LIFESTYLE RECOMMENDATIONS FOR THE PREVENTION AND MANAGEMENT OF METABOLIC SYNDROME: AN INTERNATIONAL PANEL RECOMMENDATION

Authors: Pablo Pérez-Martínez[1,2], Dimitri P. Mikhailidis[3], Vasilios G. Athyros[4], Mónica Bullo[5,2], Patrick Couture[6], María I. Covas[7,8,2], Lawrence de Koning[9], Javier Delgado-Lista[1,2], Andrés Díaz-López[5,2], Christian A. Drevon[10], Ramón Estruch[11,2], Katherine Esposito[12], Montserrat Fitó[7,2], Marta Garaulet[13], Dario Giugliano[12], Antonio García-Ríos[1,2], Niki Katsiki[4], Genovefa Kolovou[14], Benoît Lamarche[6], Maria Ida Maiorino[12], Guillermo Mena-Sánchez[5,2], Araceli Muñoz-Garach[15,2], Dragana Nikolic[16], José M. Ordovás[17,18], Francisco Pérez-Jiménez[1,2], Manfredi Rizzo[16], Jordi Salas-Salvadó[5,2], Helmut Schröder[7,19], Francisco J. Tinahones[15,2], Rafael de la Torre[20,2], Ben van Ommen[21], Suzan Wopereis[21], Emilio Ros[22,2†], José López-Miranda[1,2†]

[†]These authors contributed equally to this work.

Affiliations:

[1] Lipid and Atherosclerosis Unit, IMIBIC/Reina Sofia University Hospital/ University of Cordoba, Cordoba, Spain.

[2] CIBER Fisiopatologia Obesidad y Nutricion (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain.

[3] Department of Clinical Biochemistry, Royal Free Hospital Campus, University College London Medical School, University College London (UCL), London NW3 2QG, UK.

[4] Second Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, Hippokration Hospital, Thessaloniki, Greece.

[5] Human Nutrition Unit, Biochemistry Biotechnology Department, Faculty of Medicine and Health Sciences, Hospital Universitari de Sant Joan de Reus, IISPV, Universitat Rovira i Virgili, Reus, Spain.

[6] Institute on Nutrition and Functional Foods, Laval University, Quebec, Canada.

[7] Cardiovascular Risk and Nutrition Research Group, Hospital del Mar Research Institute (IMIM), Barcelona, Spain.

[8] NUPROAS (Nutritional Project Assessment) Handesbolag (NUPROAS HB), Nackă, Sweden.

[9] The Departments of Pathology and Laboratory Medicine, Pediatrics, and Community Health Sciences. University of Calgary, Alberta, Canada.

[10] Department of Nutrition, Institute of Basic Medical Sciences, Faculty of Medicine, University of Oslo, Oslo, Norway.

[11] Department of Internal Medicine, Hospital Clínic, Institut d'Investigacions Biomédiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain.

[12.]Division of Endocrinology and Metabolic Diseases, Second University of Naples Diabetes Unit, Second University of Naples, Naples, Italy.

[13]Chronobiology laboratory, Department of Physiology, University of Murcia and Research Biomedical Institute of Murcia (IMIB), Murcia, Spain.

[14]1st Cardiology Department, Onassis Cardiac Surgery Center Athens, Greece

[15]Servicio de Endocrinologia y Nutricion, Hospital Clinico Virgen de la Victoria, Malaga, Spain.

[16]Biomedical Department of Internal Medicine and Medical Specialties, University of Palermo, Italy.

[17]Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging, Tufts University School of Medicine, Boston, MA, USA.

[18]Department of Epidemiology, National Center of Cardiovascular Investigations, Madrid, Spain; and Madrid Institute of Advanced Studies–Food, Madrid, Spain

[19]CIBER de Epidemiologia y Salud Pública, Madrid, Spain.

[20]Human Pharmacology and Clinical Neurosciences Research Group, IMIM, Barcelona, Spain

[21]TNO, Zeist, The Netherlands

[22]Lipid Clinic, Endocrinology and Nutrition Service, IDIBAPS, Hospital Clínic, Barcelona, Spain.

***Corresponding author**: Pablo Perez-Martinez, Reina Sofia University Hospital, Lipids and Atherosclerosis Research Unit. Avda. Menéndez Pidal, s/n. 14004 Córdoba, Spain. e-mail: h02pemap@uco.es

Abstract

The importance of metabolic syndrome (MetS) is its associated risk of cardiovascular disease (CVD) and type-2 diabetes (T2DM), as well as other harmful conditions such as non-alcoholic fatty liver disease (NAFLD). In this report, the available scientific evidence on the associations between lifestyle changes and MetS and its components is reviewed to derive recommendations for its prevention and management. Weight loss through an energy-restricted diet together with increased energy expenditure in physical activity contributes to preventing and treating MetS. A Mediterranean-type diet, with or without energy restriction, is an effective treatment component. This dietary pattern should be built on the basis of an increased intake of unsaturated fat, primarily from olive oil, and emphasizes 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 (DASH, New Nordic and vegetarian diets) have also been proposed as alternatives for preventing the MetS. Quitting smoking and reducing intake of sugar sweetened beverages and meat and meat products are mandatory. Nevertheless, there are also 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 CVD and T2DM in those with the established syndrome. These recommendations should help patients and clinicians to

understand and implement the most effective approaches for lifestyle change to prevent the MetS and improve cardio-metabolic health.

Key words: metabolic syndrome, dietary pattern, lifestyle, panel recommendation

1. Introduction

The metabolic syndrome (MetS) is a constellation of risk factors reflecting over nutrition 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 health care 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 non-alcoholic fatty liver disease (NAFLD). Currently there is no effective preventive approach beyond a lifestyle based intervention 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, available evidence suggests beneficial effects on MetS of different nutrients, foods and dietary patterns, with improved metabolic profiles both in the presence or absence of weight loss, but without a definitive agreement on which is the best nutritional approach[1-3]. Thus, a position statement will update and focus current thinking on the role of lifestyle recommendations for the management of MetS.

The following levels of evidence (grades) will be used to summarize available scientific evidence and 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

C - Expert consensus/opinion or clinical experience

The information presented in this statement 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 cardio-metabolic health in MetS.

1.1. Definition of MetS

In the absence of a single definition, several closely related but individual definitions have been proposed for the MetS. In 2001 the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), defined MetS when ≥3 of the following risk factors occurred together: abdominal obesity, atherogenic dyslipidemia, hypertension or insulin resistance[4]. The International Diabetes Federation (IDF) 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 or elevated fasting plasma glucose[5]. The American Diabetes Association (ADA) in conjunction with the European Association for the Study of Diabetes (EASD) stated that there was no need for the term MetS because all its associated factors are treated individually once diagnosed[6]. The debate over the use of the term MetS continues as commented by the World Health Organization (WHO)[7]; what is not disputed is that the factors underlying the MetS are increasing worldwide. In 2005, the American Heart Association (AHA)/National Heart, Lung and Blood Institute (NHLBI) also suggested criteria for diagnosis of the MetS[8]. Finally, in 2009, there has been an attempt to reconcile existing definitions[9]. This integrated definition of the MetS assigns equal levels of importance to all 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 reaching epidemic proportions. In Western countries the estimated prevalence of MetS is about 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, or ethnicity, as well as the definition used.

2. Wine, Alcohol and MetS

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 reported 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/day for women and <40 g/day for men). With respect to the type of alcoholic beverages, whereas some authors have not found differences in MetS rates among consumers of different alcoholic drinks, others have reported lower rates among wine and beer drinkers[20,21]. In the PREDIMED (PRevención con DIeta MEDiterránea) trial, which included 7,447 participants at high CV risk, moderate wine drinkers (≥1 drink(s)/day) showed a reduced risk of prevalent MetS by 44%, compared with non-drinkers. 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, participants under 70 years of age and former or

current smokers[22]. Similarly, in the Life Lines Cohort Study that included 64,046 participants, the overall metabolic profile of wine drinkers was better than that of non-drinkers 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 non-drinkers. A long-term randomized intervention trial including 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 a lower prevalence of the MetS and 4 of it 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 MetS and alcohol exposure. Thus, intervention studies are needed to evaluate the potential benefit of moderate wine and beer intake in mitigating the MetS and 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.

3. Smoking and the MetS

A meta-analysis of 13 prospective cohort studies with 56,691 participants and 8,688 MetS cases demonstrated that active smokers have a 26% increased risk of MetS compared with non-smokers[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 concerns both genders (odds ratio (OR) 1.7-2.4 for men, 1.8-2.3 for women; all $p<0.001$) 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 (MESA) with 5,913 participants the prevalence of MetS was similar among 3 groups with different smoking status[33]. The prevalence of MetS risk factors (except impaired fasting glucose) differs among current, former and non-smokers. The Coronary Artery Risk Development in Young Adults (CARDIA) study with 4,192 participants reported 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 theoretically might lower 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 (CRP) have been shown to be elevated in smokers compared with non-smokers[36]. Low HDL-C and increased TGs are frequently present due to an increased release of FFAs as a consequence of lower lipoprotein lipase activity, higher HMG-CoA reductase activity and higher glucose-6-phosphatase dehydrogenase activity leading to increase hepatic VLDL synthesis[37]. Also, in current smokers the higher prevalence of increased WC despite lower BMI is attributable to increased cortisol production leading 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 MESA study[33], however, reported that smokers had a lower prevalence of insulin resistance compared with non-smokers, probably because of a lower BMI. Nevertheless, when adjusted for BMI, smokers were at a higher risk of MetS than non-smokers.

3.1. 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 subjects who smoked ≥20 cigarettes/day and for over 20 years in those who smoked ≥40 cigarettes/day. In this context, in an adult Porto-Rican population, Calo et al.[39] found that the MetS was more prevalent in former smokers (48.4%) compared with current (42.7%) and non-smokers (40.0%). Another study including 4,542 men without MetS at baseline who were followed for an average of 3 years also showed this pattern (8.0% in non-smokers, 7.1% in new smokers, 17.1% in ex-smokers and 13.9% in current smokers)[40]. In contrast, other authors[41] found no differences between smokers and non-smokers 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 involving 5,898,795 participants and 295,446 incident cases of T2DM, Pan et al. found that the risk of developing diabetes increased in recent quitters, but decreased noticeably as time passed after smoking cessation[42].

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

4. Physical activity and MetS

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 the MetS the excess amount of energy accumulated in adipose tissue and also stored ectopically in non-adipose tissues like the liver will cause metabolic disturbances leading 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 our knowledge on how long, what type and during what periods of life we should exercise, the available scientific evidence can be summarized as follows[50-54]:

- Increase physical activity based on observational studies of people with different levels of physical inactivity[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 min.
- 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 the 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.

5. MetS and weight control

Obesity and MetS are intimately related. Therefore, it is 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: 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 (sdLDL), NAFLD (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].

Obesity has traditionally been defined by the body mass index (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 since 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 tells us that 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](see below)

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 MetS components BP, HDL-C, TGs and blood glucose. Weight loss or medications (e.g. metformin or pioglitazone) can increase insulin sensitivity. In turn, weight loss can be assisted by lifestyle measures and medication [e.g. Contrave (naltrexone + bupropion), liraglutide, orlistat, lorcaserin and Qsymia (phentermine + topiramate)][68]. Bariatric surgery can be used for the morbidly obese or 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 they are not directly related to obesity or MetS. These 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.

6. Influence of diet on the MetS

6.1. Mediterranean diet and MetS

The term “Mediterranean Diet” refers to the traditional dietary pattern of countries in the Mediterranean basin. It is a plant-based diet, including consumption of sizable quantities of fruits, vegetables, whole grain cereals, legumes, nuts, and olive oil as principal source of fat. It also includes fish and poultry in low to moderate amounts, a relatively low consumption 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 as the total fat content ranges from 35-45% of energy, but most fat is unsaturated

because olive oil is used abundantly in the kitchen and at the table. As the MedDiet has been consistently shown to be a cardioprotective diet[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 the 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 non-adherence[79]. Moreover, the MedDiet showed beneficial effects on the MetS components 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, the MetS has been associated in both sexes 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 benefit on MetS[75,82,83]. Adoption of the MedDiet may be important for both prevention and resolution of the MetS. It is not by chance that this dietary pattern has been 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.

6.1.2. Olive oil (OO) and MetS. OO is probably the most representative component of the MedDiet. As discussed above, the OO-rich MedDiet reversed MetS status in several RCTs[75,76,84] and reduced its incidence in observational studies[79]. Here, we will focus on the available evidence from RCTs concerning the benefits of OO at doses from 20 to 50 g/day, independently of the background diet, on MetS and its individual features. Virgin and extra-virgin OO has as a major component oleic acid, a monounsaturated fatty acid (MUFA), but also contains minor components with

bioactive properties[85]. MUFA consumption promotes beneficial blood lipid profiles, improves insulin sensitivity, and regulates blood glucose levels[86-88]. Dietary OO and virgin OO, in contrast to 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 OO 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 the MetS[92,93]. Oxidative stress is associated with the number of components of the MetS[93]. MUFA-rich diets are more effective than those rich in PUFA for reducing the resistance of LDL to oxidation[94]. OO consumption decreased in vivo HDL oxidation, which would impair HDL function (i.e. cholesterol efflux from cells)[95]. The beneficial effect of OO on inflammation[96] could be conveyed through a transcriptomic effect by decreasing the expression of pro-inflammatory genes[97,98].

Minor components of OO also play a beneficial role in MetS. Pomace olive oil, rich in triterpenes, decreased postprandial TG-rich lipoproteins[99]. Compared with a low-phenolic OO, virgin OO, 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-cholesterol efflux related-genes[102,103].

These results indicate that OO 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 OO without increasing the total number of calories/day. On the basis of the health claims authorized by the United States FDA and the European Food Safety Authority (EFSA), the recommended daily quantities are conservative: 23 g/d (2 tablespoons) for OO[104] and 20 g/d for phenolic-rich virgin OO[105], respectively. In the PREDIMED study, daily consumption of virgin OO 35-45 g/d for 5 years within the frame of a MedDiet pattern reversed MetS, mainly by reducing abdominal adiposity[76]. LDL oxidation was also decreased by the MedDiet enriched with OO[106]. In the EUROLIVE study,

conducted in different European countries, consumption of 25 mL/d (22 g/d) of any type of unheated OO 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 OO administered[102,107]. Recommended daily doses of OO as the main source of dietary fat in American and European Nutritional Guidelines range from 30 to 78 g/day depending on body weight[108]. Thus, OO doses around 40-45 g/day for culinary use and dressing vegetables and around 20-25 g/day for non-culinary 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 OO and MetS.

6.2. Dietary patterns and MetS: beyond the MedDiet

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

6.2.1. Western-type diets. Consumption of Western diets characterized by high intakes of red meat, processed foods, refined grain, sugars and saturated fatty acids was 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 (ARIC) study indicated an 18% greater risk of incident MetS for participants with the highest Western dietary pattern score[111].

6.2.2. The Dietary Approaches to Stop Hypertension (DASH) diet. The 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 subjects following a DASH

diet[113]. More recently, a cross-sectional analysis conducted in Iranian women suggested that participants 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].

6.2.3. 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 adult subjects with MetS were randomized to a Nordic diet or a control diet for 18-24 week periods. The lipid profile improved significantly after the intervention diet, whereas changes in body weight, insulin sensitivity and BP were not statistically significant[116].

6.2.4. 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 on British vegetarians. In a cross-sectional analysis of 773 subjects from the Adventist Health Study-2, a vegetarian dietary pattern was associated with a significantly lower risk of prevalent MetS than a non-vegetarian diet[117]. The protective effect of vegetarian diets on MetS has also been observed in other epidemiological studies conducted mostly in Asian populations, but is not consistent[118]. No RCTs testing the effect of vegetarian diets on MetS or its components are available.

6.2.5. Other dietary patterns. Other dietary patterns with a high carbohydrate content and 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.

6.3. Legumes and the MetS

Legumes, seeds that are rich in protein, complex carbohydrates, fiber, and various bioactive micronutrients, have been tested in several RCTs for effects on blood glucose regulation. They reduced postprandial blood glucose and insulin excursions, an effect 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 subjects 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 increasing 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 on legumes and MetS.

6.4. Cereals and MetS

Cereals and 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 maintain energy balance. Several epidemiologic studies have assessed the association of MetS with dietary fiber, mainly derived from cereal consumption, concluding 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. Subjects in the highest tertile of cereal fiber intake had lower odds of MetS compared with those in the lowest tertile (OR = 0.73, 95% CI = 0.52-0.97), but the association was no longer significant after adjusting for confounders[124]. There are few long-term studies examining the relation between breakfast cereal consumption and diabetes risk. There is some evidence supporting the role of breakfast cereals, especially those higher in fiber, in the management of T2DM, but the evidence is not strong[134]. Evidence examining the relation between breakfast cereals and hypertension is limited. The most convincing evidence comes from the Physicians' Health Study[135], where a 19% reduction in hypertension risk with daily breakfast cereal consumption and a stronger relation with whole-grain than with refined-grain cereals were observed. The authors suggested that a number of components in cereals, including folate, magnesium, potassium and fiber, may be responsible for this effect. However, these results were obtained in 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.

6.5. Fruits, vegetables and MetS

Consumption of fruits and vegetables (F/V) has been shown to have favorable effects on a wide spectrum of clinical outcomes and, to that extent, most guidelines emphasize their importance. Indeed, the cardio-metabolic 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 F/V. However, because they are complex food patterns, the specific contribution of the F/V component to attenuating the risk of MetS cannot be determined and the epidemiological evidence relating F/V intake to incident MetS is relatively scarce. Epidemiological studies conducted mostly in Asian populations have reported a more favorable cardio-metabolic 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 F/V intake. However, a meta-analysis of 5 prospective studies has shown that total F/V intake, but not fruit or vegetable taken individually, 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 F/V intake 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 and data must therefore be interpreted with caution. Increasing consumption of F/V from 1 to 6-7 servings/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 F/V consumption may reduce the risk of MetS. Beyond differences in study designs, factors such as duration of intervention and “doses” of F/V investigated need to be considered when trying to reconcile data from epidemiology and clinical trials. “Displacing” potentially unhealthy foods with F/V in the diet also needs consideration when assessing the potential effect of F/V intake on MetS and health in general. Although increased consumption of F/V appears to be a justifiable and logical recommendation to manage the risk of MetS, further investigations are warranted to establish the extent to which F/V intake specifically contribute 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 F/V intake and MetS.

6.6. Fish and MetS

Consistent evidence from epidemiologic studies indicates that consumption of fish (especially fatty fish) or intake of fish oil supplements rich in omega-3 fatty acids relates to CV protection, especially coronary heart disease (CHD) mortality[141]. RCT evidence, however, is controversial[142]. Several studies have also shown benefits 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 the MetS compared with dietary patterns in which consumption of potatoes, meat and alcohol predominated in a Greek population sample[144] and was inversely associated with the risk of hypertriglyceridemia and MetS in a Korean population[145]. Further, 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 wholegrain products improved endothelial dysfunction and inflammation in overweight and obese individuals[147] and decreased MetS risk[148]. In a 4-year prospective Korean study, a high consumption of fish and n-3 fatty acids resulted in a lower MetS risk among men, but not among women[149]. Adherence to a n-3 fatty acid/fish dietary pattern showed a significant inverse association with MetS among Porto-Ricans living in the US[150], but other nutrients in fish might have influenced this effect. Also, consumption of lean fish at least 4 times/week reduced BP in CHD patients in a small 8-week RCT[151]. In The WISH-CARE RCT, which included 273 individuals with the MetS[152], an 8-week dietary intervention (with 100 g/day of white fish compared with no fish or seafood) resulted in a reduction of LDL-C, WC and BP. Also, an 8-week consumption of fatty fish 4-5 times/week decreased potential mediators of lipid-induced insulin resistance and inflammation[153], while fatty fish meals may be associated with improved glucose metabolism[154]. Further, fish oil consumption for 4

weeks improved lipid metabolism in subjects with MetS[155]. However, incorporating sardines daily to the diet of drug-naïve 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 reduced blood glucose, insulinemia and insulin resistance in women with the MetS[158], and such benefits may be seen even with a 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 subjects 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 omega-3 fatty acids and the MetS[163]. A recent review[164] concludes that long-chain n-3 PUFA 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 acids to improve MetS and its components. Nevertheless, as reviewed[165], there is little evidence that consumption of fish of any type or long-chain n-3 PUFA intake 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 omega-3 fish oils intake and MetS.

6.7. Other diet features that can influence the MetS

6.7.1. Nuts and MetS

Nuts (tree nuts and peanuts) are high-energy, nutrient-dense seeds made of complex matrices, rich in unsaturated fatty acids, fiber, non-sodium 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 diabetes[166]. Indeed, nut consumption has been consistently related to protection from fatal and nonfatal CHD, as shown in a recent meta-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 shows a protective effect of nuts on hypertension[168]. Many RCTs have compared the effects of nut-enriched diets *vs* 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 when they were elevated at baseline[169]. Although nuts are energy-dense foods, a previous meta-analysis of 31 RCTs showed small non-significant associations of nut consumption with reduced, not increased, adiposity measures (body weight, BMI and WC)[170]. The fact that, besides reducing CHD risk, nut consumption has a favorable effect on T2DM, BP and TGs and tends to be associated with reduced visceral adiposity, which all are MetS criteria, suggests that nuts might have a beneficial impact on MetS itself.

A recent meta-analysis of 49 RCTs with nuts included 2,226 participants and reported that at least one criterion of MetS shows a benefit through 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 considering the effect of nut consumption on the MetS proper, data from 3 large epidemiologic studies suggest a beneficial effect[172-174]. Thus, a 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 related to lower incident MetS in the prospective Seguimiento Universidad de Navarra cohort of Spanish university graduates[173] and to lower prevalent MetS in a cross-sectional report from the U.S. National Health and Nutrition Examination Survey for

2001–2004[174]. One of the intervention arms in the PREDIMED trial consisted of advice on a Mediterranean diet supplemented with one daily serving of mixed nuts. In a preliminary report of the PREDIMED cohort after intervention for 1 year, participants in the group receiving supplementary nuts significantly reduced the prevalence of MetS by 14%, 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=3,392) who were allocated to Mediterranean diet with nuts had a 28% higher rate of reversion of MetS compared with those in the control diet group, and this beneficial effect was driven mainly be reduced WC[76]. Of note, a similar beneficial effect was observed with the Mediterranean diet enriched with extra-virgin OO.

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

6.7.2. Dairy products, eggs and MetS

Several epidemiological studies have investigated the association between dairy product consumption and the risk of cardiometabolic disease; however little is known about the possible effects of eggs. Regarding the 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 one 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 a 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. Introduced biases 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 are limitations of epidemiologic studies that compound the results.

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 two 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 including 3 large cohorts (Nurses Health Study I and II and Health Professionals Follow-up Studies), yogurt consumption related inversely to diabetes incidence (18% lower risk of T2DM per 1 serving of yogurt)[186]. After this meta-analysis, two 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, including 579,832 subjects and 43,118 T2DM cases, showed a 3% and 4% lower risk diabetes per 200 g/day of total and low-fat dairy products consumed, respectively[188]. This meta-analysis, also showed a non-linear inverse relationship between yogurt consumption and risk of T2DM, revealing a 14% lower risk when yogurt consumption was 80-125 g/day, 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 have 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.

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 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 the 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 the MetS (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 have potential 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 on the development of T2DM. Table 13 shows the grading of the evidence and recommendations regarding dairy products and eggs intake and MetS.

7. 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 the 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]. SSBs 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].

The role of artificial sweeteners on cardio-metabolic 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 two major RCTs in children, substituting SSBs for artificially sweetened beverages reduced weight gain and fat accumulation[238,239].

In summary, while 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 supports the reduction of dietary sugars and, in particular, SSBs to protect

against the development of the MetS[240]. Table 14 shows the grading of the evidence and recommendations regarding intake of sweets, sugar-sweetened beverages and artificial sweeteners and MetS.

8. Functional foods – bioactives for treating MetS

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 NIH has defined bioactive compounds as constituents in foods or dietary supplements, other than those needed to meet basic human nutritional needs, which are responsible for changes in health status.

Although the mode of action functional foods differs, 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 directed to 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, in meta-analyses, apparently conflicting results were observed between studies, suggesting that "confounding factors" (choice of study population, type of diet, etc.) 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 single bioactive strategies, and, 2) single bioactive strategies may especially be effective for specific MetS components.

Well-known examples of food bioactives effective on MetS components are salt (sodium) in relation to BP, where genetic polymorphisms co-determine the efficacy[243,244]. Given the association between sodium intake and BP[245], its reduction could decrease BP in patients with MetS. A reduced intake of sodium may be particularly beneficial in individuals with the MetS, probably because both obesity and insulin resistance relate to salt sensitivity[246]. Other correlates of salt sensitivity of BP are advanced age, black ethnicity, 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 precursor for phosphatidylcholine, is essential for hepatic VLDL synthesis and thus could be beneficial for the hypertriglyceridemia component of MetS[250,251].

9. Influence of chronobiology on MetS

In modern society, two health concerns have emerged: an increase in the incidence of obesity and MetS and a progressive loss of sleep associated with an increase in the incidence of chronodisruption. This term suggests that rhythms over 24 h can become desynchronized with adverse health effects[252]. Human chronodisruption may be a consequence of nocturnal feeding, excessive exposure to light at night, and 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.

10. Summary of lifestyle measures and healthy food choices for managing MetS

Lifestyle interventions are the initial strategies for the prevention and treatment of the MetS. In this report, available scientific evidence on the associations between lifestyle changes and MetS and its components are identified (Table 16 and Table 17) to derive

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 and comorbidities, is essential for preventing the MetS or treating the condition when present. Regarding the dietary approach, in the last decade, research in nutritional epidemiology has moved from the single food approach to the dietary pattern, 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 on the basis of an increased consumption of unsaturated fat, primarily from OO (range from 20-40 g/day), and emphasizes 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 independently of the background diet, increased consumption of all the foods that abound 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 for preventing MetS. Quitting smoking and reducing intake of sugar sweetened beverages and meat and meat products are mandatory to prevent and treat the MetS. Advances in the field of chronobiology and nutrigenetics are expected to open new paths in customized diets for MetS prevention[266]. We also identified inconsistencies and gaps in the evidence, suggesting that additional research is needed to refine 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 CVD and T2DM in those with MetS. These recommendations should help patients and clinicians to understand and implement the most effective approaches for lifestyle change to prevent the MetS and improve cardio-metabolic health.

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Declarations of interest

PPM, DPM, VGA, MB, PC, MIC, LK, JDL, ADL, CAD, RE, KE, MF, MG, DG, AGR, NK, GK, BL, MIM, GMS, AMG, DN, JMO, FPJ, MR, JSS, HS, FJT, RT, BVO, SW, JLM declare that they have no competing interests. ER has received grants for research through his institution from the California Walnut Commission and is a nonpaid member of its Scientific Advisory Board. BL has received funding from the CIHR, NSERC, Agriculture and Agrifood Canada, the Canola Council of Canada, Dairy Farmers of Canada (DFC), Dairy Research Institute (DRI), Atrium Innovations, the Danone Institute and Merck Frosst.

TABLES

Table 1: Grading of the evidence and recommendations regarding alcohol consumption.

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

Table 2: Grading of the evidence and recommendations regarding smoking.

Evidence	**Grade**
Smoking increases the risk of MetS[30-32]	B

There is an increased risk of developing MetS after quitting smoking[38-40]	B
Recommendation	
Stop smoking to prevent and treat MetS. Smokers unable to quit smoking should be referred to a smoking cessation clinic[42]	A
Obese and overweight subjects should adopt a calorie-restricted diet after quitting smoking[44,45] United States Federal Drug Administration (FDA)-approved medications for smoking cessation may be considered to decrease post-cessation weight gain.	B C

Table 3: Grading of the evidence and recommendations regarding physical activity.

Evidence	**Grade**
Physical activity has substantial beneficial effects on MetS[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

Table 4: Grading of the evidence and recommendations regarding weight control.

Evidence	**Grade**
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 MetS[66,67]	A

Table 5: Grading of the evidence and recommendations regarding the Mediterranean diet (MedDiet) and MetS.

Evidence	**Grade**
Mediterranean diet can be a useful strategy for preventing cardiovascular diseases and diabetes in subjects with MetS[75-77,79]	B
Recommendation	
Mediterranean diet, with or without energy restriction, can be recommended for all people with MetS as an effective component of the treatment	B

strategy[76,77,79]	
Minimally processed, seasonally fresh, and locally grown foods are preferred[73,74]	C

Table 6: Grading of the evidence and recommendations regarding olive oil (OO) and MetS.

Evidence	**Grade**
OO in replacement of other fats is useful for MetS prevention and management[85-87]	B
Recommendation	
Daily consumption of OO at doses of 20-40 g/day in replacement for other fats is useful in the prevention and treatment of MetS[76,104,105,108]	A

Table 7: Grading of the evidence and recommendations regarding some diets and MetS.

Evidence	**Grade**
Western dietary patterns are detrimental for MetS and its components[109,111]	B
The DASH diet improves several components of the Mets[112-115]	A
Other dietary approaches such as the New Nordic diet or vegetarian diets are potentially effective to modulate MetS components[116]	B
Recommendation	
The DASH diet, New Nordic diet, and plant-based/vegetarian diets can be recommended for people with MetS as an effective component of the treatment strategy[109,111-116]	B

Table 8: Grading of the evidence and recommendations regarding legumes and MetS.

Evidence	**Grade**
Eating a variety of legumes is beneficial in the prevention and management of MetS[124-129]	B
Recommendation	
Daily consumption of legumes is recommended to improve cardiometabolic risk factors[128,129,131]	A
Legumes can be recommended for people with MetS as an effective component in prevention and management of diabetes and CVD[121-124,131]	A

Table 9: Grading of the evidence and recommendations regarding cereals and MetS.

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

Table 10: Grading of the evidence and recommendations regarding fruit/vegetables (F/V) intake and MetS.

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

Table 11: Grading of the evidence and recommendations regarding fish and omega-3 (n-3) fish oils intake and MetS.

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

Table 12: Grading of the evidence and recommendations regarding nuts intake and MetS.

Evidence	Grade
There is epidemiological and clinical trial evidence of a salutary effect of nut consumption on MetS components and on the full syndrome itself[76,172-174]	B
There is an added cardiometabolic 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 LDL cholesterol and	A

cardiometabolic risk[76,84,166-169,172-174]	

Table 13: Grading of the evidence and recommendations regarding dairy products and eggs intake and MetS.

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

Table 14: Grading of the evidence and recommendations regarding sweets, sugar-sweetened beverages (SSBs) and artificial sweeteners intake and MetS.

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

Table 15: Grading of the evidence and recommendations regarding chronobiology and MetS.

Evidence	**Grade**
Shift workers face potential health problems. Overall, those who work night or rotating shifts seem to have a higher risk of insulin resistance, MetS and heart disease[254,257]	B
Recommendation	**Grade**
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

Table 16: Lifestyle recommendations for management of the metabolic syndrome.

-Smoking cessation
-30 to 60 min of daily physical activity
-A healthy diet designed to achieve 5% weight loss should be prescribed for overweight -and obese patients with MetS
-Plant-based Mediterranean diet, with or without energy restriction, DASH diet, or vegetarian diets can be recommended as an effective component of the treatment strategy
-Specific dietary recommendations include limiting saturated and trans fats and increasing dietary fibre
-Reduce intake of sugar sweetened beverages
-Moderation in alcohol intake
-Salt intake should be restricted

Table 17: Foods, nutrients and dietary patterns in the prevention of metabolic syndrome

	Unfavorable	Favorable
Foods	Sugar sweetened beverages Meat products Excessive alcoholic intake	Fruits and vegetables Legumes and cereals (whole grains) Moderate intake of red wine and beer Olive oil Fish Nuts Low-fat dairy products
Nutrients	Sucrose, fructose Salt Saturated fatty acids *Trans* fatty acids	Fiber Unsaturated fatty acids Bioactives: carnitine and choline
Dietary patterns	Western diet	Mediterranean diet, DASH diet, New Nordic diet, Vegetarian diets

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