

# Role of nutrients in metabolic syndrome: a 2017 update

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**Abstract:** Metabolic syndrome (MetS) and its associated chronic disorders including cardiovascular disease and type 2 diabetes are public health concerns in the USA and worldwide. “Good health is an investment in economic growth,” and nutrition is one of the recommended preventive measures to manage these chronic diseases. However, it is unclear whether and to what extent nutrients could be beneficial to the improvement of MetS. To help answer this question, we performed a literature review of the emerging human data on single nutrients and MetS: PubMed was searched from January 1, 2005 to June 12, 2017, using a combination of the following keywords: “nutrient” OR “vitamin” OR “mineral” OR “nutraceutical” AND “metabolic syndrome.” The summary of literature comprises macronutrients (proteins/amino acids, fatty acids, fibers, and sugar), micronutrients (antioxidant vitamins, vitamin D, folate, magnesium, and chromium), polyphenols (flavonoids, resveratrol, isoflavones, and chlorogenic acid), and other compounds ( $\alpha$ -lipoic acid, benfotiamine, fucoxanthin, policosanols, and stanols). Bearing a holistic approach in mind, we also highlighted select lifestyle factors that may contribute to MetS (such as circadian rhythm and nutrition in early life). Observational studies have generated positive evidence supporting the beneficial role of numerous nutrients in MetS. Although the results of some clinical trials are consistent with the observational data, causality is not always clear or consistent across trials. Both nutrition and health are complex and dynamic systems with a hierarchical nature. When we design confirmatory trials to investigate nutrient(s) and MetS, instead of the traditional “single-nutrient” concept, it is worth considering a holistic approach to integrate groups or classes of nutrients, lifestyle influencers (ie, diet and physical activity), and population relevance (ie, healthy, at-risk, or diseased).

**Keywords:** nutrient, metabolic syndrome, obesity, hypertension, dyslipidemia, insulin resistance

## Introduction

Metabolic syndrome (MetS) is a constellation of interrelated metabolic abnormalities that are major risk factors for the development of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). There are various definitions of MetS (eg, World Health Organization, the International Diabetes Federation, and the US National Cholesterol Education Program’s Adult Treatment Panel III [NCEP/ATP III]).<sup>1</sup> The most widely used definition (from the NCEP/ATP III) is defined as the presence of three or more of the following metabolic disorders: central obesity (waist circumference:  $\geq 102$  cm for men,  $\geq 88$  cm for women), dyslipidemia (high-density lipoprotein cholesterol [HDL]:  $< 40$  mg/dL for men,  $< 50$  mg/dL for women; or triglycerides [TGs]  $\geq 150$  mg/dL), hypertension (systolic/diastolic blood pressure  $\geq 130/85$  mmHg), and insulin resistance (elevated fasting blood glucose  $\geq 110$  mg/dL).<sup>2</sup>

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MetS and its associated chronic diseases are public health concerns in the USA and worldwide. About 34% of US adults have MetS,<sup>3</sup> and 9.3% of the US population (29.1 million) are diabetic.<sup>6</sup> MetS is associated with an increase in risks of developing CVD and T2DM over the next 5–10 years.<sup>4</sup> Each year, one in every four deaths among Americans is attributed to heart disease, totaling about 610,000 deaths annually.<sup>5</sup> The annual combined cost (direct and indirect expenditures) of CVD (hypertension, heart disease, and stroke) and diabetes in the USA was \$650 billion in 2003 and is projected to be \$1.96 trillion by 2023.<sup>7</sup> Prevention and early management of MetS may help manage these disease burdens and the associated health care cost worldwide.

“Good health is an investment in economic growth,”<sup>7</sup> and nutrition is one of the recommended preventive measures to help manage chronic morbidities.<sup>8</sup> However, it is unclear whether and to what extent single nutrients could be beneficial to MetS. To help address this question, we reviewed relevant literature in the past decade and summarize emerging human data for single nutrients’ influence on MetS in this review.

## Literature search methods

We searched PubMed from January 1, 2005 to June 12, 2017, by using a combination of the following keywords: “nutrient” OR “vitamin” OR “mineral” OR “nutraceutical” AND “metabolic syndrome.” Table S1 summarizes the reviews, systematic reviews, and meta-analyses of human data published in English.

The focus of this review is on the specific role of individual nutrients in the prevention or treatment of MetS among US adults. In the section of “Literature summary/Discussion,” individual nutrients are grouped into one of the following four categories: macronutrients, micronutrients, polyphenols, and other compounds. Specific dietary patterns, food groups, gene/drug–nutrient interactions, biochemical/molecular mechanism, or pediatric studies are not included in the present review.

## Literature summary/discussion

Figure 1 summarizes the literature data on key nutrients and MetS parameters

### Macronutrients

#### Proteins/amino acids

A review of human acute feeding trials and relevant meta-analyses concludes that, compared with lower-protein diets, higher-protein energy-restriction diets containing 1.2–1.6 g

protein/kg/day improve appetite, weight management (eg, loss of fat mass while maintaining lean muscle), and some cardiometabolic risk factors (eg, lowering fasting TGs) over a short term (<1 year).<sup>9,10</sup> The long-term data ( $\geq 1$  year) are less consistent primarily due to discrepant dietary compliance, but there is persistent evidence supporting the benefits of increased protein consumption on weight maintenance.<sup>9,10</sup> Hypothesized mechanisms of action include an increase in thermogenesis and metabolic rate and a modest satiety effect after the consumption of protein-rich meals.<sup>9,10</sup>

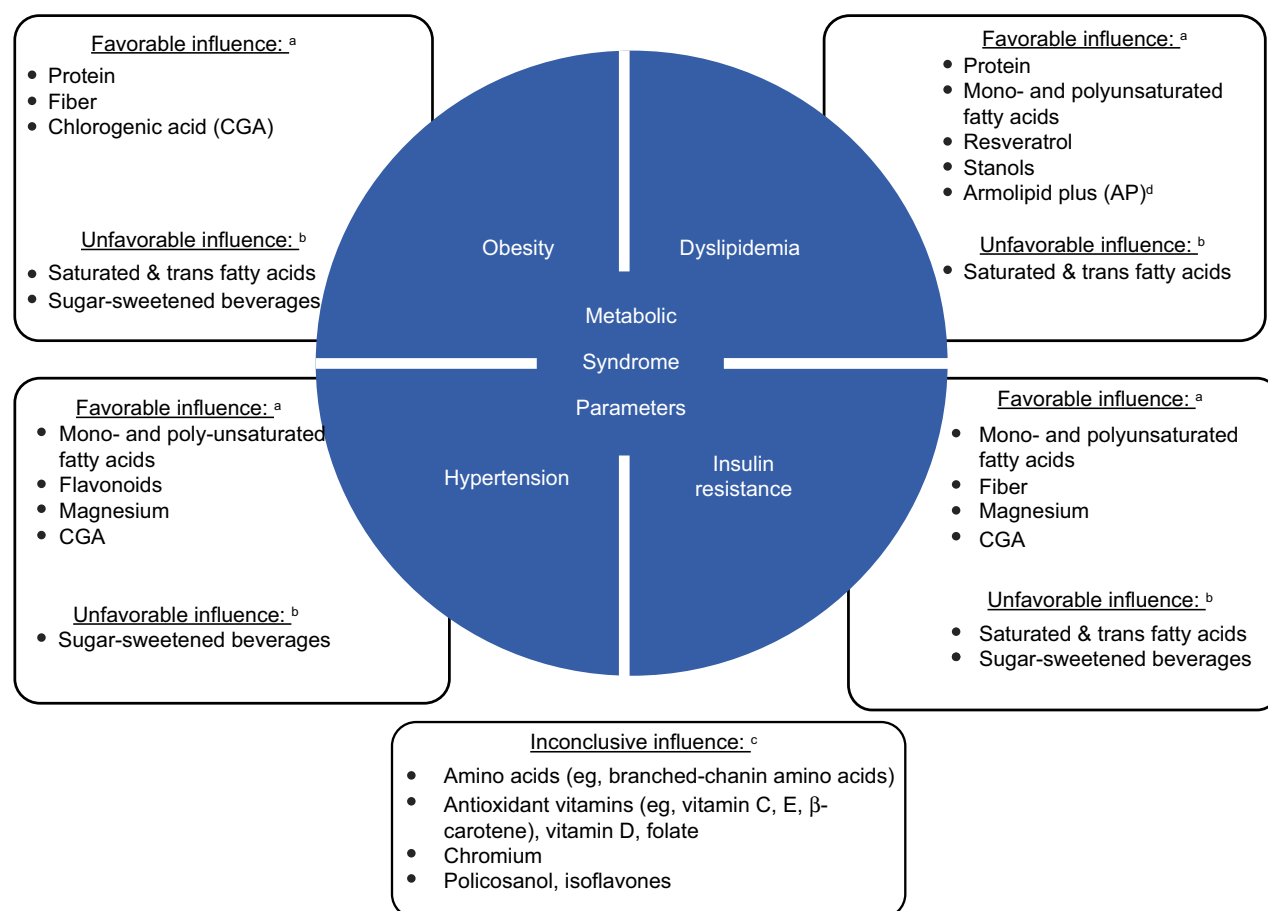
Certain amino acids including glutamine derivatives, alanine and arginine, may influence pancreatic  $\beta$ -cell function (eg, insulin secretion), but the mechanism is not completely understood.<sup>11</sup> Human studies report that consumption of dairy products rich in branched-chain amino acids (BCAAs; leucine, isoleucine, and valine) or whey/casein protein is associated with improved diabetic parameters (eg, fasting insulin levels) among obese and T2DM individuals.<sup>11,12</sup>

When human subjects with hypercholesterolemia consumed lupin protein (25 g/day) with a mixed diet for 28 days, their plasma levels of total cholesterol (TC), TGs, and low-density lipoprotein cholesterol (LDL) decreased.<sup>2</sup> Animal or in vitro data have reported benefits of peptides (synthesized or extracted from dietary proteins) for lipid metabolism, but human data are limited.

#### Fatty acids

According to recent evidence, saturated and trans fatty acids have deleterious influences on metabolic health.<sup>4,13–15</sup> In contrast, unsaturated fatty acids including monounsaturated fatty acids and omega-3/omega-6 polyunsaturated fatty acids (PUFA) improve metabolic parameters (eg, blood pressure, lipid profile, glycemic control, and insulin sensitivity).<sup>4,13–15</sup> Diets rich in conjugated linoleic acid (CLA), in particular the *cis-9 trans-11*-CLA isomer, have been shown to improve the markers of metabolic and insulin sensitivity in adipose tissue and liver, indicating a potential benefit for metabolic health.<sup>15</sup> It is important to note that these benefits are linked to the consumption of the dietary components as part of a specific diet, suggesting a need for human studies to confirm the benefit of single nutrients.<sup>13</sup> In addition, more data are needed to define the optimal composition of dietary fatty acids (eg, amount and type) to which metabolic health will be affected.<sup>4</sup>

The Japanese have the highest intake of omega-3 fatty acids in the world. Even in this population, omega-3 and omega-6 fatty acids have been reported to provide some protection against cardiac and major coronary events.<sup>16</sup> Based



**Figure 1** Select nutrients on metabolic syndrome parameters.

**Notes:** <sup>a</sup>Favorable influence: human data indicate positive influence of a single or group of nutrient(s) on metabolic syndrome parameters. <sup>b</sup>Unfavorable influence: human data indicate negative influence of a single or group of nutrient(s) on metabolic syndrome parameters. <sup>c</sup>Inconclusive influence: human data are inconsistent or lacking. <sup>d</sup>Armolipid plus (AP): a commercial dietary supplement combining policosanol, berberine, red yeast rice extract, folic acid, coenzyme Q10, and asthaxanthine.

on evidence from randomized controlled trials (RCTs), the American Heart Association concluded that omega-3 fatty acids have been demonstrated to reduce the risks of CVD events in patients with coronary artery diseases.<sup>14</sup> While there is little direct evidence that omega-3 PUFA supplementation affects insulin sensitivity in humans, epidemiological studies found that habitual fish intake is associated with the reduced incidence of T2DM.<sup>15</sup>

## Fiber

Observational data indicate an inverse relationship between dietary fiber intake (from cereals and whole grain) and body weight/diabetes/CVD.<sup>14</sup> According to a meta-analysis of six prospective studies, an increase in whole grain consumption by two servings per day may reduce the risk of diabetes by 21%.<sup>14</sup> Fiber is commonly classified as soluble or insoluble,

based on its solubility in water. Soluble dietary fiber is associated with improved glycemic control and insulin sensitivity in both diabetic and healthy subjects, generally attributable to its viscous properties. It, however, does not appear to reduce the risk of T2DM.<sup>14</sup> In contrast, insoluble fiber reduces the risk of diabetes, even though it has negligible influence on postprandial glucose levels.<sup>14</sup>

## Sugar

Sugar-sweetened beverages (SSBs) contain caloric sweeteners such as sucrose, high-fructose corn syrup, or fruit juice concentrates and are the primary source of added sugar in the US diet.<sup>17</sup> A meta-analysis pooled data from 11 prospective cohort studies and included 19,431 participants for MetS (5,803 cases) and 310,819 for T2DM (15,043 cases). Compared with individuals who rarely consume SSB (none or <1 serving/month), those

who consumed one to two servings per day were at a higher risk of developing MetS (relative risk [RR] =1.20; 95% confidence interval [CI] =1.02–1.42) and T2DM (RR =1.26; 95% CI =1.12–1.41).<sup>17</sup> In addition, a longitudinal cohort followed >88,000 women for 24 years and found that consumption of  $\geq 2$  SSBs/day was associated with a 35% increased risk for coronary heart disease compared with infrequent consumers (RR=1.35; 95% CI=1.1–1.7).<sup>17</sup> A number of prospective cohort studies have also reported positive associations between SSB consumption and incidence of hypertension.<sup>17</sup>

In response to convincing evidence linking SSBs to metabolic disorders, organizations such as the American Heart Association have called for reducing the consumption of SSBs. In addition, the US Food and Drug Administration (US FDA) announced new food-labeling rules stating that the content of added sugar must be called out on food labels in the near future. Low-energy sweeteners are emerging as a potential replacement for traditional sugar. In vivo human studies have extensively studied the influence of this group on metabolic health and indicate inconsistent evidence linking low-energy sweeteners to unfavorable metabolic changes (eg, increased appetite, altered glucose homeostasis, or blood pressure).<sup>18</sup>

## Micronutrients

### Antioxidant vitamins

Systemic inflammation and oxidative stress are core mechanisms connecting energy overload and obesity to insulin resistance and consequent metabolic disorders.<sup>14,19</sup> Antioxidant compounds can modulate oxidative stress and potentially prevent health complications that are associated with oxidative damage.<sup>19</sup> As an example, vitamin A in the form of retinol not only influences immune function, but can also reverse chronic inflammation by reducing the level of adipocytokines according to in vitro and in vivo data.<sup>20</sup> Animal data indicate retinol-binding protein (RBP4; the transport protein for retinol) concentrations are inversely related to insulin sensitivity. Furthermore, obese or diabetic individuals are found to have increased serum levels of RBP4.<sup>20</sup>

Epidemiological studies have found that diets rich in antioxidants (such as vitamin C, vitamin E, and  $\beta$ -carotene) have advantageous effects on glucose metabolism and the prevention of diabetes<sup>19</sup> and are associated with a reduced risk of CVD.<sup>16</sup> Observational data further suggest that higher dietary intake or supplementation of antioxidants (vitamins A, C, and E, folic acid, niacin,  $\beta$ -carotene, selenium, and zinc) reduces CVD-related mortalities and morbidities over a minimum of 2-year intervention.<sup>16</sup> Furthermore, natural forms of these

vitamins may be more efficacious than synthetic forms.<sup>14,21</sup> However, RCTs indicate mixed results regarding the role of any single antioxidant or a combination of antioxidants in metabolic health.<sup>14,21</sup>

### Vitamin D

T2DM is associated with systemic inflammation, impaired insulin secretion, and insulin resistance.<sup>20</sup> Experimental data indicate that vitamin D improves pancreatic function through the induction of insulin synthesis in the islet cells, stimulating the expression of insulin receptors, regulating calcium influx into pancreatic  $\beta$  cells, and inhibiting the generation of proinflammatory cytokines to decrease systemic inflammation.<sup>20</sup> It is estimated that 25%–57% of US adults and 1 billion people worldwide are vitamin D-insufficient or vitamin D-deficient,<sup>22</sup> with ethnic minorities having higher prevalence of vitamin D insufficiency compared with Caucasian counterparts.<sup>23</sup>

Many observational data (including US National Health and Nutrition Examination Survey [NHANES]) have reported that vitamin D status (dietary intake and blood concentrations) is inversely related to the risk or prevalence of MetS, hypertension, obesity, T2DM, and CVD.<sup>16,20,22–26</sup> A meta-analysis pooled data from 18 prospective studies with a total sample size of 210,107 participants (15,899 metabolic events) and a median follow-up of 10 years (range =3–22 years). Compared with individuals with the lowest baseline vitamin D level (bottom third), those with the highest baseline vitamin D status (top third) were at a lower risk of developing MetS (RR =0.86; 95% CI =0.80–0.92) and T2DM (RR =0.81; 95% CI =0.71–0.92).<sup>25,27</sup> Similarly, another meta-analysis of observational and clinical trials concluded an inverse association between vitamin D status, calcium or dairy intake, and the prevalence or incidence of MetS/T2DM (odds ratios [ORs] comparing highest to lowest 25-hydroxyvitamin D [25(OH)D]: 0.36 [95% CI =0.16–0.80] for T2DM prevalence and 0.82 [95% CI =0.72–0.93] for T2DM incidence; ORs for highest vs lowest calcium/dairy intake: 0.71 [95% CI =0.57–0.89] for MetS prevalence and 0.86 [95% CI =0.79–0.93] for MetS incidence).<sup>28</sup> Furthermore, a meta-analysis of 16 cross-sectional studies reported an increment of 25 nmol/L blood 25(OH)D to be associated with a risk reduction of 13% for MetS among adults aged  $\geq 18$  years (OR =0.87; 95% CI =0.83–0.92).<sup>29</sup> It should be noted that this inverse association does not appear to be significant in cohort or nested case-control studies ( $n=2$ ), suggesting that more longitudinal and RCT data are needed to confirm causality.<sup>29</sup>

The benefits of vitamin D supplementation on MetS and related medical conditions are not conclusive. For combined vitamin D and calcium supplementation, intervention trials suggest a benefit only in high-risk populations (eg, with glucose intolerance).<sup>28</sup> Vitamin D supplementation among high-risk individuals is reported to reduce the incidence of T2DM, indicating a protective role against diabetes.<sup>28</sup> However, results from RCTs have not shown consistent clinical improvement when supplemented with vitamin D, which may be due to a small sample size, an inappropriate vitamin D dose, baseline vitamin D status inconsistency, gene polymorphism (eg, related to vitamin D receptor), and/or poor compliance.<sup>20,30,31</sup> Therefore, vitamin D supplementation is not recommended for the prevention or treatment of diabetes due to insufficient evidence.<sup>31</sup> Well-designed intervention trials targeting generally healthy and at-risk populations are needed to confirm causality.<sup>27,31</sup>

### Folate and Biotin

Epidemiological data have linked folate deficiency to an increased risk and incidence of CVD. Furthermore, serum folate levels appear to be lower among overweight or obese people, indicating a relationship between folate status and adiposity.<sup>32</sup> However, temporal and causal associations remain uncertain. Future studies focusing on populations with low folate status and folate supplementation as the primary prevention measures are recommended.

A potential synergy between biotin and folic acid in repressing proinflammatory cytokines has been reported in some cell culture experiments.<sup>20</sup> Relevant human data are currently lacking.

### Magnesium

Magnesium is the fourth most abundant essential mineral in the body and is involved in >300 metabolic reactions, including protein/DNA/RNA synthesis, cellular energy production, and cell growth and reproduction.<sup>33</sup> There is evidence indicating the effective use of magnesium in the treatment of certain medical conditions, including eclampsia, preeclampsia, migraine, severe asthma, and constipation.<sup>33</sup>

A recent meta-analysis of 34 RCTs (2,028 participants) revealed magnesium supplementation at a median dose of 368 mg/day for a median duration of 3 months to be associated with a reduction of 2 mmHg (95% CI =0.43–3.58) and 1.78 mmHg (95% CI =0.73–2.82) in systolic and diastolic blood pressure, respectively,<sup>34</sup> suggesting an anti-hypertensive effect with magnesium supplementation.

Diabetic patients appear to have a higher incidence of hypomagnesaemia than nondiabetics (14%–48% vs 3%–15%, respectively),<sup>35</sup> and epidemiological data suggest an inverse correlation between a magnesium-rich diet and fasting insulin level and risk of diabetes.<sup>14,36</sup> In a recent meta-analysis of 13 prospective cohort studies (536,318 subjects and 24,516 diabetes cases), magnesium intake was inversely correlated to the risk of T2DM (RR =0.78; 95% CI =0.73–0.84) in a dose–response manner.<sup>39</sup> Magnesium supplementation has been demonstrated to improve insulin sensitivity and metabolic control among people with T2DM or insulin resistance in a few RCTs.<sup>35,36</sup>

Dietary magnesium intakes and serum levels are inversely associated with the risk of CVD and all-cause mortality according to observational data and a meta-analysis of 19 prospective studies (532,979 participants).<sup>35</sup> Cross-sectional and prospective studies also report that low urinary magnesium excretion, an indicator of dietary magnesium intake, is associated with a higher risk of developing hypertension and CVD.<sup>35</sup> However, clinical trials have not confirmed such beneficial effects of magnesium supplementation.<sup>35</sup> In addition, observational data indicate an inverse association between magnesium status and the risk of MetS among adults, but this potential benefit needs further investigation.<sup>33–37</sup>

### Chromium

Trivalent chromium is the form found in foods and nutrient supplements, with chromium picolinate considered the most stable and bioavailable supplemental form in the market.<sup>38</sup> It is difficult to assess the intakes of chromium from food sources partially due to the lack of standardized analytical methods, and chromium dietary intake data are currently not available in standard databases (eg, NHANES).<sup>38</sup>

Individuals with diabetes are found to have lower tissue levels of chromium than nondiabetic controls, with low circulating chromium being associated with the incidence of T2DM.<sup>38</sup> Clinical trials have shown that chromium supplementation improves glycemic control in patients with diabetes, but this benefit is not found in other trials.<sup>14</sup> Given limited and controversial data to date, the American Diabetes Association and US FDA have concluded the evidence for the benefit of chromium supplementation in individuals with diabetes as inconclusive.<sup>14,38</sup>

### Polyphenols

#### Flavonoids

Flavonoids are polyphenols commonly found in fruits, vegetables, legumes, herbs, and tea and have been examined for



their anti-inflammatory and antioxidant properties. Prospective studies indicate that the intake of flavonoids is inversely associated with CVD incidence or mortality.<sup>14</sup> Similarly, a systematic review confers favorable benefits of foods rich in flavonoids, including cocoa, chocolate, red wine, grapes, or black tea on CVD parameters (eg, reduced blood pressure and improved endothelial function).<sup>14</sup>

### Resveratrol

Resveratrol is a polyphenol found in a variety of fruits (eg, grapes, berries, and plums) and may have a beneficial effect on cardiovascular health via its antioxidant properties and regulation of nitric oxide concentrations in the body.<sup>16</sup> Consumption of resveratrol at both 10 and 100 mg/day has been linked to decreased LDL and improved endothelial cell function.<sup>21</sup> Recently, a favorable effect of trans-resveratrol on glucose homeostasis has been reported at a dose of 150 mg/day over a 1-month intervention period, indicating a potential benefit on insulin sensitivity.<sup>19</sup> In animal studies, resveratrol has also been shown to decrease fat mass via inhibiting adipocyte differentiation and lipid accumulation and to improve energy efficiency via the regulation of brown fat tissue activity.<sup>39</sup> However, human data are needed to further explore the influence of resveratrol on weight management.

### Isoflavones

Isoflavones from soy are a class of phytoestrogens that can mimic the effects of estradiol.<sup>14</sup> Animal studies have shown that soy and phytoestrogens reduce adiposity and improve insulin sensitivity, but human data are limited and inconclusive.<sup>14</sup>

### Chlorogenic acid (CGA)

Also known as 5-O-caffeoylquinic acid, is one of the main polyphenols that is widely distributed in foods including apples, coffee beans, and carrots. This ingredient and its derived compounds have been extensively evaluated both in vivo and in human studies for its role in the prevention and treatment of MetS and its associated disorders.<sup>40</sup> As described below in detail, these data have revealed beneficial effects on weight management, T2DM, and hypertension when supplemented with pure CGA or CGA-rich foods/supplements. 1) Consumption of Coffee Slender (45 mg CGA/g) for 12 weeks significantly reduced weight by 5.4 kg among overweight subjects.<sup>40</sup> A CGA-rich beverage (329 mg CGA/185 mL) was reported to increase postprandial energy expenditure and fat utilization after 4 weeks of daily consumption among healthy men;<sup>40</sup> 2) a review summarizing findings from five human trials demonstrated a positive impact of CGA-rich foods

and supplements or pure CGA on diabetic parameters (eg, glucose absorption).<sup>40</sup> Consumption of caffeinated (40 mg CGA/g) and decaffeinated coffee (30 mg CGAs/g) decreased glucose-dependent insulinotropic polypeptide, indicating a lowered rate of glucose absorption in the intestine. Coffee Slender (45 mg CGA/g) reduced glucose absorption by 6.9% among healthy subjects. Similar benefits on plasma glucose and area under the curve were observed for a CGA-rich extract from decaffeinated green coffee bean (13.9% CGA dry weight) among healthy subjects with the highest postprandial glucose levels. Emulin™ (a patented blend of CGA, myricetin, and quercetin) was reported to lower the glycemic impact of foods among subjects with T2DM; and 3) the anti-hypertension properties of pure CGA and CGA-rich green coffee extract have been investigated in subjects with and without mild hypertension. A health benefit has been reported in these human studies, including a reduction in systolic/diastolic blood pressure and improved endothelial function measured by continuous flow-mediated dilation.<sup>40</sup>

## Other compounds

### α-Lipoic acid

The supplementation of α-lipoic acid (a naturally occurring antioxidant) has been shown to increase insulin sensitivity among diabetics by 18%–20% and improve acute symptoms and disease progression of diabetic neuropathy.<sup>14</sup>

### Benfotiamine

Benfotiamine is a lipophilic derivative of thiamine (vitamin B<sub>1</sub>) and can increase plasma concentrations of thiamine five times higher than an equivalent dose of thiamine.<sup>20</sup> In clinical trials, benfotiamine has been demonstrated to prevent vascular endothelial dysfunction and oxidative stress and improve polyneuropathy among diabetic patients.<sup>20</sup>

### Fucoxanthin

Fucoxanthin is a natural carotenoid found in certain types of brown algae, including *Undaria pinnatifida* (Wakame), *Saccharina japonica* (Makonbu), and *Sargassum fulvellum* (Hondawara).<sup>41</sup> It cannot be converted to vitamin A in the body and is a potent antioxidant.<sup>41</sup> Fucoxanthin acts by downregulating adipokine secretion that is associated with inflammation in white adipose tissue (WAT) and upregulating glucose transporter 4 that is associated with insulin resistance in skeletal muscle under diabetic conditions.<sup>41</sup> Animal data indicate that fucoxanthin may reduce excess abdominal fat by inducing the expression of uncoupling protein 1 and thus upregulate thermogenesis in abdominal

WAT.<sup>41</sup> In a clinical trial, obese women with a mean body weight of 100 kg were administered 2.4 mg/day of fucoxanthin for 16 weeks and showed a significant increase in resting energy expenditure and a reduction in body weight, waist circumference, body and liver fat content, and serum triacylglycerol levels.<sup>41</sup>

## Policosanols

Policosanols are an extract from sugarcane wax and have been shown to significantly reduce LDL cholesterol.<sup>16</sup> It has been reported that policosanols reduced LDL by 17% among patients who did not reach their LDL target at the maximum dose of statin or with a combination therapy.<sup>16</sup> In a recent meta-analysis of 11 human RCTs, a specific combination of natural compounds (policosanols, berberine, red yeast rice extract, folic acid, coenzyme Q10, and astaxanthin) was supplemented to examine the benefit on the lipid profile among 3,924 hypercholesterolemic patients. This combination of compounds was reported to significantly reduce all lipid parameters (TC, HDL, LDL, and TG) compared with control.<sup>42</sup>

## Stanols

Stanols, also known as plant sterols, have been shown to decrease LDL cholesterol by reducing the uptake of cholesterol in the gastrointestinal tract; an optimal intake of ~2000 mg stanols daily is expected to decrease LDL by 6%–20%.<sup>16</sup>

## Lifestyle factors

Although the focus of this review is single nutrients, we highlight a few lifestyle factors that may influence or “program” the development of MetS.

## Circadian rhythm

According to a review of human and animal data, circadian disruption is associated with metabolic disorders.<sup>43</sup> As illustrated in night-shift workers and those with jetlag, desynchronization between the light-regulated central clock, located in the hypothalamic suprachiasmatic nucleus, and nutrient-responsive peripheral clock can contribute to unfavorable health outcomes (including obesity, T2DM, and CVD).<sup>43</sup> The influence of dietary components (eg, a high-fat diet and polyphenols) on tissue-specific peripheral clock responses has been investigated using animal, *in vitro*, and *in vivo* models, suggesting that feeding is a modulator of the internal circadian clock.<sup>43</sup> Further human studies are needed to clarify which nutrients can influence and how they can influence the circadian rhythm toward advantageous metabolic outcomes.<sup>43</sup>

## Nutrition in early life

Epidemiological studies have demonstrated that nutrition in early life is associated with MetS, obesity, and diabetes later in adulthood; this is known as the theory of “developmental origins of health and disease” proposed by Barker in the early 1990s.<sup>44–47</sup> Both maternal undernutrition and overnutrition during pregnancy are correlated with suboptimal infant birth weight (underweight or overweight), altered postnatal growth (eg, rapid catch-up growth among low-birth-weight infants), and an increased risk of adulthood obesity and MetS.<sup>44–46</sup> Low birth weight is associated with reduced fetal and adulthood muscle mass and consequently increased risks of MetS, T2DM, and CVD later in life. This is in part due to the fact that skeletal muscle is critical to maintaining resting energy expenditure and whole-body insulin sensitivity.<sup>48</sup> In addition, childhood infection and growth restriction may contribute to future metabolic and CVDs, possibly due to caloric deficit and infection-related inflammation.<sup>49</sup>

Although weaning and the introduction of complementary feeding can influence the future health of infants, the relationship between the timing of complementary feeding and the risk of metabolic disorders later in life remains unclear.<sup>50</sup> However, what is clear is that overconsumption of high-calorie beverages during infancy is associated with childhood obesity.<sup>50</sup> The addition of salt during infancy may also increase the risk of hypertension later in life, as it may stimulate the development of a preference for salty taste and subsequent high intake of salt.<sup>50</sup> Although there is evidence showing improved blood pressure among infants who received fish oil supplementation,<sup>50</sup> there is limited literature about the long-term effects of long-chain omega-3 PUFA during weaning on cardiovascular health.<sup>50</sup>

## Conclusion

Observational studies have generated positive evidence for the beneficial role of numerous nutrients in MetS. The underlying mechanisms include modulation of systemic inflammation, oxidative stress, pancreatic functions, energy absorption/production/utilization, and genetic programming in early life. Although results of some clinical trials are consistent with the findings from observational data, causality remains inconclusive due to either overall contradicting data or an inability to repeat findings or compare findings due to variance in dose, population, and clinical end points.

Both nutrition and health are complex and dynamic systems with a hierarchical nature. Nutrients are essential for health, but they do not work in isolation. When we, as nutrition scientists, design confirmatory intervention

trials for nutrients and metabolic health, instead of the traditional “single-nutrient” concept, it is worth considering a holistic and interdisciplinary approach to integrate nutrients, lifestyle factors (eg, dietary patterns, physical activity, and circadian rhythm), early risk exposure (eg, in uterus and infancy), and population relevance (eg, healthy, at-risk, or diseased).

## Acknowledgment

An abstract of this paper was presented at “The 2017 Experimental Biology Conference” as a poster presentation. Thereafter, the abstract was published in the *FASEB Journal* (available from: [http://www.fasebj.org/content/31/1\\_Supplement/789.10.short](http://www.fasebj.org/content/31/1_Supplement/789.10.short)).

## Disclosure

HJK is an employee of the Nature's Bounty Co. SHM was an employee of the Nature's Bounty Co. when the work was performed. The authors report no other conflicts of interest in this work.

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## Supplementary material

**Table SI** Summary of reviews and meta-analyses (2005–2017)

Reference	Metabolic syndrome parameters	Nutrients/factors reviewed	Main findings	Comments
25	Diabetes	Vitamin D	Human clinical trials produced controversial data on the effects of vitamin D supplementation on diabetic parameters both in healthy and diabetic subjects	A review of observational studies and clinical trials
33	Obesity/T2DM/hypertension	CGA	Human studies have revealed positive effects of pure CGA or CGA-rich foods/supplements on obesity/T2DM/hypertension. Human data are needed to evaluate the effects on dyslipidemia	Most studies are done with CGA-rich coffee. More trials are needed for pure CGA
35	Dyslipidemia	AP, a commercial dietary supplement combining policosanols, berberine, red yeast rice extract, folic acid, coenzyme Q10, and astaxanthin	AP significantly improves all lipid parameters (total cholesterol, LDL, HDL, and TG)	Meta-analysis of 11 RCTs among hypercholesterolemic patients (pre 2015 literature). Between-study heterogeneity is substantial
36	MetS	Circadian rhythm	Circadian disruption is associated with metabolic disorders. Feeding is a modulator of the internal circadian clock. Further studies among humans are needed	Nutrients and circadian clocks are from animal, in vitro, or in vivo data
28	Hypertension	Magnesium	Magnesium supplementation at a median dose of 368 mg/day for a median duration of 3 months reduces systolic and diastolic blood pressure by 2 and 1.78 mmHg, respectively	Meta-analysis of RCTs among adults (literature up to February 1, 2016); Benefits are accompanied by elevated levels of serum magnesium
43	Obesity/hypertension	Complementary feeding: EPL, salt, and LCPUFA	The correlation between the timing of complementary feeding and MetS in later life remains unclear	Limited evidence on early introduction of EPL, salt, LCPUFA, and metabolic health later in life
14	T2DM	Vitamin A, retinol-binding protein 4, vitamin D, biotin, and benfotiamine (a derivative of thiamine)	Vitamins and their derivatives have the potential as an effective adjunct prevention of T2DM	Vitamin A and biotin: in vitro or animal data only
37	MetS	Under- and overnutrition in utero	A U-shaped relationship between birth weight and adulthood metabolic diseases: babies with low or high birth weight have increased risks of MetS later in life	Epigenomic mechanisms are mainly based on animal data
29	Hypertension/T2DM/CVD	Magnesium	Magnesium status (intake, serum levels, or urinary secretion) is inversely linked to the risk of hypertension/T2DM/CVD in observational studies	Causality needs to be confirmed in RCTs
3	Obesity	Protein	High-protein diets (1.2–1.6 g protein/kg/day) improve weight management and some metabolic indicators through increased thermogenesis and satiety after the consumption	Short-term (<1 year) evidence is strong; long-term feeding trials (≥1 year) are less consistent
34	Obesity	Fucoxanthin, a natural carotenoid from brown algae	Fucoxanthin in algae has a unique anti-obesity effect by upregulating thermogenesis in human white fat tissues	The anti-diabetic properties of fucoxanthin: animal and in vitro data only
20	Hypertension/T2DM/CVD	Vitamin D	Low vitamin D status is linked to increased prevalence or risks of hypertension, T2DM, and CVD	Benefits of vitamin D supplementation on cardiovascular outcomes have not been confirmed

(Continued)

**Table S1** (Continued)

Reference	Metabolic syndrome parameters	Nutrients/factors reviewed	Main findings	Comments
38	MetS	In utero nutrition	Maternal nutrition during peri-conception, gestation, and lactation periods predisposes babies to adult-onset diseases	Known as “DOHaD”
1	Dyslipidemia	Peptides from dietary proteins (ie, soybean and milk) or synthetic	A human clinical trial shows beneficial effects of lupin protein on lowering plasma lipids	Evidence is mainly based on animal, in vitro, or cell culture data
41	MetS/T2DM/CVD	Low birth weight/reduced fetal muscle mass	Compelling associations between low birth weight/reduced muscle mass and MetS/T2DM/CVD later in life	Related to the DOHaD theory
7	MetS	Dietary components consumed as part of specific diets	Beneficial roles of unsaturated fatty acids (MUFA, omega-3/omega-6 PUFA, EPA, DHA, and ALA) on metabolic parameters; adverse influences of saturated and trans fatty acids	Systematic review of prospective and RCT studies: 2000–2012
26	Obesity/CVD	Folate	Correlation between low folate status and adiposity/CVD is observed in epidemiological studies	Causality and efficacy need to be confirmed in well-designed intervention trials
6	MetS	Dairy	Epidemiological and clinical studies suggest an inverse relationship between dairy consumption and MetS parameters	2–3 servings of dairy per day is recommended
23	MetS	Vitamin D	An inverse association between blood 25(OH) D levels and MetS risks is observed among the meta-analysis of cross-sectional data (n=16), but not in cohort or nest case–control studies (n=2)	Cross-sectional data: pooled OR per 25 nmol/L increment in 25(OH)D: OR =0.87; 95% CI: 0.83–0.92; high heterogeneity: I <sup>2</sup> =85%
5	T2DM	Branched-chain amino acids; non-esterified fatty acids	Nutrient effects on pancreatic functions are complex at the metabolic level; much is yet to be understood	Focus on the mechanism; few human data
15	MetS/CVD	Antioxidants (vitamins C and E, resveratrol)	Observational data, not RCTs, support the benefits of a minimum 2-year supplementation of antioxidant vitamins (C and E) on reduced incidence of CVD. Resveratrol is shown in two clinical trials to improve endothelial cell function and LDL profiles	A natural supplement containing resveratrol and antioxidant vitamins may be promising to manage CVD burdens
39	MetS	Nutrition during pregnancy	Maternal diet during pregnancy can influence the short- and long-term health of offspring including programming of the MetS	Related to the DOHaD theory
21	MetS/T2DM	Baseline vitamin D status measured as blood 25(OH)D and dietary intakes	Vitamin D status at baseline is inversely associated with risks of MetS and T2DM. Top versus bottom thirds of baseline vitamin D: for MetS: RR =0.86; 95% CI =0.80–0.92. For T2DM: RR =0.81; 95% CI =0.71–0.92	A meta-analysis of 18 prospective studies (literature up to August 2012); results need to be confirmed by intervention trials
2	MetS	Dietary fats	High saturated fatty acid diets have detrimental effects on metabolic health; diets rich in MUFA are advantageous for metabolic parameters. Optimal dietary fat composition for metabolic health is unknown	Epidemiological data on anti-diabetic benefits of omega-3 LCPUFA are controversial
13	Glucose metabolism	Dietary antioxidants	The involvement of oxidative stress in insulin resistance is clear; intervention studies assessing antioxidants on glucose metabolism are rare and results are not consistent	The ideal antioxidant supplements may be one that can reproduce the natural combination in plant foods
42	MetS	Childhood infection and growth failure	Childhood infection and growth restriction may be related to MetS in adulthood. Etiology is unclear	Related to the DOHaD theory

(Continued)

**Table SI** (Continued)

Reference	Metabolic syndrome parameters	Nutrients/factors reviewed	Main findings	Comments
10	CVD	Dietary components, antioxidants, vitamin D, alternative supplements (resveratrol, policosanol, red yeast rice, stanols), and exercise	Basic nutrition together with exercise plays a critical role in cardiovascular health	Alternative supplements are promising, but need more data
18	Hypertension	Vitamin D	Observational data support a protective role of vitamin D against hypertension, but RCTs do not support the benefits of vitamin D supplementation	More randomized trials are necessary to confirm the benefits of vitamin D and hypertension
4	Obesity	Proteins	Dietary proteins may help weight management through increasing thermogenesis and satiety. Long-term benefits need to be further studied	Caution for high-protein diets: risks of renal damage especially in diabetics
16	MetS/hypertension/CVD	Vitamin D	Observational data, not intervention trials, are supportive of beneficial roles of vitamin D on metabolic disorders	Future clinical trials are needed to confirm the casual relationship
17	Obesity/T2DM/CVD	Vitamin D insufficiency: 25(OH)D <50 nmol/L	Ethnic minorities have higher prevalence of vitamin D insufficiency than white counterparts. Observational data support links between vitamin D deficiency and obesity-related chronic diseases	Systematic review of observational data in minority groups (narrative synthesis)
12	Insulin resistance	Low-energy sweeteners (aspartame, saccharin, sucrose, acesulfame-K, cyclamate, saccharin, sucralose, stevioside, and rebaudioside-A)	Low-energy sweeteners are not associated with unwanted effects on appetite, glycemic control, or blood pressure	Based on in vivo human and animal data
24	Prediabetes	Vitamin D	Observational data are supportive. Intervention trials indicate no benefits of vitamin D supplementation among people with adequate vitamin D status and normal glucose tolerance. A few short-term trials with a small sample size indicate possible benefits in prediabetes	Systematic review of literature from January 1969 to July 2009; well-designed trials considering relevant confounders (ie, vitamin D status and glucose metabolism) are needed to confirm the efficacy
8	MetS/T2DM	Antioxidants (vitamins, polyphenols, and ALA), minerals (chromium and magnesium), omega 3, soy isoflavones, and fiber	An inverse association between antioxidants and CVD prevention is strong in observational studies, but this is not supported by currently available large clinical trials	More clinical data involving people with high oxidant stress or depletion of natural antioxidant defense systems are needed to confirm the causality
11	MetS/hypertension/T2DM/CVD	SSBs	Clear evidence on SSB consumption and increased risks for metabolic disorders	Meta-analysis of prospective studies
27	MetS	Magnesium	Possible evidence but further investigation is needed	Use with caution in the presence of kidney dysfunction and medications
19	MetS/diabetes/CVD	Vitamin D	Positive evidence from epidemiological data	Similar information to Pittas et al <sup>22</sup>
30	MetS/T2DM	Magnesium	Positive evidence on magnesium and MetS/T2DM/insulin resistance from observational studies (cross-sectional and prospective) and a few RCTs	Literature review: 2000–2008; more prospective or RCTs are needed to clarify the benefits
32	MetS/T2DM	Chromium	Supportive evidence but not conclusive according to FDA/American Diabetes Association positions	Literature review: 1996–2006 suggests future studies on certain forms (ie, chromium picolinate) and doses (ie, ≥200 µg/day)

(Continued)

**Table S1** (Continued)

Reference	Metabolic syndrome parameters	Nutrients/factors reviewed	Main findings	Comments
22	MetS/T2DM	Vitamin D/calcium	Observational data support an inverse association of vitamin D and calcium with MetS/T2DM (prevalence or incidence). Intervention data are limited	Systematic review with meta-analysis: observational and clinical data up to January 2007
31	MetS	Magnesium	Magnesium intakes are inversely related to the prevalence and incidence of MetS and its components	Evidence from a few cross-sectional and prospective studies
40	Diabetes	Early nutrition	Pool fetal nutrition, early feeding, high-nutrient diet, and rapid growth in infancy may adversely impact the metabolic health later in life	Relevant to the theory of DOHaD
9	MetS	Fatty acids	Replacement of dietary saturated fats with unsaturated fatty acids may benefit metabolic health. Evidence on benefits of individual fatty acids is not conclusive	Diet–gene interactions need to be considered when assessing dietary responsiveness
44 <sup>a</sup>	Inflammation (CRP & IL-6)	Vitamin-mineral supplementation	There are no differences in CRP and IL-6 between subjects with vitamin–mineral supplementation and placebo controls	A meta-analysis of 18 trials (1,747 participants) for CRP and 9 trials (1,037 subjects) for IL-6 (literature up to May 2009)

**Notes:** n=44. <sup>a</sup>Sun CH, Li Y, Zhang YB, Wang F, Zhou XL, Wang F. The effect of vitamin-mineral supplementation on CRP and IL-6: a systemic review and meta-analysis of randomised controlled trials. *Nutr Metab Cardiovasc Dis*. 2011;21(8):576–583. (Not referenced in the paper.)

**Abbreviations:** 25(OH)D, 25-hydroxyvitamin D; ALA, alpha-linoleic acid; AP, Armolipid Plus; CGA, chlorogenic acid; CRP, C-reactive protein; CVD, cardiovascular disease; DHA, docosahexaenoic acid; DOHaD, developmental origins of health and diseases; EPA, eicosapentaenoic acid; EPL, energy-providing liquids; FDA, Food and Drug Administration; HDL, high-density lipoprotein; IL-6, interleukin-6; LDL, low-density lipoprotein; LCPUFA, long-chain polyunsaturated fatty acids; MetS, metabolic syndrome; MUFA, monounsaturated fatty acids; OR, odds ratio; PUFA, polyunsaturated fatty acids; RCTs, randomized clinical trials; RR, relative risk; SSBs, sugar-sweetened beverages; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglycerides.

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