intakes of total sugars or SSBs are associated with weight gain or higher BMI[215–218] and greater risk of T2DM,[219–221] dyslipidemia,[222] and high BP.[222–224] Among the different sugars consumed, fructose has been singled out because it stimulates de novo lipogenesis, hypertriglyceridemia, visceral adipogenesis, and insulin resistance.[225,226] However, recent meta-analyses of controlled feeding studies suggest that fructose produces similar effects as other sugars except when fructose provides excess energy (increased weight gain, lipids) or among diabetic patients (poorer glycemic control).[227–231]

*Table 14* **Grading of the evidence and recommendations regarding sweets, sugar-sweetened beverages, and artificial sweetener intake and metabolic syndrome**

| Evidence and recommendation | Grade |
|---|---|
| Evidence | |
| Meta-analyses of long-term prospective cohort studies and short-term randomized controlled trials indicate that total sugars or sugar-sweetened beverages are associated with a greater risk of metabolic syndrome and type 2 diabetes[219–221] | A |
| Recommendation | |
| Reduce intake of sugar-sweetened beverages[240] | B |
| Replace sugar-sweetened beverages with artificially sweetened beverages[238,236] | C |
| Reduce intake of fructose versus other sugars[230,231] | C |

The role of artificial sweeteners on cardiometabolic health is an issue of great interest, with studies focusing almost exclusively on diet soda intake. Findings from prospective cohort studies have been heterogeneous,[232] including inverse,[197] null,[233,234] or direct[219,221,223,235] associations with MetS components. However, many studies were likely contaminated by individuals consuming artificially sweetened beverages in an effort to lose weight, prevent weight gain, or in response to a disease diagnosis—all of which could bias associations.[234,236,237] In 2 major RCTs in children, substituting SSBs for artificially sweetened beverages reduced weight gain and fat accumulation.[238,239]

In summary, although few long-term RCTs of sugar intake have been performed to verify the results of prospective cohort studies and short-term trials, the overall evidence suggests a reduction of dietary sugars and, in particular, SSBs protects against the development of MetS.[240] Table 14 shows the grading of the evidence and recommendations regarding consumption of sweets, SSBs, and artificial sweeteners and MetS.

## FUNCTIONAL FOODS—BIOACTIVES FOR TREATING METABOLIC SYNDROME

In addition to the time-honored dietary therapy, several single nutrients, bioactives, and "functional foods" could improve aspects of MetS. The Office of Dietary Supplements at the National Institutes of Health in the United States has defined bioactive compounds as constituents in foods or dietary supplements, other than those needed to meet basic human nutritional needs, that are responsible for changes in health status.

Although the mode of action of various functional foods differ, many share a common mechanistic principle. Glucose uptake in liver, muscle, and adipose tissue is inhibited due to insulin resistance, muscle metabolic flexibility decreases, hepatic lipid handling is "blunted," and

vascular flexibility decreases, resulting in loss of cholesterol homeostasis and inflammatory control. Actually, MetS is characterized by a systemic loss of flexibility (phenotypic flexibility).[241] The mode of action of many bioactive nutritional compounds potentially effective against MetS is related to restoring or optimizing these mechanisms. Again, under maintained metabolic stress, these compounds will perform better than many pharmacological strategies that are directed at MetS manifestations but that do not restore flexibility or sensitivity.[242] Also, these compounds may be used in a personalized manner as, within the spectrum of MetS, many different subtypes and subgroups manifest. Often apparently conflicting results were observed between studies in meta-analyses, suggesting that confounding factors (eg, choice of study population, type of diet) influence the results. Finally, many studies show temporal effects, suggesting compensatory mechanisms. Taken together, this suggests that (1) whole food/dietary interventions that contain high amounts of multiple classes of food bioactives and also address caloric imbalance are more effective and preferred above strategies involving single bioactives, and (2) single-bioactive strategies may be especially effective for specific MetS components.

A well-known example of a food bioactive demonstrating an effect on a MetS component is salt (sodium) in relation to BP, where genetic polymorphisms codetermine the efficacy.[243,244] Given the association between high sodium intake and elevated BP,[245] salt reduction could decrease BP in patients with MetS. A reduced intake of sodium may be particularly beneficial in individuals with MetS because both obesity and insulin resistance relate to salt sensitivity.[246] Other factors affecting the correlation of salt sensitivity with BP are advanced age, black race, diabetes, and chronic kidney disease.[247] Both a healthy dietary pattern, as exemplified by the DASH diet, and reduced sodium intake independently reduce BP.[112] However, the BP-lowering effect is even greater when these dietary changes are combined. Carnitine facilitates fatty acid oxidation and, as such, was shown to be effective in reducing fatty liver, a feature of MetS.[248,249] Similarly, choline, as a precursor for phosphatidylcholine, is essential for hepatic very-low-density lipoprotein synthesis and, thus, could be beneficial for the hypertriglyceridemia component of MetS.[250,251]

## INFLUENCE OF CHRONOBIOLOGY ON METABOLIC SYNDROME

Several health concerns have emerged in modern society, including (1) an increase in the incidence of obesity and MetS and (2) a progressive loss of sleep associated with an increase in the incidence of chronodisruption. The term chronodisruption refers to the desynchronization of 24-hour rhythms with adverse health effects.[252] Human chronodisruption may be a consequence of nocturnal feeding, excessive exposure to light at night, or instability of exposure to environmental synchronizers, among other factors.[253] Clinical and epidemiological studies over the last few years coupled with a large body of evidence have shown the interaction between the circadian system and different MetS components such as impairment of carbohydrate and lipid metabolism, adipose tissue function, and heart, vascular and hemostatic function.[253] Moreover, epidemiological studies show that shift work is associated with obesity, hypertriglyceridemia, low HDL-C, abdominal obesity, T2DM, and CVD.[254] Experiments performed in animal models and in tissue culture[255,256] are contributing to a deeper knowledge of the relationship between chronobiology and MetS.[257]

Although there is an effect of the endogenous circadian clock on multiple human metabolic pathways,[258] modifications of sleep or other external synchronizers of the internal clock, such as light intensity, and changes from fasting to eating and from resting to activity may alter the circadian system. In principle, whatever allows the establishment of temporal organizational order should also be capable of disrupting such order when present or applied in excess or deficit and, most importantly, at unusual and inappropriate times. Several studies performed in experimental animals have demonstrated that when animals eat at the "wrong time" they become obese.[259] Moreover, a recent randomized, crossover clinical study has demonstrated that eating late is associated with several metabolic alterations.[260] Sleep is not a clear "output" of our internal clock. However, it is modifiable by the subject and, because it can also change the individual exposure to the external synchronizers such as light, it is able to influence the internal clock function.[261] Other factors such as inadequate hours of physical activity may also alter the circadian system. Indeed, physical activity acts as an "input" of the circadian timing system.[262] Studies have suggested that scheduled physical activity can alter circadian rhythms[263]; for example, physical activity performed in the late evening might not be as beneficial as in the morning.[262] Table 15 shows the grading of the evidence and recommendations regarding chronobiology and MetS.

## SUMMARY OF LIFESTYLE MEASURES AND HEALTHY FOOD CHOICES FOR MANAGING METABOLIC SYNDROME

Lifestyle interventions are the initial strategies for the prevention and treatment of MetS. In this report, the available scientific evidence on the associations between lifestyle changes and MetS and its components are identified (Box 2 and Table 16) with the goal of deriving

*Table 15* **Grading of the evidence and recommendations regarding chronobiology and metabolic syndrome**

| Evidence and recommendation | Grade |
|---|---|
| Evidence | |
| Shift workers face potential health problems. Overall, those who work night or rotating shifts seem to have a higher risk of insulin resistance, metabolic syndrome, and heart disease[254,257] | B |
| Recommendation | |
| Avoid intense light exposition during night time and sleep in total darkness when possible[261] | B |
| Eat the main meal of the day before 3 PM[260] | B |

*Box 2* **Lifestyle recommendations for management of metabolic syndrome**

- Smoking cessation
- 30–60 min of daily physical activity
- For overweight and obese patients with metabolic syndrome: a doctor-prescribed healthy diet designed to achieve 5% weight loss
- Plant-based Mediterranean diet, with or without energy restriction, Dietary Approaches to Stop Hypertension diet, or vegetarian diet as a component of the treatment strategy
- Specific dietary recommendations include:
  - Limit saturated and trans fats and increase dietary fiber
  - Reduce intake of sugar-sweetened beverages
  - Moderate alcohol intake
  - Restrict salt intake

recommendations for the prevention and management of MetS. In overweight or obese individuals, weight loss through calorie restriction and increased physical activity, which must be individualized based on fitness level and comorbidities, is essential for preventing MetS or treating the condition when present. Regarding the dietary approach to prevention and treatment, over the last decade, research in nutritional epidemiology has moved from the single food approach to the dietary pattern strategy, which better reflects the complexity of interactive effects of multiple nutrients on health status.[264,265] A MedDiet pattern, with or without energy restriction, can be recommended for all people with MetS as an effective component of the treatment strategy. This dietary pattern should be built upon an increased consumption of unsaturated fat, primarily from olive oil (range of 20–40 g/d), and should emphasize the consumption of a variety of legumes, cereals (whole grains), fruits, vegetables, fish, nuts, and dairy products, as well as a moderate consumption of alcohol (red wine and/or beer). Indeed, in isolation and independent of the background diet, increased consumption of all of the abundant foods in the MedDiet has shown a beneficial effect on MetS components. Other dietary patterns (DASH, new Nordic, and vegetarian diets) have also been proposed as alternatives to the MedDiet for preventing MetS. Quitting smoking and reducing intake of sugar-sweetened beverages and meat and meat products are mandatory to prevent and treat MetS. Advances in the field of chronobiology and nutrigenetics are expected to open new paths in the realm of customized diets for MetS prevention.[266] The inconsistencies and gaps in evidence described here suggest that additional research is needed to refine the most appropriate therapies for MetS.

*Table 16* **Foods, nutrients, and dietary patterns in the prevention of metabolic syndrome**

| Dietary component | Unfavorable | Favorable |
|---|---|---|
| Foods | Sugar-sweetened beverages<br>Meat products<br>Excessive alcoholic intake | Fruits and vegetables<br>Legumes and cereals (whole grains)<br>Moderate intake of red wine and beer<br>Olive oil<br>Fish<br>Nuts<br>Low-fat dairy products |
| Nutrients | Sucrose, fructose<br>Salt<br>Saturated fatty acids<br>Trans fatty acids | Fiber<br>Unsaturated fatty acids<br>Bioactives: carnitine and choline |
| Dietary patterns | Western diet | Mediterranean diet, Dietary Approaches to Stop Hypertension diet, new Nordic diet, vegetarian diets |

## CONCLUSION

A healthy lifestyle is critical to prevent or delay the onset of MetS in susceptible individuals and to prevent CVD and T2DM in those with MetS. The recommendations presented here should help patients and clinicians understand and implement the most effective approaches for lifestyle change to prevent MetS and improve cardio-metabolic health.


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