Dietary patterns, inflammation and the metabolic syndrome

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Abstract

Aim. – The study of dietary patterns offers a comprehensive, real-life approach towards examining the complex diet and disease relationship. The simultaneous association of dietary patterns with inflammation and the metabolic syndrome (MetS) has not been extensively reviewed. This report reviews the association of dietary patterns with inflammation in the context of the MetS.

Methods. – Original English-language research studies with humans were identified via MEDLINE, using inflammation, MetS, whole diets and dietary patterns as keywords. The findings were carefully examined and synthesized along consistent axes.

Results. – Many observational and a few prospective studies, as well as some randomized controlled trials (RCTs), support an inverse association between a Mediterranean dietary pattern and markers of inflammation. The link is generally independent of traditional cardiovascular disease (CVD) risk factors and weight loss. The few studies that have examined the association between following a healthy dietary pattern, evaluated using various diet quality scores, and inflammation report an inverse association; however, this association was attenuated upon adjusting for CVD risk factors. A Mediterranean dietary pattern has also been associated with a reduced risk of the MetS in several cross-sectional studies and a few prospective studies conducted with healthy people. Few RCTs (lasting 1–2 years) have confirmed the benefits of following a Mediterranean diet on MetS risk in obese individuals, in those with the MetS or in those at CVD risk. The evidence, albeit limited, for a link between healthy diets based on other diet quality scores and the MetS supports a similar inverse association for the primary and secondary prevention of the MetS.

Conclusion. – Adhering to healthy diets such as the Mediterranean diet and/or national dietary guidelines can reduce inflammation and the MetS.

Keywords: Dietary patterns; Diet scores; Inflammatory markers; The metabolic syndrome; Obesity; Review

Résumé

Comportements alimentaires, inflammation, et syndrome métabolique.

Objectif. – L’étude des comportements alimentaires constitue une approche globale et réaliste pour analyser les relations entre nutrition et pathologies. L’association des comportements alimentaires avec à la fois l’inflammation et le syndrome métabolique n’a pas été recensée en détail à ce jour. Tel est l’objectif de cette revue.

Méthodes. – Les mots clés « inflammation, syndrome métabolique, alimentation globale et comportements alimentaires » ont été utilisés pour identifier dans Medline les articles pertinents en langue anglaise portant chez l’homme. Ils ont été soigneusement examinés et synthétisés en plusieurs axes.

Résultats et conclusion. – De nombreuses études d’observation dont quelques études prospectives et essais contrôlés randomisés suggèrent une association inverse entre des typologies alimentaires de type méditerranéen et des marqueurs de l’inflammation. Ce lien est indépendant des facteurs de risque cardiovasculaire (CV) et de la perte de poids. Quelques études ont trouvé une association inverse entre les comportements alimentaires favorables à la santé (évalués par différents scores de qualité nutritionnelle) et le statut inflammatoire, mais cette association est atténuée après ajustement sur les facteurs de risque CV. Une alimentation de type méditerranéen a été également trouvée associée à une fréquence moindre de syndrome métabolique dans plusieurs études transversales et quelques études prospectives réalisées chez des sujets sains. Quelques essais randomisés d’une durée d’un ou de deux ans confirment le bénéfice du modèle d’alimentation méditerranéen sur le risque de syndrome métabolique chez les sujets obèses, les patients à risque de syndrome métabolique ou de maladies CV. Globalement le lien entre alimentation saine...
Traditionally, studies have focused on the relationship between food groups, specific foods and nutrients and health and risk of disease. These studies can offer specific mechanistic insights and serve as a basis for hypothesis validation, but they do not allow a comprehensive and realistic evaluation of the complexity of the diet and disease relationship. Examination of diet as a whole through analysis of dietary patterns represents a burgeoning field of research addressing the complex diet–disease paradigm. A number of studies have addressed the role of dietary patterns in cardiovascular disease (CVD), inflammation, and the metabolic syndrome (MetS). The latter is a cluster of risk factors (dysglycaemia, elevated blood pressure, dyslipidaemia and central adiposity) that has been shown to be predictive of CVD and diabetes [1–3]. A state of low-grade chronic inflammation is associated with several metabolic abnormalities and chronic diseases, and could serve as the link mediating diet and chronic illness [4–6]. Although several reports have addressed the association of dietary patterns with the MetS and with inflammation separately, including recent reviews [7,8], few have examined the two related issues at the same time. Thus, the present review aims to synthesize findings on the relationship of diet with inflammation as demonstrated in the context of the MetS.

Using MEDLINE, 479 papers were identified that described studies of an adult population published in English by searching for inflammation and whole diets or dietary patterns as well as for the MetS (but not components of the MetS individually) and whole diets or dietary patterns. Abstracts of these papers were then reviewed to include all studies that focused on a priori or a posteriori dietary patterns (but not individual components of diets) and those reporting on inflammatory markers such as proinflammatory cytokines, including interleukin (IL)-1, IL-6 and IL-18, tumour necrosis factor (TNF)-α and C-reactive protein (CRP), adiponectin, and adhesion molecules such as soluble intercellular adhesion molecule (sICAM)-1 and soluble vascular cell adhesion molecule (sVCAM)-1. The present report is a summary of the literature identified through this systematic review process along a consistent axis: review of studies on diet and inflammation; review of studies on diet and the MetS; and a final synthesis section. More details are provided from key reports of prospective studies and interventional trials offering stronger proof of evidence.

1. Dietary patterns

Many studies have focused on the role of specific food groups, and individual foods and nutrients, to evaluate the diet–disease link. However, such research is subject to certain limitations such as the synergistic or interactive effects among nutrients, confounding by other dietary variables, multiple testing and insufficient statistical power related to the small effect sizes [9–12]. For this reason, attention has been shifting to the study of overall dietary or food patterns to assess the effect of a combination of foods and nutrients on health and disease outcomes [9,10,12,13].

Dietary pattern research commonly relies on patterns derived using a priori and a posteriori methods [9,10,13]. The former is based on dietary indices and scores that are easier to understand by the general public [14], and are used to assess adherence to such predefined dietary patterns in a given population. A priori approaches also encompass evaluation of the study population’s adherence to well-known diets such as the Mediterranean diet [15] and the prudent diets recommended by expert bodies, such as the ‘Dietary Approaches to Stop Hypertension’ (DASH) [16] and the Healthy Eating Index (HEI) [17]. On the other hand, a posteriori methods involve extracting patterns of habitual food consumption from the population under study, using statistical multidimensional analysis techniques such as factor or cluster analysis based on the dietary consumption data collected for that population [12,14,18]. Such patterns are population-specific and so have high internal validity, but limited generalizability. For this reason, the relationship between dietary patterns and inflammation and the MetS is reviewed here with an emphasis on studies using a priori indices of the Mediterranean diet, DASH and HEI to facilitate cross-population inferences.

1.1. Dietary indices

The Mediterranean diet is one of the most studied dietary patterns in the context of the MetS and other diseases. It is characteristic of countries around the Mediterranean basin. The traditional Mediterranean diet relies on unrefined cereals, legumes, nuts, fruit, vegetables, moderate/high consumption of fish and yoghurt, low/moderate intakes of poultry, low intakes of red/processed meats and moderate consumption of wine, generally with meals [19]. Olive oil serves as the principal source of fat in this dietary pattern [15,20–23]. Adherence to the Mediterranean diet is typically assessed by scoring the consumption of its individual components [11,24]. Trichopoulou and colleagues [25] were the first to develop a Mediterranean diet score (MDS), consisting of eight dietary components typical of the Mediterranean diet, although recently, our group has published a revised definition of the original MDS incorporating an additional two components: the consumption of refined grains and sweetened beverages [26]. Despite some heterogeneity, most studies use the median intake of the study population as the cut-off point for assigning a dichotomous score (0/1) for the consumption of these individual components that contribute to an overall score reflecting adherence to the Mediterranean diet [15,21,25]. Scores obtained in this manner are highly population-specific.
Another approach [22,27,28] is to give a score according to the recommended frequency of intake defined by the Mediterranean Diet Pyramid [20,27]. The Mediterranean-Style Dietary Pattern Score (MSDPS), for example, was developed specifically for the US population to assess the conformity of an individual’s diet to the traditional Mediterranean-style diet [28]. This score is based on the recommended intakes of 13 food groups in the Mediterranean Diet Pyramid, and exceeding the recommendations results in a lower score in relation to the degree of overconsumption. The sum of the component scores is then standardized and weighted by the proportion of energy consumed from Mediterranean diet foods. Despite subsequent revisions to the MDS, these various adaptations of the original MDS generally capture well the overall adherence to the Mediterranean-style dietary pattern, although the need for a more precise and quantified definition of the pattern is recognized [24].

The DASH diet was developed by the US National Heart, Lung, and Blood Institute (NHLBI). It is low in cholesterol and in saturated and total fats, and it advocates an increased consumption of fruit, vegetables, whole grains, nuts, fat-free/low-fat milk and/or milk products, fish and poultry while discouraging intakes of red meat, sweets and sugar-containing beverages. The DASH index is rich in magnesium, potassium, calcium, protein and fibre, and low in sodium [16].

The HEI, developed by the US Department of Agriculture using the Dietary Guidelines for Americans and the Food Guide Pyramid, has the following ten components: fruit; vegetables; grains; dairy; meats; cholesterol; fats; saturated fat; sodium; and dietary variety. Each component is scored from 0 to 10 according to the individual’s typical intakes, with a maximum possible HEI score of 100. The revised HEI (alternate HEI) places an emphasis on healthier items in the Food Guide Pyramid [17], such as cereal fibre, protein sources, ratio of polyunsaturated to saturated fats, cis vs trans fats, moderate alcohol consumption and long-term multivitamin supplement use. In addition, adherence to the eight dietary and health recommendations of the US National Academy of Sciences is reflected by the Diet Quality Index (DQI) and the revised DQI (DQI-R), which also includes iron and calcium intakes [29]. Similar indices have been developed in other countries such as France, based on the guidelines of the National Nutrition and Health Programme (Programme National Nutrition Santé [PNNS]). The PNNS score thus reflects adherence to these general nutrition and health recommendations in France [30].

2. Dietary patterns and low-grade inflammation

Inflammation results from tissue injury or infection, and a state of chronic low-grade inflammation has been associated with insulin resistance, diabetes, atherosclerosis, obesity, the MetS and CVD [2,8,31–38]. The postulated mechanisms involve increased levels of proinflammatory, and decreased levels of anti-inflammatory, adipokines and cytokines, thereby creating a proinflammatory environment with an increase in reactive oxygen and nitrogen species [8,39,40]. Over time, this proinflammatory state leads to several metabolic disturbances and the development of the MetS.

Because diet can have an impact on the balance between pro- and anti-inflammatory cytokines and adipokines, a state of low-grade inflammation is also subject to the influence of a person’s dietary habits [8]. A number of epidemiological studies worldwide have documented a link between various dietary patterns and markers of inflammation. Much of this literature is based on analysis of data from large-scale studies in the US, such as the Nurses’ Health Studies (n = 35,340 and n = 89,311 in its two cycles) [41] and n = 732 [42], the MESA study (n = 5089) [43] and the Carotid MRI Study, a subset of the Atherosclerosis Risk in Communities (ARIC) study (n = 1101) [44]. For the most part, these studies have shown that Western dietary patterns derived a posteriori are positively associated with concentrations of CRP, platelet glycoprotein IIb (CD41), platelet granulocyte aggregates, E-selectin, sICAM-1 and sVCAM-1 [41–44]. In line with this, healthy patterns have also been associated with lower inflammatory markers in studies in the US — namely, the MESA study (n = 5042 adults) [45] and the Health, Aging and Body Composition (Health ABC) study, based on data from 1751 older adults [46]. In the MESA study, a healthy dietary pattern was inversely associated with concentrations of CRP, IL-6 and fibrinogen whereas, in the Health ABC study, a “healthy foods” cluster characterized by higher intakes of low-fat dairy products, fruit, whole grains, poultry, fish and vegetables was associated with lower IL-6 levels [46]. Elsewhere, studies of Iranian women (n = 486) also showed a positive association between adherence to a Western diet and levels of serum amyloid A and IL-6 [47]. Similarly, in a study involving a Japanese population (n = 7802), adherence to diets rich in fruit, vegetables, soy products and fish were inversely related to CRP levels [48]. A dietary pattern characterized by high consumption of whole-grain cereals and low-fat dairy products, and low consumption of refined cereals, was positively associated with plasma adiponectin levels in healthy Greek women (n = 220) [49]. In addition, a recent study in Germany showed that a dietary pattern, derived by reduced rank regression and characterized by high intakes of meat, soft drinks and beer, and low intakes of several foods such as vegetables, fresh fruit, wholemeal bread and cereals, was related to higher levels of inflammatory markers in 981 middle-aged adults in the MONICA/KORA Augsburg cohort; crude Spearman correlations were 0.27 and 0.33 for IL-6 and CRP, respectively [50].

Thus, most of these cross-sectional studies support a positive association between a Western dietary pattern and inflammatory markers as well as an inverse correlation between a healthy dietary pattern and inflammation, with a few exceptions in specific population groups such as the Inupiat Eskimos in Alaska (n = 1214) [51]. However, more comparable ecological evidence between dietary patterns and inflammation can be seen in studies based on a priori patterns (see below).

2.1. Mediterranean diet and inflammation

There is substantial and consistent evidence from epidemiological studies of an independent protective effect
of the Mediterranean diet on inflammatory and endothelial dysfunction markers such as circulating IL-6, CRP, TNF-α, adiponectin, sICAM-1, sVCAM-1 and E-selectin based on findings from the Nurses’ Health Study \( (n = 690) \) [21], ATTICA \( (n = 1514 \text{ men and } 1528 \text{ women}) \) [22] and the ATTICA substudy \( (n = 532 \text{ adults}) \) [52], as well as from a study of 345 middle-aged twin pairs [23]. In these studies, adherence to a Mediterranean diet was usually estimated via the MDS or the alternate MED score. Crossover studies [53,54], albeit only a few, of short duration and involving small samples of young adults \( (n = 22 \text{ and } n = 20, \text{ respectively}) \), further support the evidence from observational studies demonstrating that, in healthy individuals, the Mediterranean diet can reduce the number of leucocytes and platelets as well as VCAM-1 and E-selectin expression. In particular, a Swedish randomized crossover trial [53] demonstrated lower inflammatory activity when randomized to a Mediterranean-type diet compared with a Swedish-type diet followed for a month; however, none of the changes in CRP and IL-6 concentrations with this intervention were significant, a finding that was partly attributed to the small study sample size \( (n = 22) \). Finally, in another clinical trial \( \text{(pre-post study)} \) of obese individuals \( (n = 41) \) followed for 8 weeks while on a low-calorie diet based on a Mediterranean dietary pattern to induce weight loss, adherence to the diet was associated with significantly improved inflammatory profiles in the participants \( \text{reduced IL-6 and TNF-α independent of calorie restriction and weight loss} \) [55]. Although this study found interesting associations between following a Mediterranean diet pattern and reduced inflammatory markers independent of weight loss, it lacked a control group.

The impact of the Mediterranean diet on inflammatory markers has been evaluated in a few well-designed randomized controlled trials \( \text{(RCT)} \) that have provided stronger proof of evidence. Indeed, RCT involving individuals who have the MetS, are obese or at high CVD risk have consistently shown reductions in levels of inflammatory markers along with an improvement in endothelial function following a Mediterranean diet \([56–58]\). Significant reductions in hsCRP, IL-6 and IL-18 with increases in adiponectin concentrations were observed in premenopausal obese women \( (n = 60) \) assigned to nutritionist-guided sessions \( \text{aimed at } \geq 10\% \text{ weight reduction with a low-calorie Mediterranean-style diet and increased physical activity} \) for 2 years compared with controls \( (n = 60) \), who received general information about healthy food choices and exercise [56]. The favourable changes in cytokines in the intervention group were correlated with weight loss; nevertheless, the authors stated that “the magnitude and significance of the weight-loss-induced difference in cytokines and CRP were similar” in both the intervention and control groups.

In another study by the same investigators, individuals with the MetS \( (n = 180) \) allocated to a Mediterranean-style diet showed greater weight loss, lower levels of hsCRP, IL-6, IL-7 and IL-18, and improved endothelial function after 2 years compared with the controls [57]. The effect of a Mediterranean diet on inflammatory markers persisted even after controlling for weight loss in this study, suggesting that the anti-inflammatory effect of the Mediterranean diet is mediated by several mechanisms besides weight loss.

In addition, findings from the PREDIMED \( \text{(Prevención con dieta Mediterránea)} \); Prevention with the Mediterranean Diet \) study, involving participants at high CVD risk \( (n = 772) \) followed for 3 months, demonstrated that those assigned to a Mediterranean diet supplemented with olive oil had lower hsCRP levels than those assigned to a Mediterranean diet supplemented with nuts or a low-fat diet \([5,58]\). Body weight and adiposity measures were slightly reduced in the three study groups, although no between-group differences were noted [58]. This suggests that changes in body weight or adiposity did not explain the reduction in hsCRP level following the Mediterranean diet supplemented with virgin olive oil. Furthermore, a recent meta-analysis of interventional trials involving overweight/obese individuals reported that, after 2 years of follow-up, those assigned to a Mediterranean diet had more favourable changes in weighted mean differences for cardiovascular risk factors and hs-CRP \((-1.0 \text{ mg/L}; 95\% \text{ CI: } -1.5 \text{ to } -0.5 \text{ mg/L}) \) [59].

Along these lines, in a substudy of the PREDIMED trial involving 106 high-risk subjects, intervention with Mediterranean diets \( \text{supplemented with either virgin olive oil or nuts} \) for 3 months was effective in reducing serum IL-6 and sICAM-1 as well as in downregulating cellular inflammatory markers related to atherogenesis, particularly the proinflammatory ligand \( \text{(CD40)} \) and \( \text{CD49d} \) \( \text{(crucial for leucocyte homing)} \). The groups did not differ in body mass index \( \text{(BMI)} \) at baseline and adiposity measures remained essentially unchanged post-intervention [5]. A recent report from the same authors affirms that intervention with these Mediterranean diets modulated the expression of key genes involved in vascular inflammation, foam-cell formation and thrombosis in a population at high-risk for CVD \( (n = 49) \) and, as seen in previous reports from this trial, the weight changes across interventions did not differ [60].

Overall, the literature suggests that the effect of a Mediterranean diet might be stronger in people at risk for CVD than in healthy individuals who exhibit low levels of vascular inflammation and in whom the cardioprotective effects of the Mediterranean diet may be less evident [53,54].

2.2. Other diet quality scores and inflammation

Links between diet quality indices and markers of low-grade inflammation have also been examined in epidemiological studies carried out in the US and Belgium. These studies adjusted for BMI [21,61,62] and waist circumference [63] in their multivariate analysis models. Specifically, the alternate HEI diet was shown to be protective against inflammation \( \text{(higher adiponectin, and lower CRP and E-selectin concentrations)} \) in the Nurses’ Health Study \( (n = 1922) \) [61]. In an initial report from this study \( (n = 690) \), evidence for a negative association among several diet quality scores (HEI, alternate HEI, DQI-R) and various markers of low-grade inflammation, such as CRP, IL-6, E-selectin and sICAM-1, was noted [21]. However, the authors also observed heterogeneity in the predictive potential of the various diet quality indices, with stronger effects noted for the alternate HEI, and non-significant effects noted for the HEI and
DQI-R. It is therefore possible that the alternate HEI and MED score capture somewhat different dietary patterns. An independent negative correlation between the HEI and CRP levels was observed among participants in the Third National Health and Nutrition Examination Survey (NHANES III; n = 13,811) in the US, although this association was significant only in women [62].

A recent Belgian epidemiological study involving 2524 middle-aged adults showed that a dietary index considering dietary quality, diversity and equilibrium was inversely associated with leucocyte counts and IL-6 concentrations [63]. However, not all cross-sectional studies have reported significant findings possibly because the inverse associations between DQI and inflammatory markers could be mediated by obesity, as shown in the study by Boynton et al. [64] of 110 overweight/obese postmenopausal women. The associations observed between DQI and inflammatory markers (CRP and serum amyloid A) became non-significant upon adjusting for percent body fat. On the other hand, in a recent report of the results of a randomized crossover clinical trial, 31 type 2 diabetes patients followed a control diet or the DASH diet for 8 weeks, with the result that hs-CRP and fibrinogen levels decreased significantly following the DASH diet, an effect that was maintained despite controlling for weight loss [65].

In another recent interventional study, 187 men aged 41–50 years (50% of whom had the MetS) were randomly assigned to a diet protocol, an exercise protocol, a protocol of diet plus exercise or a control protocol [66]. The diet protocol was consistent with an individualized target weight loss of 0.5–2 kg/month in the most overweight participants, and recommended an increased consumption of fish and fish products, vegetables and fibre-rich products as well as a reduction in sugar and saturated fat intakes. An a priori diet score was determined by summing up the tertile rankings of 35 food-group variables (considered to have beneficial, neutral or adverse effects on health), with a higher score indicating greater adherence to recommendations. Although adiponectin levels increased in the dietary intervention groups (and correlated with an increase in diet score), this effect became statistically non-significant when intervention and percent body fat were also considered in statistical models. The authors speculated that the lack of association between improved diet score and inflammatory markers in this study may have been due to the fact that the subjects were relatively healthy and had no overt CVD, and inflammatory markers might be more related to a healthy diet in people with atherosclerotic disease who are more likely to have greater activation of these pathways [66].

It is important to assess, considering the bulk of the literature reviewed above, whether the effect of dietary patterns on inflammatory indices simply reflects their association with obesity/body fat percentages or is in addition to this well-accepted association [8,56,67]. Of the cross-sectional studies described above, almost all — with the exception of the dietary patterns derived by reduced rank regression using inflammatory markers as response variables [43,50] — were adjusted for some measure of obesity/body fat (BMI, waist-to-hip ratio, waist circumference or percent body fat) in multivariate models. In a few studies, the associations between dietary pattern/diet score and inflammation were attenuated after adjusting for obesity [23,53,64]; however, for the rest of the studies reviewed above, greater adherence to ‘healthy’ diets (dietary patterns or other dietary indices) was significantly associated with reduced inflammatory markers despite adjusting for obesity/body fat.

In addition, in the few prospective or interventional studies where weight loss was recorded, either weight change did not differ across interventions, as seen notably in the PRED-IMED study [5,58,60] or, despite controlling for weight loss in the adjusted models, intervention with a Mediterranean diet independently reduced inflammatory markers [57]. Considered altogether, these findings suggest that the effect of healthy dietary patterns is partly mediated by associated weight loss, but also related to other effects, such as less oxidative stress and inflammation via the diet itself and/or the nutrients and food components present in such diets. Also, the healthy dietary patterns and indices discussed above share a common emphasis on plant-based foods (and so are rich in fibre, antioxidants and polyphenols), with avoidance of highly processed, energy-dense foods. Polyphenols, for example, have been shown to protect against the postprandial dysmetabolism associated with an increase in CRP levels [68,69].

3. Dietary patterns and the metabolic syndrome

The MetS is a cluster of risk factors for CVD and type 2 diabetes, including dysglycaemia, elevated blood pressure, dyslipidaemia (high triglyceride and low high-density lipoprotein [HDL] cholesterol levels) and obesity, particularly central adiposity. The first definition of the MetS, proposed in 1998 by a consultation group working on a definition of diabetes for the World Health Organization (WHO), required evidence of insulin resistance in conjunction with other metabolic manifestations [70]. Since then several other definitions have been proposed over the past decade (Table 1) and have been commonly used [1,71,72]. The National Cholesterol Education Program Adult Treatment Panel Third Report (NCEP-ATP III) does not require the presence of insulin resistance per se, but three out of five risk factors instead (Table 1) to establish the presence of the MetS [71]. The American Heart Association (AHA)/NHLBI definition is similar to the NCEP-ATP III definition except for slightly different cut-off points for hyperglycaemia, and considers the metabolic conditions as abnormal if a person is taking medications for these disorders [72]. The International Diabetes Federation (IDF) definition [1] differs from the AHA/NHLBI recommendation in terms of waist circumference (WC) in two ways. First, the cut-offs for WC in the IDF recommendation are ethnicity-specific and lower for those of European origin (Europeans). More important, the IDF definition requires abdominal adiposity (which is highly correlated with insulin resistance) as a mandatory criterion in the presence of two other risk factors (essentially the same four remaining factors as in the AHA/NHLBI definition). Recently, the Joint Interim Statement (JIS) by representatives of the IDF, AHA/NHLBI, other prominent international associations of obesity and atherosclerosis, and the World Heart Federation was released to resolve differences in the various definitions of the MetS and to pro-
pose a unified recommendation for international use [3]. The JIS criteria consider abdominal obesity as one of the five criteria, so the presence of three out of five risk factors comprises a diagnosis of the MetS; nevertheless, the use of population/ethnicity and gender-specific WC cut-offs, with notably lower cut-offs for Asians (≥ 90 cm for men and ≥ 80 cm for women, respectively) is also recommended [3].

The MetS is associated with diabetes, atherosclerosis and CVD [2,72–75]. Individuals with the MetS are at higher risk for coronary heart disease (CHD) events [76,77] as well as increased CVD mortality [73,77] and increased all-cause mortality [73]. More important, with the growing prevalence of obesity and sedentary lifestyles, the prevalence of the MetS is also increasing worldwide [78]. For this reason, identification of lifestyle factors that have an impact on the cluster of MetS components individually and, more significantly, on the MetS itself is of major importance.

Williams et al. [79] were among the first to report on the association of dietary patterns derived using *a posteriori* methods with the MetS. In their cross-sectional study of middle-aged subjects (*n* = 802) selected randomly from a population-based sampling frame (Isle of Ely Study), the healthy balanced dietary pattern identified in the study was negatively associated with several components of the MetS. In a cross-sectional study of 486 middle-aged Tehrani female teachers, Esmaillzadeh and colleagues [80] identified three dietary patterns by factor analysis. After controlling for potential confounders, adherence to the healthy pattern was associated with lowered odds ratios for the MetS (OR = 0.61; 95% CI: 0.30–0.79). Similarly, greater adherence to a Western dietary pattern (women in the highest quintile) had 68% greater chances of developing the MetS than women in the lowest quintile. An “empty-calorie pattern”, characterized by high intakes of total fat, calories and sweetened beverages, and low intakes of dietary fibre and vegetables, has also been related to increased odds of having the MetS in 1615 young adults from a semirural US community (Bogalusa Heart Health-workers cohort study (*n* = 5240) [82] and in Samoan adults (*n* = 785) [83]. In other cross-sectional studies involving specific populations, such as Korean adult women (*n* = 1984) and young adults from a semirural US community (Bogalusa Heart Study, *n* = 995), no association was found between a Western dietary pattern and MetS prevalence [84,85], although an inverse association between a healthy dietary pattern and MetS prevalence was noted in these studies. Accordingly, in the ATTICA study (1514 men and 1528 women), greater adherence to a

### Table 1

Summary of commonly used definitions of the metabolic syndrome.

|-------------------|-------------------|-----------------|-----------|-----------|
| Presence of three or more criteria | Presence of three or more criteria | MANDATORY presence of increased waist circumference (WC) using ethnicity-specific cutoffs*
≥ 94 cm (Europid men) or ≥ 80 cm (Europid women) PLUS presence of two or more criteria |
| Abdominal obesity | WC ≥ 102 cm (men) and ≥ 88 cm (women) | WCb ≥ 102 cm (men) and ≥ 88 cm (women) | | Population- and country-specific definitions: WC ≥ 94 cm (Europid men) and ≥ 80 cm (Europid women); lower cut-offs for Asians (≥ 90 cm for men and women, respectively) |
| Elevated fasting glucose | ≥ 110 mg/dL (6.1 mmol/L) | ≥ 100 mg/dL (5.6 mmol/L) OR drug treatment for this disorder | ≥ 100 mg/dL (5.6 mmol/L) OR drug treatment for this disorder |
| Reduced HDL cholesterol | < 40 mg/dL (1.0 mmol/L) in men, < 50 mg/dL (1.3 mmol/L) in women | < 40 mg/dL (1.0 mmol/L) in men, < 50 mg/dL (1.3 mmol/L) in women OR drug treatment for this disorder | < 40 mg/dL (1.0 mmol/L) in men, < 50 mg/dL (1.3 mmol/L) in women OR drug treatment for this disorder |
| Elevated triglycerides | ≥ 150 mg/dL (1.7 mmol/L) | ≥ 150 mg/dL (1.7 mmol/L) OR drug treatment for this disorder | ≥ 150 mg/dL (1.7 mmol/L) OR drug treatment for this disorder |
| Elevated blood pressure | Systolic ≥ 130 mmHg, diastolic ≥ 85 mmHg | Systolic ≥ 130 mmHg, diastolic ≥ 85 mmHg OR drug treatment for this disorder | Systolic ≥ 130 mmHg, diastolic ≥ 85 mmHg OR drug treatment for this disorder |

*a* BMI > 30 kg/m² assumes central adiposity, so WC need not be measured.

*b* Lower WC cut-offs (≥ 90 cm for men; ≥ 80 cm for women) are more appropriate for Asian Americans.

* Recommended to also present results using higher thresholds of ≥ 102 cm and ≥ 88 cm for Europid men and women, respectively, to allow international comparisons.

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prudent/healthy dietary pattern was associated with a reduced MetS prevalence [86] and, in the Adventist Health Study-2 (n = 773; mean age: 60 years), a vegetarian dietary pattern was negatively associated with the MetS compared with a non-vegetarian dietary pattern after controlling for relevant CVD risk factors as well as dietary caloric intake [87]. However, similar to the relationship between a Western dietary pattern and the MetS, different findings between a healthy dietary pattern and the MetS have been noted in specific population groups, ranging from no association in Mexican adults [82] to a positive association between a traditional rice-and-bean dietary pattern and MetS prevalence in older Puerto Rican adults (n = 1167) living in Massachusetts in the US [88].

Nevertheless, an analysis of a prospective association between dietary patterns and MetS incidence over 9 years of follow-up in the ARIC study, involving 9514 participants (age: 45–64 years), showed that the consumption of a Western diet was significantly associated with an increased risk of the MetS. Subjects in the uppermost quintile of adherence to the Western dietary pattern had an 18% greater risk of developing the MetS vs those in the lowest quintile. Also, contrary to other findings from cross-sectional studies, no prospective association was noted between a prudent diet and MetS incidence in this study, which may have been partly related to the limited discrimination in the 66-item food frequency questionnaire (FFQ) for certain healthy foods such as whole grains and nuts [89]. Furthermore, it is important to note that there is limited information available on a posteriori dietary patterns and MetS risk from prospective studies. Overall, the bulk of studies conducted in various countries have linked dietary patterns with the MetS: a Western dietary pattern was positively associated and a healthy dietary pattern was negatively associated with the MetS in several studies, with some variations across age and countries. However, these so-called a posteriori patterns are country-specific and therefore not easily comparable. For this reason, the following section reviews in greater depth the studies focusing on the a priori diets and dietary scores that have been applied across nations to evaluate diet quality and its relationship to the MetS.

3.1. The Mediterranean diet and the MetS

The Mediterranean diet has been shown to have a beneficial effect on all components of the MetS, as described in a recent meta-analysis [7]. Of the few previous cross-sectional studies in Mediterranean populations, two studies conducted in individuals at low risk of CVD (aged >18 years; n = 578 and n = 714, respectively) showed no association between a Mediterranean-style dietary pattern and the MetS [90,91]. In the latter study of naval recruits in Greece, the lack of any association was speculated to be related to poor adherence to the Mediterranean diet [91]. However, in another larger study of a randomly selected sample of 1128 men and 1154 women (aged >18 years) residing in the greater Athens area, adherence to the dietary pattern was associated with 20% lower odds of having MetS (OR: 0.81; 95% CI: 0.68–0.98) after accounting for sociodemographic, physical activity and CVD risk factors [92]. Similarly, greater adherence to a Mediterranean diet in individuals at high CVD risk (n = 808) [93] and in those who are overweight/obese (n = 226) [94] has been associated with lower odds of having the MetS.

Prospective studies conducted in the US and in Mediterranean populations confirm an inverse relationship between a Mediterranean-style dietary pattern and MetS incidence. In an analysis of data from 2563 Spanish university graduates from the Seguimiento University of Navarra (SUN, University of Navarra) cohort followed for 6 years, Tortosa et al. [95] reported that participants with the highest adherence to the Mediterranean food pattern had a significantly lower cumulative incidence of the MetS (0.8%) compared with those with the lowest adherence (2.6%). In the Framingham Heart Study Offspring Cohort (baseline median age: 54 years; mean follow-up time: 7 years; n = 2730), participants in the highest quintile of MSDPS had a lower (30.1%) incidence of the MetS than those in the lowest quintile (38.5%) [28]. Recently, our group has reported similar findings among middle-aged French adults (n = 3232) showing a reduced prospective risk of the MetS with greater adherence to the Mediterranean diet, as evaluated by the original MDS score and revised MED score incorporating refined grains and sweetened beverage consumption [96], thus supporting an association between the Mediterranean-style dietary pattern and the MetS that is consistent across different populations.

In addition, strong and consistent evidence in this regard has been provided by two RCTs, one involving participants with the MetS in Italy (n = 180) [57] and the other involving subjects at high risk for CVD (n = 1224) in the Spanish PREDIMED study [97]. In the RCT by Esposito and colleagues (described above), at the end of the 2-year intervention (involving instructions to increase daily intakes of whole grains, fruit, nuts and olive oil), the prevalence of the MetS was reduced by ∼50%, despite adjusting for weight changes, in the group following a Mediterranean diet compared with the group following a cardioprotective diet with a fat intake <30%. The PREDIMED study assessed the effects of two high-fat Mediterranean diets (one supplemented with virgin olive oil, the other with mixed nuts) vs a control diet (advised on a low-fat diet) consumed ad libitum on the MetS after 1 year. At baseline, 61% of the participants had the MetS. Both Mediterranean-diet groups improved significantly in their post-intervention Med Diet scores; at the same time, the prevalence of the MetS was reduced in both these groups (compared with controls). However, the reduced MetS prevalence was significant only in the Mediterranean-diet group that consumed an additional daily serving of nuts (30 g/day at the end of study vs 12 g/day at baseline). The beneficial effect of this diet in reducing the prevalence of the MetS at the end of the study was due to higher rates of MetS reversal among participants with the condition at baseline, and not because of reduced MetS incidence. Specifically, after adjusting for gender, age, baseline obesity status and weight changes, the ORs for MetS reversal were 1.3 (95% Cl: 0.8–2.1) and 1.7 (1.1–2.6) for the Mediterranean diet supplemented with virgin olive oil and nuts, respectively, compared with the control diet.

Taken together, the findings of these two clinical studies demonstrate the usefulness of a Mediterranean diet for secondary prevention in high-risk populations. However, it should be noted that both these interventional studies were relatively
short in duration, so the longer-term effects of this dietary pattern need to be established in future trials, and particularly in non-Mediterranean regions, to extend these exciting findings to other populations.

3.2. Other diet quality scores and the MetS

As only limited information is available on the association of diet quality scores with the MetS as an entity, the following description also includes a recent study of adolescents. In this large study of adolescents \( (n=4450) \) based on the 4-year combined data from NHANES 1999–2002, 3.5% of US adolescents had the MetS (age-specific cut-offs using >90th percentiles for certain risk factors and clinical cut-offs whenever available) [98]. The prevalence of the MetS decreased with increments of overall HEI score quartiles. In addition, two recent large-scale cross-sectional studies showed an inverse association between an index that evaluated adherence to the 2005 Dietary Guidelines for Americans (DGAII) and MetS prevalence. The Tehran Lipid and Glucose Study involved a random sample of 1120 men and 1384 women [99], and showed that being in the highest quartile category of DGAI score was significantly associated with a reduced prevalence of the MetS (by 21%) after adjusting for potential confounders.

Although a similar result was seen in a study of 3177 participants from the Framingham Heart Study Offspring Cohort, the association was marginally significant overall, but stronger and statistically significant in younger people (aged <55 years) and in those not taking medications for any of the associated risk factors [100]. In one prospective study recently reported by our group, there was an inverse association between the French PNNS guidelines score (PNNS-GS) and MetS risk in middle-aged adults \( (n=2763) \) over a 7-year follow-up [30]. In multivariate models, each unit increase in the PNNS-GS score was associated with a 9% lower risk for developing the MetS (OR: 0.91; 95% CI: 0.83–1.00). The association was even stronger for the risk of developing severe MetS with larger waist circumference and having more than two MetS components (OR: 0.76; 95% CI: 0.63–0.91). After adjusting for baseline BMI and changes in BMI over the follow-up, this association remained significant for severe MetS. Taken together, the bulk of the literature on dietary scores and the MetS support an inverse association, with variations in the strength of the association in relation to age and health status.

Few studies have examined the role of healthy diets in the secondary prevention of the MetS although, recently, Akbaraly et al. [101] reported on the impact of adherence to the alternate HEI on reversal of the MetS (no MetS after the 5-year follow-up) in middle-aged participants \( (n=339) \) from the Whitehall II study. After adjusting for potential confounders, adherence to dietary guidelines for healthy eating was associated with increased odds of MetS reversal (OR: 1.88; 95% CI: 1.04–3.41). This association was stronger in participants with central obesity and with high triglycerides, indicating the possibility of greater benefit with adhering to the HEI in these subgroups. The importance of healthy dietary patterns on the MetS and its components has also been confirmed in an RCT involving people \( (n=116) \) with the MetS [102]. Subjects were randomized to follow one of three diets for 6 months: a control diet; a weight-reducing diet emphasizing healthy choices; and the DASH diet, with fewer calories and greater consumption of fruit, vegetables, low-fat dairy and whole grains, and lower consumption of saturated fat, total fat and cholesterol, with sodium restricted to 2400 mg. Those following the latter two diets reduced their calorie intakes (by 500 Kcal/day), and lost 16 kg and 15 kg of body weight, respectively, at the end of the study. The prevalence of the MetS was also reduced significantly in the DASH diet group vs the weight-reduction and control diets; at post-intervention, prevalence of the MetS was 65% in the DASH diet group compared with 81% in the weight-reducing group and 100% in the control group. Although the improvement in MetS prevalence was related to weight reduction, the greater benefit of MetS reduction in the DASH diet group again suggests that mechanisms other than weight reduction are also involved. The authors in this case underscored the fact that the DASH diet is rich in low-fat dairy foods, rich in calcium and potassium, and low in sodium (compared with the Mediterranean diet). These factors, along with the high levels of flavonols, flavanones, carotenoids and phytosterols in the DASH diet [102,103] could be improving antioxidant capacity and reducing oxidative stress, thereby contributing to greater benefit in terms of MetS reduction.

4. Conclusion and future needs

MetS prevalence is increasing worldwide with increasing obesity, sedentary behaviours and population ageing. The aetiology of the MetS involves a complex interaction of genetic, metabolic and environmental factors, including dietary habits. At present, there is no consensus on the most appropriate dietary recommendations for the prevention and treatment of the MetS [104], although various diets are recommended for each of its components.

Over the past decade, research has focused on dietary patterns, inflammation and the MetS, and the available evidence, based on several observational studies in adults, generally supports a negative association between the MetS and several \textit{a priori} indices and dietary patterns consistent with healthy eating, such as the Mediterranean dietary pattern and food/nutrition-based guidelines such as the DASH and HEI in the US, and the PNNS guidelines in France. In fact, many of these \textit{a priori} indices share several commonalities despite certain specificities. Thus, it is not surprising that, for most of these \textit{a priori} dietary scoring systems and patterns, a consistent negative association has been observed with the MetS across several countries. This is also true for several markers of inflammation, including proinflammatory cytokines, adhesion molecules and markers of endothelial dysfunction. In addition, evidence from well-designed interventional studies in Mediterranean countries in subjects with the MetS or at risk for CVD have shown benefits with following a healthy dietary pattern, such as the Mediterranean diet, not only on markers of inflammation, adhesion molecules and endothelial dysfunction [5,56–58], but also on the MetS and its individual components [57,97,102]. Evidence in the literature supports the idea that healthy diets reduce
inflammation and the MetS through their association with weight control, among other mechanisms. For the most part, studies adjusting for obesity/body fat as well as weight changes (in RCTs) also show that greater adherence to healthy diets is associated with reduced inflammation and reduced MetS incidence, independent of obesity. Furthermore, recent studies have demonstrated that the effect of the Mediterranean diet on components of the MetS and CVD may be mediated by the modulation of several genes involved in inflammation, foam-cell formation and thrombosis [60].

Unhealthy diets promote a proinflammatory milieu marked by higher levels of cytokines (IL-1, IL-6, TNF-α) and CRP, and lower concentrations of circulating adiponectin. A prolonged proinflammatory state could induce insulin resistance, dyslipidemia and endothelial dysfunction [5,33,39], leading to the MetS and its associated complications, including type 2 diabetes and CVD.

Nevertheless, the findings of our present review offer a positive message for public action that involves improved adherence to healthy diets, such as the Mediterranean dietary pattern, and/or following national dietary guidelines to obtain potential benefits in terms of reduced inflammation and MetS incidence. Further prospective studies examining dietary patterns, inflammation and the MetS all at the same time would strengthen these present findings, particularly from the primary prevention perspective. In addition, it would be of interest to concomitantly examine various dietary scores in the same cohort to delineate approaches that are more strongly associated with the MetS. As for secondary prevention of the MetS, although the literature is limited, the few prospective studies and intervention trials that have been conducted in individuals with MetS clearly demonstrate the benefits of following healthy dietary patterns like the Mediterranean diet and those based on dietary guidelines (such as the HEI). Advocating healthier eating patterns consistent with dietary guidelines and a Mediterranean-style diet would also be consistent with reducing inflammation and the MetS while improving overall health.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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