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# Dietary strategies to reduce metabolic syndrome

**Catherine J. Andersen · Maria Luz Fernandez**

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**Abstract** Metabolic syndrome (MetS) is a cluster of metabolic abnormalities characterized by central obesity, dyslipidemias, hypertension, high fasting glucose, chronic low-grade inflammation and oxidative stress. This condition has become an increasing problem in our society where about 34 % of adults are diagnosed with MetS. In parallel with the adult situation, a significant number of children present lipid abnormalities and insulin resistance, which can be used as markers of MetS in the pediatric population. Changes in lifestyle including healthy dietary regimens and increased physical activity should be the first lines of therapy to decrease MetS. In this article, we present the most recent information on successful dietary modifications that can reduce the parameters associated with MetS. Successful dietary strategies include energy restriction and weight loss, manipulation of dietary macronutrients—either through restriction of carbohydrates, fat, or enrichment in beneficial fatty acids, incorporation of functional foods and bioactive nutrients, and adherence to dietary and lifestyle patterns such the Mediterranean diet and diet/exercise regimens. Together, the recent findings presented in this review serve as evidence to support the therapeutic treatment of MetS through diet.

**Keywords** Metabolic syndrome · Dyslipidemia · Insulin resistance · Inflammation · Energy restriction · Carbohydrate-restricted diets · Fatty acids · Functional foods · Mediterranean diet

**Abbreviations**

| | |
|---|---|
| ALA | α-linoleic acid |
| Apo | Apolipoprotein |
| CHD | Coronary heart disease |
| CRD | Carbohydrate-restricted diet |
| CRP | C-reactive protein |
| CVD | Cardiovascular disease |
| DHA | Docosahexanoic acid |
| EPA | Eicosapentanoic acid |
| FFA | Free fatty acids |
| GPX | Glutathione peroxidase |
| HDL-C | HDL-cholesterol |
| HOMA | Homeostatic model assessment |
| IL | Interleukin |
| Keap1 | Kelch-like ECH-associated protein 1 |
| LDL-C | LDL-cholesterol |
| MCP-1 | Monocyte chemoattractant protein-1 |
| MetS | Metabolic syndrome |
| MUFA | Monounsaturated fatty acid |
| NAFLD | Non-alcoholic fatty liver disease |
| NFE2L2 | Nuclear factor (erythroid-derived 2)-like 2 |
| NF-κB | Nuclear factor κ B |
| PBMC | Peripheral blood mononuclear cells |
| PUFA | Polyunsaturated fatty acid |
| PYY | Peptide tyrosine tyrosine |
| RESMENA | Metabolic Syndrome Reduction in Navarra dietary pattern |
| ROS | Reactive oxygen species |
| SFA | Saturated fatty acid |
| sICAM-1 | Soluble intercellular adhesion molecule 1 |
| T2DM | Type 2 diabetes mellitus |
| TG | Triglyceride |
| TLR | Toll-like receptor |
| TNFα | Tumor necrosis factor α |
| TXNRD1 | Thioredoxin reductase 1 |
| WC | Waist circumference |

C. J. Andersen · M. L. Fernandez (✉)
Department of Nutritional Sciences, University of Connecticut, 3624 Horsebarn Road Ext., Unit 4017, Storrs, CT 06269-4017, USA
e-mail: maria-luz.fernandez@uconn.edu

## 1 Introduction

The metabolic syndrome (MetS) constitutes a cluster of metabolic abnormalities, which double the risk for coronary heart disease (CHD) and increase the risk for type 2 diabetes mellitus (T2DM) 5-fold [1]. In the US, 34 % of the adult

population has been classified as having MetS, with prevalence being higher in other regions of the world [2, 3]. More alarmingly, children as young as 8 years old are now presenting with dyslipidemias and insulin resistance associated with MetS [4, 5]. Thus, MetS has become a significant public health problem associated with increased health costs as it develops into T2DM and CHD [6].

Although MetS definitions can vary across different regions of the world and by different organizations, each definition similarly defines MetS to include central obesity, hypertension, low HDL cholesterol (HDL-C), high triglycerides (TG), and elevated concentrations of fasting blood glucose [7]. In addition to these defining characteristics, MetS is also associated with chronic low-grade inflammation, insulin resistance, atherogenic dyslipidemias and dysfunctional lipoproteins, elevated oxidative stress, a prothrombotic state, and endothelial dysfunction [8, 9]. Physiological parameters associated with MetS are depicted in Fig. 1. Research has clearly demonstrated that these MetS parameters can be reduced with dietary interventions that are targeted for weight reduction, management of plasma lipids and glucose, and reductions in blood pressure and inflammatory markers [10, 11]. The purpose of this review is to present some of the dietary strategies that are commonly used to resolve MetS and associated metabolic abnormalities—particularly emphasizing studies published within the last year. The dietary strategies presented include changes in daily energy intake, macronutrient composition, consumption of functional foods and bioactive nutrients, and adherence to dietary/lifestyle programs. Together, the recent findings presented in this review serve as evidence to support the therapeutic treatment of MetS through diet.

## 2 Energy restriction

Energy restriction is known to be an effective strategy to promote weight loss and ameliorate MetS status [11], while it has also been associated with improved immunity and prolonged lifespan [12]. Energy restriction is often achieved by reducing fat intake [13]; therefore, the majority of findings from energy-restricted diets presented in this section can similarly be classified as low-fat diet interventions.

Energy restriction has been shown to improve body composition, blood pressure, plasma lipids, inflammatory markers, and insulin sensitivity in children [14], as well as overweight/obese adults following an energy-restricted diet containing low fructose or moderate natural fructose levels [15]. While reducing fructose as added sugar is beneficial in ameliorating MetS

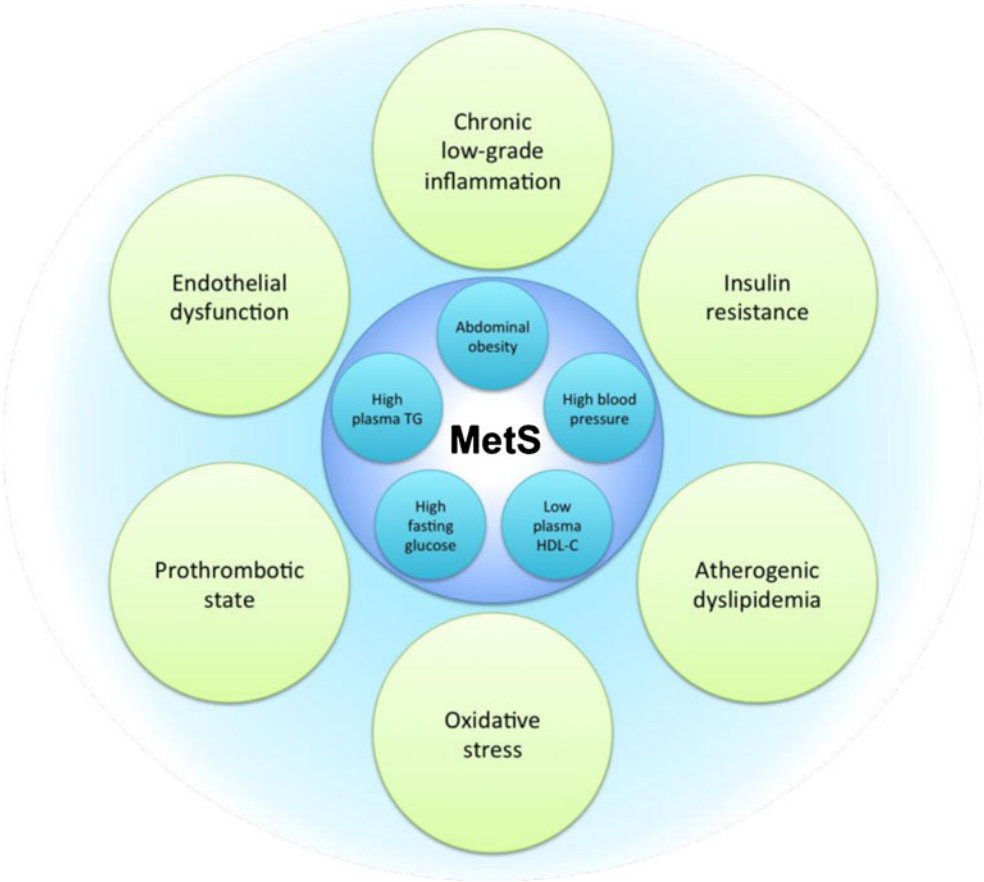


**Fig. 1** Overview of MetS parameters. Regardless of the metabolic syndrome (MetS) definition used, individuals classified with MetS possess a combination of key parameters, including abdominal obesity, high fasting blood glucose, reduced HDL-cholesterol (HDL-C), elevated fasting plasma triglycerides (TG), and elevated blood pressure (inner circles). In addition to these defining characteristics, MetS is additionally associated with chronic low-grade inflammation, insulin resistance, atherogenic dyslipidemias and dysfunctional lipoproteins, elevated oxidative stress, a prothrombotic state, and endothelial dysfunction (outer circles). All of these factors contribute to the increased risk of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) in this population

parameters during energy restriction, the consumption of whole grains vs refined grains provides further benefit. In 50 obese male and female subjects with MetS following a hypocaloric diet (−500 kcal/day), body composition and plasma lipids were improved by caloric restriction regardless of grain type intake. However, whole grain intake promoted greater decreases in waist circumference, as well as a 38 % decrease in C-reactive protein (CRP) that was not observed in the calorie-restricted refined grain group [16]. Whole grain intake was associated with greater intakes of fiber and magnesium, which have independently been implicated in protection against MetS [11]. Magnesium deficiency promotes oxidative stress and inflammation, and may also affect pathways implicated in dysfunctional endothelium and maintenance of body weight [17].

Energy restriction has also been shown to alter lipoprotein kinetics and metabolism in MetS [18–21]. Weight loss from energy restriction has been shown to induce favorable shifts in markers of TG-rich lipoproteins, including reductions in apolipoprotein (apo) C-III, VLDL-apoB, and remnant-like particle-cholesterol and -TG levels in men with MetS [18]. Using stable isotope tracers, Ng et al. [19]. reported that consumption of a low-fat, hypocaloric diet reduced the production of VLDL apoB-100, as well as the catabolism of LDL apoB-100, corresponding to reductions in plasma TG, LDL-cholesterol (LDL-C), and apoB. Further, this diet reduced the catabolic and production rates of HDL apoA-I without changing plasma HDL-C or apoA-I levels [19]. Reductions in plasma apoA-II in this population were similarly explained by reduced fractional catabolic and production rates of apoA-II [20]. A combination of a free-living hypocaloric diet combined with an isocaloric Mediterranean diet similarly increased HDL-C through reducing apoA-I fractional catabolic rate, without changing production rate [21]. In addition, energy restriction has further been shown to reverse features of MetS and improve vascular integrity in aged high-fat diet-fed rats [22].

Together, these findings support the notion that weight-loss programs targeting energy restriction can be effective approaches to ameliorating numerous MetS parameters, and can yield benefits similar to those achieved with diets focused on portion control and glycemic index. However, these programs have also been found to reduce HDL-C [23]—a potentially detrimental effect in populations that already have suboptimal HDL-C levels [9]. Additional concerns arise with long-term dietary adherence, since energy-restricted diets can be more difficult to follow when compared to diets based on food groups and dietary patterns, such as diets emphasizing carbohydrate restriction or Mediterranean-style food choices [24, 25].

## 3 Macronutrient composition

Aside from restricting total calories, manipulation of dietary macronutrient distribution and type has been associated with varying degrees of efficacy in treating MetS. This section will highlight recent studies examining the effects of macronutrients on MetS parameters.

### 3.1 Carbohydrate restriction

For the purpose of this review, carbohydrate-restricted diets (CRD) will be defined as a dietary prescription with 10–35 % of energy from carbohydrate sources. CRD have been shown to efficiently target all parameters of MetS [26]. CRD decrease plasma TG, increase HDL-C, lower blood pressure, reduce plasma glucose and are very effective in reducing visceral obesity [27]. The effect of CRD on plasma lipids is particularly important since few lifestyle modification interventions have been shown to successfully increase HDL-C [10]. Thus, CRD are possibly the best dietary approach to effectively resolve MetS. Diets containing 10 % [28] to 40 % [29] of energy from carbohydrate sources have been shown to effectively ameliorate the dyslipidemias and inflammatory markers associated with MetS. A 25 % CRD similarly reduced these parameters in populations with a high prevalence of MetS [30].

Some evidence from animal studies suggests that the beneficial effects of CRD on MetS parameters may occur at the expense of the liver. In a hereditary hypertriglyceridemic rat model of MetS, high-sucrose feeding promoted VLDL secretion, down-regulated free fatty acid (FFA) oxidation, and increased *de novo* FFA synthesis from glucose, whereas the reverse effect was observed with high-fat feeding [31]. These changes corresponded to greater plasma TG and FFA in the sucrose group, as well as increased liver TG deposition in both fed and fasting states in the high-fat-fed animals [31]. While this study suggests that more data may be needed to properly assess the benefits of carbohydrate-restriction in MetS, human studies have shown that carbohydrate restriction may benefit hepatic steatosis and MetS [32–34]. Further, carbohydrate-restriction was shown to be more effective in reducing liver TG than calorie restriction (−55 % vs. −28 %) in subjects with non-alcoholic fatty liver disease (NAFLD), despite similar weight loss between groups [35].

While CRD have been shown to ameliorate numerous MetS parameters, a recent cross-sectional study by Merino et al. [36]. reported that reduced carbohydrate intake (as a percentage of total energy) was associated with more adverse small artery vascular function in subjects with both MetS and T2DM. However, additional markers of MetS, cardiovascular disease (CVD), and inflammation did not differ between quartiles of carbohydrate intake [36]. Additionally, a 12-week hypocaloric CRD (12 % carbohydrate, 59 % fat, 28 % protein) increased postprandial flow-mediated dilation when compared to a hypocaloric low-fat diet (56 % carbohydrate, 24 % fat, 20 % protein) in overweight men with moderate hypertriglyceridemia [37], thereby suggesting that CRD improves endothelial function.

### 3.2 Dietary fat composition

Various dietary strategies for MetS are based on manipulation of dietary fat—whether through restriction of total fat (as % of energy), or through dietary enrichment of specific fatty acids.

For instance, a variety of monounsaturated fatty acids (MUFA) and MUFA-rich foods have been found to be protective against MetS and various CVD risk factors [38], whereas *n*-3 polyunsaturated fatty acids (PUFA), including α-linoleic acid (ALA), eicosapentanoic acid (EPA) and docohexanoic acid (DHA), have similarly been found to exert beneficial effects on MetS parameters—particularly in regard to inflammation [39].

Restriction of total dietary fat as a "low-fat" diet prescription is typically accompanied by restriction of total calories [13]. As described above, energy-restricted, low-fat diets are known to be effective at improving MetS parameters, including body composition, blood pressure, plasma lipids, inflammatory markers, and insulin sensitivity [14, 15]. However, low-fat diets are less effective at decreasing biomarkers for MetS when compared to CRD [26] or the Mediterranean diet [40]. Further, compliance to low-fat diets is particularly important since low-fat diets without caloric restriction may increase plasma TG while reducing HDL-C [41], thereby exacerbating MetS. Similarly, high-fat feeding without carbohydrate-restriction can also promote adverse metabolic outcomes. Interestingly, high-fat feeding (42 % of energy) has also been shown to alter adipocyte progenitor cell populations and gene expression profiles in C57BL/6 mice. In addition to impairing glucose tolerance and insulin sensitivity, high-fat feeding reduced adipocyte progenitor cell populations in thermogenic brown adipose tissue, while also promoting vascular dysfunction and oxidative stress in perivascular adipose tissue arteries [42]. Together, these findings emphasize the importance of adhering to dietary guidelines when significantly manipulating dietary macronutrient distribution, while also suggesting that dietary therapies that optimize intake of beneficial fatty acids may be preferable to reducing total dietary fat in the treatment of MetS.

Numerous publications have recently highlighted the findings of the LIPGENE study, which compared the effects of a MUFA- or saturated fatty acid (SFA)-rich diet, in addition to low-fat, high complex carbohydrate diets (LFHCC) either with or without *n*-3 PUFA supplementation in MetS [43–48]. In the LIPGENE cohort, consumption of a MUFA-rich diet reduced postprandial nuclear factor κB (NF-κB) activity and p65 subunit protein expression in peripheral blood mononuclear cells (PBMC), whereas postprandial tumor necrosis factor α (TNFα) and metalloproteinase 9 mRNA expression were lower when compared to intake of a SFA-rich diet [43]. Proteomic analysis revealed that a SFA-rich meal further increased postprandial PBMC proteins related to oxidative stress and DNA damage, whereas a MUFA-rich meal additionally increased some oxidative stress proteins [44].

Dietary fat has also been shown to differentially affect antioxidant defenses and inflammation in adipose tissue [45, 46]. In the LIPGENE MetS cohort, SFA consumption reduced postprandial expression of antioxidant enzymes catalase, glutathione peroxidase 1 and 3 (GPX1; GPX3), and thioredoxin reductase 1 (TXNRD1), while also increasing mRNA expression of reactive oxygen species (ROS)-generating NADPH oxidase subunits, and kelch-like ECH-associated protein 1 (Keap1)—the negative regulator of antioxidant-promoting transcription factor nuclear factor (erythroid-derived 2)-like 2 (NFE2L2). Conversely, the MUFA-rich diet increased postprandial catalase, GPX1, GPX3, and TXNRD1 when compared to SFA, while also inducing lower Keap1 expression [45]. Interestingly, adipose tissue mRNA expression of interleukin (IL)-1β increased over the 12-week intervention in all diet groups, as did postprandial expression of NF-κB p65, IL-6, monocyte chemoattractant protein (MCP-1), and IL-1β. Plasma levels of IL-6 similarly increased postprandially in both LFHCC groups, with a trend toward increasing in SFA and MUFA groups [46]. These findings suggest that MUFA promotes increases in adipose antioxidant defenses, despite increasing expression of inflammatory cytokines.

Interestingly, MUFA- and LFHCC *n*-3 PUFA-rich diets further promoted postprandial plasma TG and TG-rich lipoprotein clearance when compared to SFA-rich diet and a LFHCC diet alone (without *n*-3 PUFA) in the MetS LIPGENE cohort [47]. In skeletal muscle, MUFA- and LFHCC *n*-3 PUFA-rich diets reduced lipogenic gene expression and in a subset of insulin resistant LIPGENE subjects when compared to insulin sensitive subjects, suggesting that MUFA- and *n*-3 PUFA-rich diets promote insulin sensitivity [48].

Dietary fatty acids have been shown to supplement the beneficial effects of other dietary treatments. The addition of MUFA and ALA-rich rapeseed oil to a 6-month energy-restricted diet was more effective in reducing diastolic blood pressure and serum TG when compared to an olive oil-enriched energy-restricted diet in European men and women with MetS [49]. ALA has similarly been shown to improve abdominal obesity, insulin resistance, dyslipidemia, and vascular function in a high-carbohydrate, high-fat diet—fed rat model of MetS, in addition to improving cardiac and liver inflammation and tissue integrity. Similar beneficial effects were observed in DHA and EPA-fed rats in all parameters other than glucose tolerance [50]. Conversely, oleic acid-rich macademia oil and linoleic-rich safflower oil were shown to increase plasma glucose in the same MetS rat model, and were less favorable in regard to improving adiposity [51]. In women with MetS, microencapsulated conjugated linoleic acid intake during a 90-day hypocaloric diet reduced body fat mass and plasma insulin without altering waist circumference, plasma lipids or blood pressure. Although the placebo (calorie-restricted) group reduced fat mass and waist circumference (WC), the changes in body composition occurred at a slower rate [52].

Similar benefits of MetS parameters have been demonstrated by intake of foods rich in MUFA and n-3 PUFA. In the NHANES 2001–2008 cohort, consumption of MUFA-, fiber-, and antioxidant-rich avocados was associated with a reduced risk of MetS [53]. Consumption of pistachio nuts (42 g or 70 g) during a 12-week American Heart Association step I diet reduced aspartate transaminase in MetS, while also promoting faster glucose clearance from plasma following a glucose challenge. While intake of 42 g of pistachio nuts reduced plasma TG, intake of 70 g pistachio nuts increased LDL-C; however, LDL-C was similarly increased in the control, pistachio-free diet [54]. Fish oil has also been shown to protect against renal injury while promoting anti-inflammatory renal eicosanoid metabolism in a JCR:LA-corpulent rat model of MetS [55]. Together, these data provide evidence to support optimization of diet plans through enrichment of specific fatty acids in the treatment of MetS.

### 3.3 Protein and amino acids

MetS parameters can be favorably modulated by altering total dietary protein (as % of energy), whole food protein sources, and supplementation with specific amino acids. A recent study compared the effects of normal (0.8 g protein .kg$^{-1}$day$^{-1}$) vs. high protein (1.4 g protein .kg$^{-1}$day$^{-1}$) on parameters of MetS in overweight/obese men following an energy-restricted (−750 kcal/day) diet for 12 weeks [56]. All subjects improved body composition and markers of dyslipidemia and insulin resistance during the intervention, with no effect on resting energy expenditure or blood pressure; however, the high protein group lost less lean body mass when compared to the normal protein group [56]. Increased protein intake during calorie restriction has been shown to be an important consideration in older MetS populations to maintain adequate blood protein homeostasis [57].

Beneficial effects on MetS parameters have also been observed from intake of specific protein sources. Sardine protein was more effective than casein in diminishing high-fat diet-induced insulin resistance, inflammation, and adipose tissue oxidative stress in a fructose-induced rat model of MetS [58]. Similar benefits from sardine powder feeding were observed in control chow-fed animals when compared to those fed casein. Cod protein (for 4 weeks) has been shown to reduce CRP [59] and insulin sensitivity [60] in insulin resistant men and women, although it was less effective at reducing total cholesterol, LDL-C, and apoB concentrations when compared to diets rich in beef, pork, veal, egg, and milk product protein [59].

In a placebo-controlled cross-over trial, consumption of L-arginine-enriched biscuits in combination with a hypocaloric diet reduced body weigh, fat mass, plasma glucose, and the proinsulin/insulin ratio in MetS when compared to placebo [61]. The addition of L-arginine further improved markers of endothelial function, such as post-ischemic blood flow, and plasma nitrite and nitrate, and cyclic guanosine monophosphate. Similar benefits were observed postprandially in healthy subjects [61]. Similar to the role of fatty acids in treating MetS, these findings suggest that intake of high-quality protein and amino acids may provide further benefits to diet therapies.

## 4 Functional foods and nutrients

In addition to restriction of energy or modulation of dietary macronutrient content, favorable effects on MetS parameters have been observed through intake of various functional foods and bioactive nutrients. The findings from the recent studies highlighted below provide evidence for incorporation of specific foods into dietary patterns to enhance the effects of therapeutic diet strategies.

### 4.1 Alcohol

Alcohol consumption has been shown to both ameliorate and worsen parameters of MetS. The relationship between alcohol and risk of MetS has been shown to vary according to the type and quantity of alcohol consumed, while also differentially affecting the various MetS parameters [62]. In a recent cross-sectional study, alcohol consumption was shown to dose-dependently increase risk of MetS due to negative impact on triglycerides, abdominal obesity, and fasting glucose. Conversely, a dose-dependent inverse relationship was observed between alcohol intake and risk of low plasma HDL-C [62]. Moderate alcohol consumption has been shown to increase plasma HDL-C, while also increasing the cholesterol-accepting capacity of HDL from cholesterol-laden cells [63, 64]. Moderate consumption of beer, red wine, and spirits has additionally been shown to increase the activity of paraoxonase [65]—an HDL-associated antioxidant enzyme [66]. Together, these findings support the notion that moderate alcohol intake can reduce CVD risk, perhaps in part by improving the atherogenic functions of HDL [67].

Conversely, recent findings suggest that alcohol may worsen glucose insensitivity in a hypercaloric/high-fat diet-fed swine model of MetS by altering hepatic and skeletal muscle insulin signaling pathways [68]. Heavy drinking has also been associated with an increased risk of MetS in Korean [69, 70] and US populations [71]. Therefore, while moderate alcohol consumption favorably affects HDL, careful consideration must be made to ensure that additional MetS parameters are not worsened.

### 4.2 Antioxidants

Antioxidant compounds provided by bioactive foods (i.e. fruits and vegetables) and supplements are known to possess

a wide range of biological activities with antioxidant, anti-inflammatory and hypolipidemic effects [72, 73]. Accordingly, greater dietary and serum antioxidant status has been associated with lower incidence of MetS and MetS parameters [74–76]. While supplementation of vitamins A, C, and E protected against sodium-induced MetS in albino rats by improving plasma lipids (dyslipidemia), insulin sensitivity, and antioxidant defenses [77], antioxidant supplementation (vitamins C and E, $\beta$-carotene, selenium, and zinc) for 7.5 years did not appear to influence risk of developing MetS in French SU.VI.MAX study participants [78]. However, serum $\beta$-carotene and vitamin C were negatively associated with risk of developing MetS, whereas serum zinc was positively associated with MetS risk, suggesting that diets containing antioxidant-rich foods are still protective against MetS development [78].

Although results remain inconclusive, numerous flavonoids and polyphenols have been shown to improve parameters of MetS, including markers of dyslipidemia, endothelial dysfunction, hypertension, obesity and energy expenditure, and insulin resistance [73, 79]. Similar beneficial effects have been demonstrated with functional foods such as pomegranate, which contain a diverse array of bioactive nutrients and phytochemicals that possess insulin-sensitizing, anti-inflammatory, and anti-atherosclerotic properties [80]. In a 30-day placebo-controlled, double-blind study conducted in men with MetS, a polyphenol-rich, freeze-dried grape preparation reduced systolic blood pressure and plasma soluble intercellular adhesion molecule 1 (sICAM-1) while increasing flow-mediated vasodilation [81]. In a swine model of MetS, resveratrol has been shown to protect against chronic ischemia by preserving myocardial function [82], while transgenic resveratrol-enriched rice further improved blood glucose and plasma lipids in high-fat diet fed C57BL mice [83]. Further, antioxidant-rich cocoa lowered TG, glucose, and blood pressure in a rat model of MetS, while additionally reducing liver steatosis when fed in combination with either oats or fish oil [84]. Dietary total antioxidant capacity has similarly been associated with improvements in body composition and liver enzymes in MetS subjects participating in clinical intervention trials [85].

A number of recent studies have reported beneficial effects of blueberry intake on MetS parameters. In a placebo-controlled cross-over study, a wild blueberry drink further reduced oxidized DNA bases in blood mononuclear cells in men with American Heart Association-designated CVD risk factors, while also increasing resistance to $H_2O_2$-induced DNA damage; however, no differences in additional markers of dyslipidemia, inflammation, antioxidant defenses, or vascular function were observed [86]. Conversely, consumption of polyphenol-rich bilberries have similarly been shown to improve plasma and PBMC inflammatory markers in MetS, including suppression of genes involved in toll-like receptor (TLR) signaling, and monocyte transmigration, adhesion and differentiation to macrophages [87]. Similarly, obese Zucker rats (a model of MetS) fed a wild blueberry-enriched diet displayed favorable reductions in pro-inflammatory TNF$\alpha$, IL-6 and CRP in the plasma, while liver and abdominal adipose tissue mRNA expression of TNF$\alpha$, IL-6, and NF-$\kappa$B were further suppressed by blueberry feeding. Interestingly, lean Zucker rats similarly benefited from wild blueberry feeding, as evidenced by reduced NF-$\kappa$B and CRP mRNA expression in the liver, as well as increased adiponectin expression in adipose [88]. It has been hypothesized that some of the beneficial effects of wild blueberries may be attributable to their effect on modulating intestinal microbiota populations in the human gut [89]. Regardless of the mechanism, these recent findings support the concept that antioxidant- and phytonutrient-rich foods and supplements favorably modulate MetS parameters.

### 4.3 Dairy

Several studies have assessed the effects of dairy consumption on MetS, as dairy products are rich sources of protein and micronutrients [90]. Rideout et al. [91]. compared the effects of low- (no more than 2 servings/day) vs. high-dairy (4 servings/day) consumption for 6 months in a randomized, cross-over intervention in MetS. At the end of the intervention, both low- and high-dairy diets were equally effective in lowering plasma glucose and lipids and in reducing blood pressure; however, high-dairy intake resulted in lower plasma insulin and insulin resistance when compared to low-dairy intake [41]. Similarly, when associations of markers of insulin resistance and dairy intake were assessed in a Japanese population [92], authors reported that the individuals in the highest quartile for dairy intake presented the lowest mean of insulin resistance markers. In addition, while they found no association between low-fat dairy and homeostatic model assessment (HOMA), consumption of high-fat dairy was inversely associated with insulin resistance among Japanese adults [92]. Accordingly, high dairy intake was associated with a lower risk of MetS in Korean adults from the Korean National Health and Examination Surveys ($n$=4862) [93].

While dairy appears to benefit markers of insulin sensitivity in MetS, conflicting data has been reported on the effects of dairy on weight loss and body composition. Jones et al. [94]. demonstrated that a calcium-rich dairy diet was not associated with greater weight loss in individuals with MetS, although the high-dairy group were more satiated, had lower dietary fat intake, and had higher concentrations of peptide tyrosine tyrosine (PYY) when compared to the low-dairy group. Conversely, high intake of dairy was associated with lower body mass index and WC in men over the course of 5 years, whereas no significant on changes in metabolic profile were observed in women [95]. However, daily intake of 500 ml skim milk for 12 weeks increased HDL-C in overweight men and women

with MetS, whereas the addition of conjugated linoleic acid-supplementation further reduced total fat mass [96]; although, no other changes in MetS parameters, plasma lipids, or insulin sensitivity were observed. These findings suggest that inclusion of dairy into a habitual diet may promote improvements in markers of insulin sensitivity, blood pressure, dyslipidemia, and potentially body composition.

### 4.4 Eggs and carbohydrate-restriction

Numerous recent studies have demonstrated that the addition of daily egg intake to CRD provides benefits on reducing MetS parameters beyond that of CRD alone [97–100]. Eggs are a rich source of protein and bioactive phospholipids, in addition to antioxidant carotenoids lutein and zeaxanthin provided in the yolk [99, 100]. Blesso et al. [98]. conducted a clinical intervention with 37 individuals (25 females and 12 males) who were randomly allocated to consume either 3 eggs per day ($n$=20) or the equivalent amount of egg substitute ($n$=17). In agreement with previous reports on CRD, all subjects experienced improvements in MetS biomarkers, including low HDL-C, high TG, atherogenic lipoproteins, blood pressure and plasma glucose; however, improvements were greater in the volunteers consuming 3 eggs per day. Individuals in the egg group had more favorable increases in LDL and HDL particle size [97], higher increases in HDL-C, greater reductions in pro-inflammatory TNFα and serum amyloid A [98], and more pronounced decreases in plasma insulin and insulin resistance [97]. Further, lutein and zeaxanthin concentrations increased in plasma, LDL, and HDL fractions as a result of whole egg consumption, which may be attributable to increased bioavailability of these carotenoids from egg yolk [99]. These findings corresponded to an increased capacity of subject serum to accept cholesterol from cholesterol-laden macrophage foam cells, further supporting the notion that egg intake during carbohydrate-restriction provides greater benefit to MetS in the prevention of CVD [100].

### 4.5 Fiber

MetS parameters have been shown to be ameliorated by intake of both soluble and insoluble fiber. β-glucans—types of soluble fiber—have been shown to improve various parameters of MetS, including abdominal obesity, appetite, hypertension, hyperglycemia and insulin levels. β-glucans may also serve as a beneficial prebiotic to exert favorable effects on gut microbiota [101]. Supplementation with soluble fiber from partially hydrolyzed guar gum for 4–6 weeks reduced waist circumference, serum *trans*-fatty acids, glycosylated hemoglobin, and urinary albumin excretion in male and female patients with MetS and T2DM [102]. Intake of soluble fibers have additionally been shown to promote greater improvements in plasma lipids and glucose when compared to insoluble fiber [103].

Beneficial effects on MetS parameters have also been demonstrated with intake of soluble fiber-rich foods. Consumption of pulses (beans, lentils, chickpeas, yellow peas) for 8 weeks has been shown to be more effective at increasing HDL-C and C-peptide when compared to energy restriction (−500 kcal/day) in overweight/obese adults, while both dietary strategies improved waist circumference, systolic blood pressure, glycosylated hemoglobin, and glucose sensitivity. Interestingly, energy restriction was more effective at reducing insulin in women, whereas the pulse-rich diet was more effective at reducing insulin in men [104].

While benefits may not be as pronounced [103], similar beneficial effects on additional MetS parameters have been observed with intake of insoluble fiber. In men and women with MetS, intake of high-amylose maize-derived insoluble fiber increased glucose uptake by forearm muscle, reduced plasma FFA, and increased mRNA expression of adipose tissue lipases and perilipin [105]. Lipases are important for lipid mobilization and uptake, and have been shown to be reduced in obesity and T2DM [106, 107]. These changes corresponded to lower fasting plasma glucose, insulin, and HOMA measures; however, no differences were observed in hepatic insulin sensitivity as measured by euglycemic-hyperinsulinemic clamp [105].

### 4.6 Probiotics

An increasing amount of evidence has highlighted an important role for gut microbiota in the prevention, development, and severity of chronic metabolic diseases. Modulation of intestinal microflora populations has therefore become a target for diet therapies [108]. Supplementation with probiotics has recently been shown to exert beneficial effects on MetS, and has been associated with reducing body, liver, and adipose tissue weight in animal models [109]. Supplementation with *Bifidobacterium adolescentis* helped preserve insulin sensitivity in a high-fat diet-induced rat model of MetS [110], whereas similar protection from high-fat/fructose feeding against insulin resistance was observed in rats fed *Lactobacillus pantarum* K68 [111]. Supplementation with *Lactobacillus plantarum* and *Lactobacillus curvatus* similarly decreased plasma TG, glucose, and insulin in a fructose-fed rat model of MetS, as well as reductions in thiobarbituric acid reactive substances—a marker of oxidative stress [112]. Higher daily probiotic doses further altered hepatic gene expression to increase β-oxidation genes, while reducing mRNA expression of lipogenic genes. These changes corresponded to reduced liver mass and cholesterol levels from probiotic intake when compared to the high-fat diet-fed rats without probiotic treatment [112].

Although probiotic treatment has favorable effects of lipid metabolism, conflicting effects on inflammation have been reported. In addition to reducing hepatic lipids, heat-inactivated

*Lactobacillus gasseri* TMC0356 increased blood leukocyte counts, in addition to increasing CRP, TNFα, IL-6, and immunoglobulin G in a high-fat/salt-fed rat model of MetS [113]. Conversely, plasma TNFα and IL-1β were found to be reduced by probiotics in high-fat/cholesterol-fed C57BL/6 J mice [109] and in a high-fat/fructose rat model of MetS [111]. These differences may be attributable to variations in probiotic strains and experimental models.

In humans, a recent probiotic supplementation study conducted in MetS subjects found that supplementation of *Lactobacillus casei* for 3 months increased serum levels of CRP and lipopolysaccharide-binding protein [114]—both markers of inflammation associated with acute-phase responses to infection, obesity, and MetS [115]. Although MetS subjects also had greater gut permeability when compared to healthy controls, supplementation had no effect on circulating levels of endotoxin, neutrophil function, or TLR-2, -4, or -9 neutrophil expression [114]. Together, these findings suggest that further research is warranted to determine the effects of probiotic supplementation on dyslipidemia, inflammation, immunity, and CVD outcomes in MetS before recommendations can be made.

## 5 Dietary and lifestyle regimens

The goal behind the development of dietary patterns and lifestyle regimens is to enhance global diet quality and the ease of adherence to a therapeutic program. These dietary patterns often incorporate many of the functional foods and nutrients described above to enhance metabolic benefits obtained from energy restriction and macronutrient manipulation.

### 5.1 Mediterranean diet

There is consistent evidence from epidemiological data and clinical interventions that the Mediterranean diet is an effective approach to reduce risk of MetS, as well as lower the incidence of individual MetS parameters [7, 116]. This nutrient-dense dietary pattern promotes incorporation of beneficial fatty acids and phytonutrient-rich foods to exert therapeutic benefits under both weight-stable and weight-loss conditions.

Jones et al. [117]. conducted a dietary intervention in which 89 women with MetS followed a Mediterranean-style diet for 12 weeks. Half of the subjects ($n$=45) were additionally given a medical food rich in soy protein and soy sterols while the remaining subjects ($n$=44) only followed the Mediterranean dietary prescription. Independent of group assignment, all subjects experienced significant reductions in body weight, plasma TG, blood pressure and WC, as well as decreases in atherogenic lipoproteins [118] and inflammatory markers [119]. At the end of the intervention, almost 50 % of the women no longer had MetS [117]. In addition to reductions in inflammation, Mediterranean diets have additionally been shown to improve markers of insulin resistance and lipoprotein metabolism [120–122]. A 3-month Mediterranean diet decreased plasma TG and chylomicron-associated apolipoprotein B-48 after a test meal in MetS [123], whereas LDL-C and apo B were reduced after a 4-week isoenergetic Mediterranean diet in men and women with MetS risk factors [124].

Other studies have reported a significant decrease in body weight even after 2 years of following the Mediterranean diet, where weight loss was greater than for those who were following a low-fat diet [25]. In addition to promoting greater weight loss, the Mediterranean diet appears to be more effective in reducing dyslipidemias, plasma glucose, CRP [40], and markers of oxidative stress [125] when compared to a low-fat diet. Interestingly, other studies have also shown decreases in CRP in the absence of weight loss [122]. Further, in a study that examined 7,447 individuals aged 55–80 years who were followed for 4.8 years, a significant decrease in the incidence of major coronary events was reported when compared to a control low-fat diet [126]. Results from these studies suggest an overall protection of this dietary prescription on biomarkers for MetS.

### 5.2 Meal timing and energy density

In addition to regulating specific food intake and overall dietary composition, the timing, energy density, and food patterns of meals have been associated with MetS outcomes. A case-control study by Menegotto et al. [127]. reported that MetS patients with T2DM consumed lunches with higher energy density, in addition to lower intake of beans, vegetables and meat at lunch. Almoosawi et al. [128]. additionally reported that carbohydrate intake for breakfast and mid-morning meals while reducing fat was protective against developing MetS in middle age, while also protective against abdominal obesity and high plasma TG. In Korean adults, breakfast patterns consisting of eggs, breads, and processed meat were associated with worse MetS outcomes, whereas breakfasts consisting of potato, fruit, and nuts were associated with lower risk of having high fasting glucose and blood pressure [129]. These findings suggest that distribution of energy and food groups throughout the day contribute to the efficacy of dietary interventions.

### 5.3 Combined dietary and lifestyle regimens

In contrast to focusing on specific foods and nutrients, recent studies have also examined the impact of global dietary and lifestyle changes on MetS outcomes, which often include a universal overhaul of dietary practices and incorporation of physical activity. Japanese men had a lower risk of MetS with closer adherence to the American Heart Association Diet and

Lifestyle guidelines, which promote consuming diets rich in fruits, vegetables, whole grains, oily fish, while limiting total fat, saturated fat, dietary cholesterol, added sugars, sodium, and excessive alcohol intake [130]. High-sodium intake has similarly been associated with MetS incidence, as well as associated insulin resistance, hypertension, low HDL-C, and cortisol levels [131].

The efficacy of two energy-restricted diets (<30 %) on ameliorating MetS dysfunction in conjunction with hyperglycemia was recently investigated by de la Iglesia et al. [132].. The two diets were based on 1) the American Heart Association recommendations (55 % carbohydrate, 15 % protein, 30 % fat over 3–5 meals per day while keeping cholesterol <300 mg/d), or 2) the Metabolic Syndrome Reduction in Navarra (RESMENA) diet, which was characterized by a target macronutrient distribution of 40 % carbohydrates, 30 % protein, and 30 % fat, low-glycemic load, high *n*-3 fatty acid content, high dietary antioxidant capacity, and increased meal frequency (seven meals per day). After 180 days, both diets improved body composition, blood pressure, TG, and markers of insulin sensitivity; however, only the RESMENA diet improved plasma oxidized LDL, glucose, FFA levels, and android fat mass. Conversely, the American Heart Association diet had more favorable effects on HDL-C, AST, and malondialdehyde [132].

Combined diet and exercise programs have also been shown to reduce rates of MetS development and incidence in impaired glucose tolerant subjects [133]. Both high- and low-glycemic diets (non-energy restricted) while following an exercise program were equally effective in reducing blood pressure, TG, and glucose in MetS, whereas the low-glycemic diet was more effective at reducing waist circumference [134]. The addition of physical activity aided in additional reductions in visceral adiposity in men following an energy-restricted diet (−500 kcal/

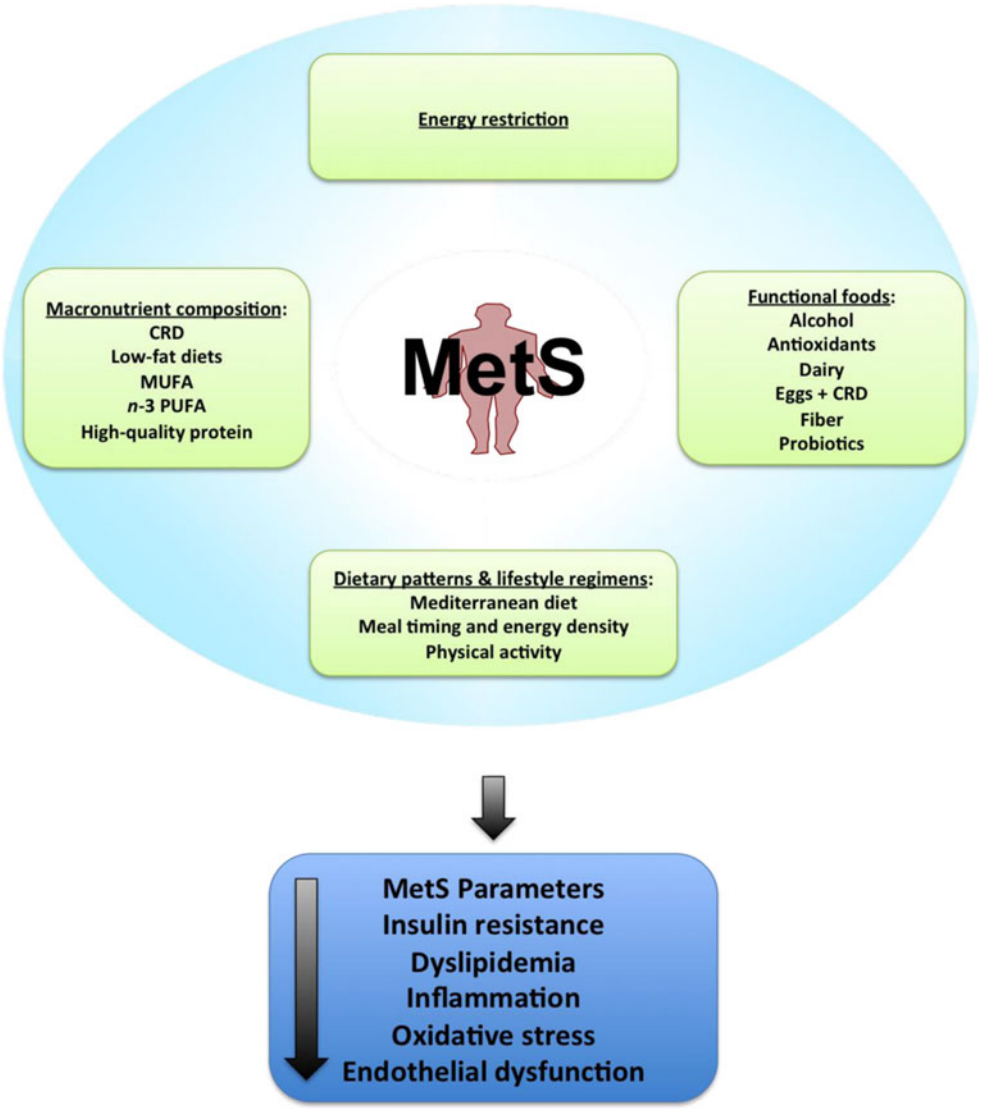


**Fig. 2** Dietary strategies to reduce MetS. Lifestyle modification that includes healthy dietary regimens and increased physical activity should be the first-lines of therapy to decrease metabolic syndrome (MetS). Successful dietary strategies include 1) energy restriction, 2) manipulation of dietary macronutrients; either through restriction of carbohydrates, fat, or enrichment in monounsaturated fatty acids (MUFA) or *n*-3 polyunsaturated fatty acids (PUFA), or inclusion of high-quality protein sources, 3) incorporation of functional foods and bioactive nutrients, such as alcohol, antioxidants-rich foods, dairy, eggs in combination with carbohydrate-restricted diets (CRD), fiber, and probiotics; and 4) adherence to dietary/lifestyle patterns such the Mediterranean diet and diet/exercise regimens. Together, these therapeutic dietary strategies reduce the classical defining MetS parameters, in addition to markers of insulin resistance, dyslipidemia, inflammation, oxidative stress, and endothelial dysfunction

day) [135], where high intensity exercise (either resistance or endurance) has been found to be more effective in reducing visceral fat than moderate exercise [136].

## 6 Conclusion

It is clear from the studies presented in this review that dietary and lifestyle modifications can significantly improve metabolic abnormalities associated with MetS [10, 11]. An overview of the effects of energy restriction, dietary macronutrient composition, functional foods and bioactive nutrients, and dietary/lifestyle regimens on MetS parameters is depicted in Fig. 2. Together, these therapeutic dietary strategies reduce the classical defining MetS parameters—including abdominal obesity, high fasting blood glucose, reduced HDL-C, elevated fasting plasma TG, and elevated blood pressure—in addition markers of chronic low-grade inflammation, insulin resistance, atherogenic dyslipidemias and dysfunctional lipoproteins, elevated oxidative stress, a prothrombotic state, and endothelial dysfunction. While different dietary strategies have varying degree of efficacy on the broad range of MetS parameters, the findings presented in this review provide comprehensive evidence to support the therapeutic treatment of MetS through diet.

**Conflict of interest** Catherine Andersen and Maria Luz Fernandez have no conflict of interests in the data presented in this review.

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