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THE PRESENT AND FUTURE

COUNCIL PERSPECTIVES

A Clinician's Guide for Trending Cardiovascular Nutrition Controversies

Part II

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ABSTRACT

The potential cardiovascular (CV) benefits of many trending foods and dietary patterns are still incompletely understood, and scientific inquiry continues to evolve. In the meantime, however, a number of controversial dietary patterns, foods, and nutrients have received significant media attention and are mired by "hype." This second review addresses some of the more recent popular foods and dietary patterns that are recommended for CV health to provide clinicians with current information for patient discussions in the clinical setting. Specifically, this paper delves into dairy products, added sugars, legumes, coffee, tea, alcoholic beverages, energy drinks, mushrooms, fermented foods, seaweed, plant and marine-derived omega-3-fatty acids, and vitamin B12. (J Am Coll Cardiol 2018;72:553–68) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ALA = alpha-linolenic acid

ASCVD = atherosclerotic vascular disease

BP = blood pressure

CHD = coronary heart disease

CI = confidence interval

CV = cardiovascular

CVD = cardiovascular disease

DM = diabetes

FDA = U.S. Food and Drug Administration

HDL-C = high-density lipoprotein cholesterol

HFCS = high fructose corn syrup

LDL-C = low-density lipoprotein cholesterol

MI = myocardial infarction

OM3 = omega-3 fatty acids

RCT = randomized controlled trial

RR = risk ratio

SSB = sugar-sweetened beverages

TG = triglyceride

A heart-healthy diet has been the cornerstone of atherosclerotic cardiovascular disease (ASCVD) prevention and treatment for decades. Each year, patients are bombarded with new "miracle" foods that claim to promote health, affect weight loss, and reduce disease risks. Although the scientific evidence base for some of these foods is limited, there are a number of dietary components and patterns that have clearly been demonstrated to reduce the risk of many chronic diseases, including cardiovascular disease (CVD). Evidence-based healthy dietary patterns are high in fruits, vegetables, whole grains, and legumes, in addition to nuts in moderation; some may include modest quantities of lean meats (including poultry and fish), low-fat dairy products, liquid vegetable oils, and alcoholic beverages (1). There are several food groups, specific foods, nutrients, and supplements that remain controversial in the scientific community, which results in confusion for patients, consumers, and the media.

Following our last review (2), we received much feedback about additional topics and suggestions from our expert group; accordingly, we voted on which topics to include in this iteration. Each topic was covered by a group of experts familiar with the corresponding science and published data; the highest-quality papers were included. In cases of debate or divide, the group as a whole weighed in to achieve consensus. The current review addresses additional contemporary nutrition controversies and provides evidence-based recommendations to facilitate dietary counseling by clinicians (**Central Illustration**).

NUTRITION "HYPES" AND CONTROVERSIES

DAIRY PRODUCTS. Dairy products are the leading source of saturated fat in the U.S. diet, as well as a source of cholesterol and sodium. The evidence base addressing the health consequences of dairy products on CVD, as well as other chronic diseases associated with increased cardiovascular (CV) risk, including obesity and diabetes (DM), is challenging to interpret. Many studies have used observational designs, rather than intervention trials, and they vary widely in specific dairy products evaluated, methodology, and populations (3,4). In meta-analyses, such heterogeneity could lead to null results because of a loss of statistical power (5). In addition, a recent meta-analysis of industry-sponsored studies suggests that some studies funded by commercial entities favored the sponsor(s); however, the findings were nonsignificant (6).

The 2013 American Heart Association/American College of Cardiology guideline on lifestyle management (7) and the 2015 to 2020 Dietary Guidelines for Americans (1) currently suggest that a healthy diet could include some amount of fat-free and low-fat dairy products. Nonetheless, there is a divergence of opinion on the data about the health effects of specific dairy products and dairy products as a whole. Observational studies of dairy consumption and CVD and stroke risk have yielded mixed results. Three systematic reviews and meta-analyses published between 2015 and 2017 (8–10), as well as a systematic review of meta-analyses of prospective population studies (n = 21) (4) evaluated the association between dairy product consumption and risk of CVD and reported inconsistent associations. To further complicate the issue, the DASH (Dietary Approach to Stop Hypertension) dietary pattern (high in fruits, vegetables, and low-fat dairy) reduced systolic blood pressure (BP) even further by 2.7 mm Hg ($p = 0.001$) and diastolic BP by 1.9 mm Hg ($p = 0.002$) when compared with the fruits and vegetables only diet group alone, although both significantly lowered BP (11).

In contrast, an analysis of 3 cohorts of U.S. adults in the Health Professionals Follow-Up Study (n = 43,652), NHS (Nurses' Health Study) (n = 87,907),

California Walnut Commission. Dr. O'Keefe has an ownership interest in CardioTabs; and has received royalties as an author and honoraria as a speaker for Amgen, Boehringer Ingelheim, and Sanofi Regeneron. Dr. Miller has served as a scientific advisor for Pressed Juicery. Dr. Ornish has served as a consultant for Healthways and TerraVia; and has received author royalties and speaker honoraria from the Leukemia & Lymphoma Society, ACLM annual scientific sessions, and Cedar Sinai Medical Grand Rounds. Dr. Batts has served as a consultant and has lectured for Phillips Ultrasound. Dr. Kris-Etherton has served on the scientific advisory committee for the California Walnut Commission, Avocado Nutrition Science Advisory, and Seafood Nutrition Partnership Scientific and Nutrition Advisory Council; and has received research funding from the California Walnut Commission, McCormick Spice Institute, and National Cattlemen's Beef Association. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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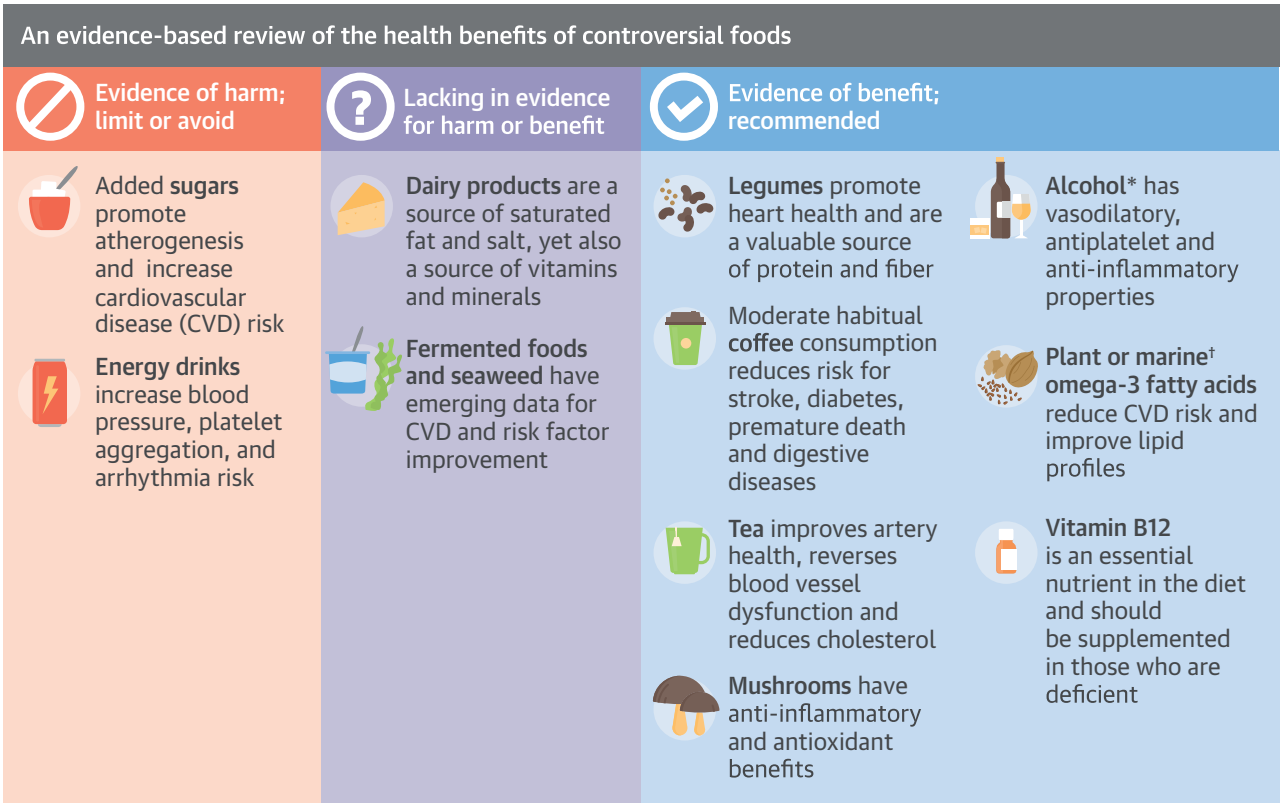
CENTRAL ILLUSTRATION **Cardiovascular Health Benefits Based on Evidence of Controversial Foods**



Freeman, A.M. et al. J Am Coll Cardiol. 2018;72(5):553–68.

This illustration depicts the health benefits of the controversial food items discussed in this paper using the "evidence of harm," "lacking in evidence," and "evidence of benefit" designations. *It is not recommended that individuals initiate alcohol consumption for health benefit, and for those already drinking, consumption should be limited to recommended amounts and preferably consumed with meals. A patient's risk of cancers and other organ system diseases need to be weighted carefully when making recommendations. †There are some environmental and toxin (heavy metals, dioxins, polychlorinated biphenyls, and others) concerns in marine sources.

and the NHS II (n = 90,675) by Chen et al. (12) showed that replacing 5% of energy intake from dairy fat with polyunsaturated fatty acid or vegetable fat was associated with 24% and 10% lower risk of CVD, respectively, and replacing 5% of energy intake from other animal fat for dairy fat was associated with a 6% increase in CVD risk. The same has also been shown in a larger analysis (n = 131,342) by Song et al. (13), which found associations between dairy intake, CVD and all-cause death. Finally, several recent studies have shown that dairy intake was associated with increased risk of bone fractures (14), breast cancer (15,16), ovarian cancer (17), prostate cancer (18,19), and all-cause mortality (14,20). However, there is evidence refuting these studies for hip fractures (21), breast cancer and ovarian cancer (3), and all-cause mortality (10). The observed discrepancies could reflect the foods that were substituted for dairy products or the type of dairy product evaluated.

Some investigators have attempted to separate out the possible effects of specific dairy products, such as butter or cheese, on risk of CVD, type 2 DM, and other outcomes. However, such associations have been hampered by the lack of intervention studies, confounders in observational data, and challenges in extracting components of overall diets. Data related to fermented dairy products are reported in the section on fermented foods.

Effects of dairy products on risk factors for CVD. A meta-analysis from 20 randomized controlled trials (RCTs) (22) that evaluated high- and low-fat dairy products reported that both caused modest weight gain and a nonsignificant increase in low-density lipoprotein cholesterol (LDL-C) (+1.85 mg/dl

increase, −2.89 to 6.60 mg/dl). However, in a prospective investigation with nearly 121,000 participants in the NHS, the NHS II, and the Health Professionals Follow-up Study, consumption of cheese, whole milk, and skim milk were not associated with weight change (23). Another meta-analysis of RCTs (24) showed that cheese consumption raised total and LDL-C, compared with tofu or fat-modified cheeses, but did so to a lesser degree than butter. In a comprehensive review on milk fat-containing dairy products and CV health (25) diets higher in saturated fat from whole milk and butter increased LDL-C when substituted for carbohydrates or unsaturated fatty acids. In the analyses by both Drouin-Chartier et al. (26) and Benatar et al. (22), BP was not affected by dairy products.

DAIRY: THE BOTTOM LINE. An understanding of the effects of dairy products on CVD risk has been hampered by the observational nature of most studies and the paucity of non-industry-sponsored clinical trials. The clinical trial studies have evaluated different dairy products and dietary patterns that contained dairy products on CVD risk factors. It appears that there is no clear consensus in the published data or among experts on the effects of dairy products on CVD, although there seems to be a link between some dairy products and increases in LDL-C concentration, fractures, and overall mortality, in addition to lowering of BP, but the magnitude of these effects is unclear. Importantly, however, there is general consensus that full-fat dairy products are major sources of saturated fat and sodium in the U.S. diet, and thus, should be limited; nevertheless, reduced fat dairy products remain a convenient source of some essential vitamins and minerals, as well as high-quality protein.

ADDED SUGAR. An association between excess intake of added sugars, metabolic abnormalities and CVD risk first surfaced in the 1950s. Scientific reviews funded by the sugar industry in the 1960s concluded that there was insufficient evidence to support associations between sugar consumption and health consequences (27,28). More recently, however, a growing evidence base has causally linked increased consumption of dietary added sugars to coronary heart disease (CHD), stroke, and CVD mortality (29).

The principal dietary added sugars are the granular sweetener sucrose (table sugar) and the liquid, high fructose corn syrup (HFCS), which has a slightly higher fructose to glucose ratio than sucrose (55:45 vs. 50:50, respectively) (30). Almost 75% of packaged foods in the United States contains added sugars (31), but the sugar-sweetened beverage (SSB) category (soda, sweet teas, fruit drinks) accounts for one-half of all added sugar intake (30,32). Although data from NHANES (National Health and Nutrition Examination Survey) show consumption of added sugars in the United States began declining after 2000 (33), intake remains far above current recommendations (34) and is about 25-fold higher than 250 years ago (35).

Although sucrose and HFCS are now believed to be metabolically equivalent, their fructose and glucose moieties are not. Fructose uptake by the liver is unregulated and induces greater hepatic lipogenesis than does glucose (30). A series of human feeding studies demonstrated that pure fructose (and to a lesser extent HFCS) fed to young adults at up to 25% of energy requirements for just 2 weeks induces greater levels of atherogenic lipoproteins than does pure glucose, these effects are independent of, though accentuated by, weight gain (36). Similarly, a recent meta-analysis of 39 RCTs showed that a higher versus lower intake of dietary free sugars was associated with significant increases in triglycerides (TGs), LDL-C, and BP (37). In aggregate, excess intake of dietary added sugar induces a pro-atherogenic risk profile independent of weight gain.

Aligned with these data are observational studies that show worsened ASCVD outcomes from excess dietary added sugars. The Health Professionals Follow-Up Study has shown that men in the highest quartile of SSB intake had a 20% higher relative risk of CHD than those in the lowest quartile (38). A NHANES study of 11,733 healthy subjects with a median follow-up of 14.6 years showed an adjusted hazard ratio for CVD death of 1.0 at <10% of calories, 1.3 at 10% to 24.9%, and 2.75 at ≥25% of calories from added sugars (39). Of 197,981 diet-related deaths from CHD in 2012, 20.2% were associated with consumption of SSB (i.e., 1 or more 8-ounce servings/day) (40). Finally, in a cohort of 84,628 women and 42,908 men followed for 24 to 30 years, Li et al. (29) found no reduction in CHD risk (and a trend toward increased risk) when calories from saturated fat were substituted with equal calories from sugars and refined carbohydrates. This finding was in contrast to a reduction in CHD risk when saturated fat calories were replaced with those from polyunsaturated or monounsaturated fats or whole-grain carbohydrates (29).

Expert recommendations for dietary restriction of added sugars. Based on the previously mentioned evidence, numerous expert bodies have now made recommendations to limit dietary added sugar intake (**Table 1**) (41,42).

ADDED SUGAR: THE BOTTOM LINE. Good-quality evidence has now linked added sugars to cardiometabolic

TABLE 1 Expert Recommendations for Added Sugar Consumption

Expert Group (Ref. #)	Recommendations
AHA/ACC (7)	Consume a dietary pattern that limits intake of sweets and SSB.
AHA (148)	Adults should minimize the intake of beverages and food with added sugars; a prudent upper limit of intake is one-half of the discretionary calorie allowance, which for most American women is ≤100 calories/day and for most American men is ≤150 calories/day from added sugars. Children and adolescents should limit their intake of SSB to 1 or fewer 8-ounce beverages/week; it is reasonable to recommend that children consume ≤25 g (100 calories or ~6 teaspoons) of added sugars/day and children <2 yrs of age avoid added sugar.
American Academy of Pediatrics (149)	Limit consumption of SSB in children. Pediatricians should work to eliminate SSB in schools.
American Diabetes Association (150)	People with DM and those at risk should avoid SSB to control weight and reduce risk for CVD and fatty liver, and should minimize the consumption of foods that have the capacity to displace healthier, more nutrient-dense food choices.
2015 Dietary Guidelines Advisory Committee (42)	Limit added sugars to a maximum of 10% of total daily caloric intake; when added sugars in foods and beverages exceeds 3% to 9% of total calories, depending on calorie level, a healthful food pattern may be difficult to achieve and nutrient density may be adversely affected.
Healthy People 2020 (151)	Reduce consumption of calories from added sugars to a target of 9.7% of total daily energy intake.
World Health Organization (41)	Reduce intake of free sugars throughout the life-course; in both adults and children, intake of free sugars should not exceed 10% of total energy; a further reduction to below 5% of total energy is a conditional recommendation (would have additional benefits in reducing the risk of certain noncommunicable diseases in adults and children).

ACC = American College of Cardiology; AHA = American Heart Association; CVD = cardiovascular disease; DM = diabetes mellitus; SSB = sugar-sweetened beverages.

and ASCVD risk. Until food labeling changes are phased in, individuals should limit added sugar to <10% of calories and preferably <100 calories daily for women and <150 calories daily for men. Clinicians should recommend consumption of a whole foods diet with a low intake of processed foods, careful selection of foods with no or low amounts of added sugars in any form, and elimination of SSB. Patients should also be taught how to read the Nutrition Facts Label for added sugars, which will be required on most packaged food labels by July 2018.

LEGUMES. Legumes are nutrient-dense seeds that encompass pulses, beans, chickpeas, lentils and peas, and oil seeds like soybeans. Legumes are low in fat but rich in protein, complex carbohydrates, dietary fiber, polyphenols, and saponins (glycosylated triterpenes with cholesterol-lowering properties) (43).

High legume consumption is associated with a small reduction in all-cause mortality (risk ratio [RR]: 0.96; 95% confidence interval [CI]: 0.93 to 1.00) in a recent meta-analysis of 17 cohort studies (44). A meta-analysis of 8 prospective studies related consumption of legumes within a Mediterranean diet to CVD outcomes (CVD mortality, CHD, myocardial infarction [MI], and stroke) and found an RR of 0.91 (95% CI: 0.83 to 0.98) when comparing the highest to the lowest consumption (45). A summary of recent meta-analyses (46) found that legume consumption of ≥4 100-g servings/week was inversely associated with CHD risk, with RR: 0.86 (95% CI: 0.78 to 0.94), but not with stroke or DM. Moreover, data from 41 RCTs indicate that pulses improve glycemic control, predominantly by the main mechanism of reducing postprandial blood glucose and insulin excursions. For dyslipidemia, a meta-analysis of 25 feeding studies found dietary pulses at a median dose of 130 g/day reduced LDL-C by a mean of 0.17 mmol/l (95% CI: 0.09 to 0.25). The likely mechanisms are saponins and soluble fiber, and the effect of their fermentation products on reducing cholesterol production. A meta-analysis of 8 RCTs also demonstrated that 1 serving of cooked dietary pulses/day reduced systolic BP by 2.25 mm Hg (95% CI: 0.28 to 4.22), but had no significant effects on diastolic BP (47).

Concerning body weight, a meta-analysis of 21 RCTs testing the effect of dietary pulses on adiposity concluded that about 1 cup of legumes/day reduced weight by 0.34 kg (95% CI: 0.04 to 0.63 kg), while body fat was reduced nonsignificantly by 0.34% (95% CI: 0.03% to 0.71%) (48). These changes may be due to the satiating properties of pulses (49).

LEGUMES: THE BOTTOM LINE. Legumes are an affordable and sustainable source of protein and fiber. Consumption is associated with a reduction in CHD incidence and improved blood glucose, LDL-C, systolic BP, and body weight (50). Western populations' current consumption of pulses and derived products (bean dip, hummus, etc.) is very low despite their health benefits (51). Legumes should be part of any diet aimed at promoting cardiometabolic health.

COFFEE. Coffee is one of the most widely consumed beverages globally. It is rich in bioactive polyphenols, which are responsible for its characteristic bitter

taste. In addition to polyphenols (mainly chlorogenic acid) and caffeine (an alkaloid with stimulating properties), the coffee infusion maintains the high potassium concentration of the original seeds (43). Coffee intake often acutely increases BP in caffeine-naive individuals, but generally not in habitual coffee drinkers (52). A large meta-analysis showed no clinically important effects of long-term coffee consumption on BP or risk of hypertension (53). The NHS showed no association between coffee and hypertension development (54).

Polyphenolic antioxidants in coffee tend to improve glucose metabolism and insulin sensitivity (55). Several large epidemiological studies have reported a dose-dependent relationship between consumption of coffee (both caffeinated and decaffeinated) and reduced risk of type 2 DM (56,57). A recent study of nearly 186,000 subjects who drank more than 4 cups of coffee a day showed an 18% lower risk of dying prematurely over 16 years of follow-up, compared with nondrinkers (58). Even a single cup of coffee consumed daily reduced mortality 12% compared with no coffee consumption. Further, in a 10-country European study of more than one-half million subjects, researchers found that daily coffee drinkers had a 7% to 12% lower risk of dying prematurely compared with nondrinkers, and lower rates of digestive diseases and stroke (59). Studies have also reported that it is safe for patients with established CVD to continue habitual coffee consumption (60).

A comprehensive and statistically rigorous review of meta-analyses concluded that drinking 3 to 4 cups/day was associated with risk reductions in all-cause mortality (RR: 0.83; 95% CI: 0.78 to 0.88), CV mortality (RR: 0.81; 95% CI: 0.72 to 0.90), and CV disease (RR: 0.85; 95% CI: 0.80 to 0.90). These authors also concluded that high versus low coffee intake was associated with an 18% lower risk of cancer (61).

Coffee contains diterpenes that can raise cholesterol (62). However, these compounds are largely absent in filtered coffee. Large prospective observational studies and meta-analyses consistently find no effect of filtered coffee on blood lipid levels (63). A recent observational study of 25,000 men and women found that coffee intake was significantly associated with a risk-adjusted reduction in the incidence of coronary artery calcification (CAC). The lowest risk was observed in the subset who consumed 3 to 5 cups of coffee daily, in whom CAC scores were 40% lower compared with noncoffee drinkers (64).

A large meta-analysis reported a U-shaped association (more at lower and higher intakes, less in moderate intakes) between coffee intake and the incidence of heart failure. Further, in 5 randomized placebo-controlled trials, caffeine in doses as high as 500 mg/day (equivalent to 4 or 5 cups of coffee) did not increase the frequency, inducibility, or severity of ventricular arrhythmias (65,66). Multiple large prospective observational studies have reported consumption of coffee and/or caffeine is not associated with an increased risk of incident atrial fibrillation (67,68).

COFFEE: THE BOTTOM LINE. Overall, large analyses indicate that coffee intake is correlated with a dose-response protective benefit: habitual consumption of coffee is associated with lower risks of all-cause mortality and CVD mortality (69,70), but not with an increased risk of arrhythmias, hypertension, or hyperlipidemia. It should be noted that coffee-based drinks may be loaded with sugars and fats that reduce their health benefits.

TEA. Tea contains a significant antioxidant mix including flavonoids and polyphenols. In a study following 66 patients with proven CHD randomized to consume black tea or water in a crossover design, both short- and long-term tea consumption improved endothelium-dependent flow-mediated dilation of the brachial artery; water had no effect. Short- and long-term black tea consumption reversed endothelial vasomotor dysfunction in CHD patients (71). A very large study in China, which included nearly 200,000 men and 300,000 women, found daily consumption of any tea was associated with an 8% reduction in ischemic heart disease and a 10% reduction in major cardiac events (72).

Green tea may also be associated with beneficial CV effects. In the Ohsaki study cohort of more than 40,000 Japanese men and women, green tea consumption at 5 cups/day (more than most people may consume daily) was associated with decreased all-cause mortality by 12% in men and 23% in women (73). Tea has been associated with favorable effects on the lipid profile, especially the low-/high-density lipoprotein ratio (74).

TEA: THE BOTTOM LINE. Tea (plain, and multiple varietals) consumption appears to be safe and may be associated with improved CVD health and blood lipids based on large observational studies and meta-analyses. Of note, the evidence is based on tea consumption (sometimes >5 cups/day) without added sugars, sweeteners, or milks and creams (both animal- and plant-based).

WINE, LIQUOR, AND BEER. The relationships between alcohol consumption and CVD outcomes are complex and vary based on age, sex, ethnicity, genetic

factors, patterns of alcohol intake, and form of alcoholic beverage consumed (75-77). Low-to-moderate intake (<1 ounce) is associated with reduced risks of total CVD, new-onset CHD, angina, MI, total and CVD mortality, heart failure, and ischemic stroke (78-80), as well as improved intermediate CV endpoints such as insulin sensitivity, high-density lipoprotein cholesterol (HDL-C), adiponectin, platelet aggregation and thrombosis/hemostasis, and systemic inflammation (79,81-83). However, heavy and binge alcohol consumption are associated with increased risks of atrial fibrillation and ventricular arrhythmias, sudden cardiac death, impaired diastolic and systolic left ventricular function, alcohol-induced cardiomyopathy, heart failure, hemorrhagic and ischemic stroke, arterial hypertension, DM, hypertriglyceridemia, and inflammation (75,84,85). Among women, there are limited data suggesting that even modest alcohol consumption is associated with increased risk of developing breast cancer (86).

A 2017 analysis of >330,000 subjects demonstrates that light to moderate habitual alcohol consumption is associated with reduced all-cause mortality by up to 29% and CVD mortality by ≤24% (87). Studies demonstrate consistent CV benefits with all forms of alcohol, suggesting an ethanol-specific effect. The phenolic compounds in wine (i.e., flavonoids and nonflavonoids, including resveratrol and quercetin) have been shown in experimental models to have antioxidant, vasodilatory, antiplatelet, hypoglycemic, and anti-inflammatory properties (88).

ALCOHOLIC BEVERAGES: THE BOTTOM LINE. Research has shown some benefits of alcohol consumption, however, there is not sufficient high-quality evidence to recommend specific alcoholic beverages for CV risk reduction. There is also some risk of falls, certain cancers, and liver disease. As such, it is not recommended that individuals initiate alcohol consumption for CV benefit, and for those already drinking, consumption should be limited to recommended amounts, preferably consumed with meals. Mixing of alcoholic beverages with sodas, creams, and sweeteners adversely affects their health benefits.

ENERGY DRINKS. It appears that energy drinks, usually mixtures of vitamins and caffeine or caffeine-containing compounds, may increase the risk of adverse health effects ranging from arrhythmia, coronary spasm, and even death (89) and have been associated with increased morbidity and mortality, especially in young individuals (90). All energy drinks greatly surpass (by 2 to 4 times) the U.S. Food and Drug Administration (FDA) approved concentration of caffeine permissible in a soft drink (91).

Adolescents and young adults are some of the highest consumers of these drinks, with 31% to 34% of 12- to 24-year-old individuals reporting regular use (90). Consumption of energy drinks has been associated with elevated BP, seizures, agitation, increased heart rates, and supraventricular and ventricular rhythms. There have been cases of Takotsubo cardiomyopathy reported as well as coronary artery vasospasm, MI, and death (92,93). In addition, 50 healthy volunteers (34 men, age 22 ± 2 years) were tested before and 1 h after drinking 1 can of a sugar-free energy beverage. Following energy drink consumption, there was a significant increase in platelet aggregation (13.7 ± 3.7% vs. 0.3 ± 0.8% aggregation, respectively; $p < 0.01$) and a decrease in reactive hyperemia index (a measure of endothelial function) (−0.33 ± 0.13 vs. 0.07 ± 0.12 [control]; $p < 0.05$). The mean arterial pressure also increased ~3 mm following energy drink consumption ($p < 0.005$) (94). Collectively, the evidence indicates that caffeinated energy drinks adversely affect CVD health.

The International Society of Sports Nutrition recommends that children and adolescents not consume energy drinks without parental permission (95). The American Academy of Pediatrics is even more conservative, advocating that energy drinks never be consumed by children and adolescents (96). Many other countries and the European Union have implemented restriction on caffeine as well as marketing to minors (97). In 2014, the FDA classified energy drinks as beverages that require manufacturers to report caffeine content through nonbinding guidelines (98). The FDA is currently evaluating further recommendations.

ENERGY DRINKS: THE BOTTOM LINE. There is limited evidence, which is of relatively low quality, regarding energy drinks and CVD outcomes. Energy drinks should be avoided until more definitive research can be conducted. For now, there appears to be some evidence of harm.

MUSHROOMS AND CV HEALTH. Evidence from both preclinical and clinical studies suggests that consuming mushrooms can be cardioprotective through various mechanisms (99,100). Most studies indicate that mushrooms have anti-inflammatory and antioxidant benefits and are vitamin D producers (99). Bioactive compounds such as ergothioneine (amino acid), ergosterol (sterol), and beta-glucans (polysaccharides) are responsible for these effects and have been noted in RCTs to have antiatherosclerotic, hypocholesterolemic, antihypertensive, and immunomodulatory effects (101,102). Consuming mushrooms has also been associated with a reduction

in comorbidities related to CVD, such as metabolic syndrome, type 2 DM, and obesity (103,104).

Further, vitamin D deficiency is receiving much attention in studies for its relationship in the development of chronic disease (105). All mushrooms contain ergosterol, a molecule that is converted to vitamin D2 when exposed to ultraviolet light. RCTs have demonstrated that this form of vitamin D is bioavailable to humans and will increase serum vitamin D post-consumption (106,107). The popular white button variety (when fresh) can provide 100% of the daily value for vitamin D (400 IU) in 3 ounces. Species of mushroom, location grown, time of year, and duration of ultraviolet light exposure can all influence vitamin D levels (107). Khatun et al. (108) studied diabetic patients who consumed oyster mushrooms and found a significant decrease in both systolic and diastolic BP, plasma glucose, total cholesterol, and TGs. No changes were noted in HDL-C or weight (108). Mushroom consumption has also been associated with a lower risk of breast cancer (109). Finally, recent work has also shown that when mushrooms are substituted for meat, satiety is maintained (103).

MUSHROOMS AND CV HEALTH: THE BOTTOM LINE. Although there is no high-quality evidence of improved CV health outcomes, mushrooms may be associated with improvement in inflammatory and antioxidative pathways (110,111) and may have beneficial effects on known CVD comorbid risk factors. Caution should be made that some wild mushrooms are poisonous.

FERMENTED FOODS AND SEAWEED. Probiotics are microorganisms found in fermented foods. They are known to up-regulate production of T and dendritic cells that have the potential to suppress inflammation (112). Probiotics are postulated to reduce cholesterol by deconjugating bile acids, using cholesterol for nourishment, and/or incorporating cholesterol into the cell wall of the probiotic bacteria (113,114).

Kimchi. Kimchi (fermented cabbage) has long been touted for its medicinal properties and is rich in dietary fiber, vitamin C, β-carotene, β-sitosterol, and minerals (115). In a 2-week study in 22 overweight and obese patients who consumed 3 servings (100 g) of kimchi daily, significant decreases in mean weight (3.3 lbs), fasting glucose (100 ± 10.2 mg/dl to 94.1 ± 11.3 mg/dl), and systolic BP (126.1 ± 12.1 mm Hg to 121.3 ± 6.9 mm Hg) were observed compared with baseline ($p < 0.05$) (116). In another study, kimchi was given to patients in "low" and "high" amounts. After just 1 week, there was a notable drop in fasting blood glucose, total cholesterol, and LDL-C in the high-kimchi group (115). Despite the high sodium content in kimchi, studies do not show elevated BP in Koreans who ingest it regularly despite a daily sodium intake of >5,000 mg/day. The lack of the effect of sodium on BP could be reflective of kimchi's high potassium content (117).

Fermented milk (dairy and nondairy) and yogurt. The fermented milk (dairy and nondairy) products and yogurts have been shown to alter microbial flora in the gut (118). In 2 separate studies, adding yogurt daily for 3 or 4 weeks to subjects' regular diets caused a 2.4% or 3.2% decrease in total cholesterol concentration, respectively (119). In another RCT, giving hypercholesterolemic patients probiotics daily over a 9-week period was associated with an 11% reduction in LDL-C and a reduction in inflammatory markers (113). More recently, 21 subjects with type 2 DM randomized to probiotic yogurt containing Lactobacillus acidophilus 300 g daily for 8 weeks experienced a 23% reduction in LDL-C and a 15% increase in HDL-C compared with baseline (133 mg/dl vs. 103 mg/dl; $p = 0.01$; 43.7 mg/dl vs. 50.4 mg/dl; $p = 0.007$) (120).

Seaweed. Seaweed includes a variety of algae that are excellent sources of dietary fiber as well as antioxidants and other compounds that are beneficial for CVD health. Compounds in seaweed (e.g., alginates, fucoxanthin, fucoidan) exhibit antiobesity and cholesterol-lowering properties, in part by promoting satiety (121). In a 4-month study of 151 obese premenopausal women, daily intake of 300-mg brown seaweed extract containing 2.4 mg fucoxanthin resulted in significantly decreased body weight (~5 kg), waist circumference, TGs, and inflammatory biomarkers compared with baseline ($p < 0.05$) (122).

Seaweed is also a rich source of bioactive peptides that, when concentrated, exhibit BP-lowering properties similar to ACE inhibitors and improve insulin sensitivity. In a recent study of 25 overweight or obese men and women, intake of 500 mg of fucoidan daily for 3 months resulted in lower LDL-C (15-mg/dl), diastolic BP (–3.9 mm Hg), and improvement in insulin sensitivity as measured by HOMA (123).

Spirulina. A recent meta-analysis suggests that Spirulina, a filamentous, spiral-shaped, water blue-green microalgae (Cyanobacterium), which is considered a nutraceutical, has cholesterol-lowering properties (124).

FERMENTED FOODS AND SEAWEED: THE BOTTOM LINE. There is no high-quality evidence of CVD outcome benefits with fermented foods and seaweed. Observational studies and clinical trials suggest that both natural probiotics and seaweed have potential benefits on CVD, dyslipidemia, and weight. However,

TABLE 2 Dietary Pattern, Foods, Nutrients, and Other Dietary Factors: Available Evidence

Nutrition/Food Item	Level of Evidence Available and Included in This Paper	Recommendations for Patients
Dairy products	RCTs, prospective studies, systematic reviews, and meta-analyses.	Conflicting evidence prevents making a clear recommendation. Full-fat dairy products are major sources of saturated fat and sodium in the U.S. diet, and should be limited.
Added sugars	Prospective studies, RCTs.	Avoid.
Legumes	RCTs, prospective studies, systematic reviews, and meta-analyses.	Frequent.
Coffee	Prospective studies.	Frequent.
Tea	Prospective studies.	Frequent.
Alcoholic beverages	RCTs, prospective studies, systematic reviews, and meta-analyses.	Avoid or limit to <1 serving/day for women, <2 servings/day for men.
Energy drinks	Small uncontrolled studies, case reports.	Avoid.
Mushrooms	RCTs, prospective studies, cross-sectional, and meta-analyses.	Frequent.
Fermented foods: kimchi, sauerkraut, tempeh, milk-based kefir, yogurt, kombucha	RCTs, prospective studies.	Encourage, if desired.
Omega 3 fatty acids	RCTs, prospective studies, systematic reviews, and meta-analyses.	Frequent per dietary recommendations. The best source (plant vs. animal) unclear.
Vitamin B12	RCTs, prospective studies.	Supplement if deficient in diet, but too much may raise cancer risk.

RCT = randomized controlled trial.

there is not enough evidence to routinely recommend them at the current time, although there is also no evidence of harm from their consumption.

OMEGA-3 FATTY ACIDS. There are 2 distinct classes of omega-3 fatty acids (OM3): 1) long-chain n-3 polyunsaturated fatty acids of marine origin; and 2) alpha-linolenic acid (ALA) of plant origin. Both have CV benefits.

Fish and marine OM3. Marine-derived OM3, principally eicosapentaenoic acid (EPA) (20:5n-3) and docosahexaenoic acid (DHA) (22:6n-3), abound in the flesh of fatty fish.

Mechanistically, following intake and absorption, OM3 are preferentially shunted into cellular phospholipids rather than TGs, thereby decreasing very low-density lipoprotein synthesis and reducing serum TG levels, with more modest effects on BP, insulin signaling, and inflammatory pathways; they also may exert an antiarrhythmic effect, specifically in sudden cardiac death and atrial fibrillation (125).

In a meta-analysis of cohort studies focusing on dietary fatty acids in relation to CVD outcomes, significant benefit was reported with EPA/DHA (RR: 0.87; 95% CI: 0.78 to 0.97) in the 16 studies reviewed (n = 422,786) (126). Also, a consortium of 19 observational studies from 16 countries found that higher levels of EPA/DHA in plasma and in adipose tissue (both objective biomarkers of intake) were associated with a lower risk of fatal CVD and reduced risk of incident MI among the highest compared with lowest quintiles of OM3 intake (127). These data extend results from a prior meta-analysis of 11 prospective studies (n = 222,364, with mean follow-up of 11.8 years) that found fish consumption to be inversely associated with CVD mortality: each 20 g increase in fish consumption per day was associated with a 7% reduced risk of coronary death (128).

There are concerns about putative detrimental compounds in fish, mainly contaminants such as methylmercury, and specifically the potential harm of their ingestion (125). Another concern has been the relatively high content of trimethylamine N-oxide in fish (129), a molecule that may be detrimental for CV and general health (130). A recent study by Song et al. (13) also suggested an adverse outcome with fish protein consumption of all types when compared with plant protein in the realms of CVD and all-cause death, although the study only included patients with CVD risk factors and did not distinguish the types of fish consumed (13).

Most RCTs evaluating the effect of OM3 on CVD risk have employed concentrated fish oil supplements, as opposed to OM3 obtained via diet. A recent AHA science advisory (131) concludes that treatment with marine OM3 supplements is reasonable for patients with prevalent CHD due to a modest reduction in mortality, but that benefits are less certain for CHD patients treated with "optimal guideline-based therapy in 2017." Per the authors, there is not an "entirely settled" role for the use of fish oil in these patients. A very recent meta-analysis suggested no benefit for CHD patients (132).

TABLE 3 Key References Behind Recommendations

Nutrition/Food Item	Key Publication(s) on the Topic First Author (Ref. #)	Brief Summary of the Study	Key Conclusions
Dairy products	1. Chen et al. (12)	1. Analysis of 3 large U.S. cohorts.	1. Replacement of 5% of energy intake from dairy fat with polyunsaturated fatty acid or vegetable fat was associated with 24% and 10% lower risk of CVD, respectively.
	2. Benatar et al. (22)	2. Meta-analysis of 20 RCTs (n = 1,677). The median diet change duration was 26 weeks (IQR:10–39 weeks), mean dairy food intake increase was 3.6 servings/day (SD 0.92).	2. High- and low-fat dairy products caused modest weight gain and a nonsignificant increase in LDL-C (+1.85 mg/dl, −2.89 to 6.60 mg/dl).
Added sugars, as the caloric sweeteners HFCS or sucrose, or other sources	Yang et al. (39)	A NHANES study of healthy subjects (n = 11,733) with a median follow-up of 14.6 yrs.	The study documented an adjusted hazard ratio for CVD death of 1.3 for participants who consumed 10%–24.9% of energy from added sugars, and 2.75 for those who consumed >25% of energy from added sugars, compared with those who consumed added sugars at <10% of calories. Thus, consuming added sugars at 10% or higher of total daily calories raises the risk of death from CVD in a dose-dependent manner in otherwise healthy individuals.
Legumes/pulses	1. Schwingshackl et al. (44)	1. Meta-analysis of prospective studies relating exposure to various food groups, including legumes, to all-cause mortality.	1. An inverse association with all-cause mortality was observed for the highest compared with lowest legume consumption categories (RR: 0.96; 95% CI: 0.93–1.00).
	2. Grosso et al. (45)	2. Meta-analysis of prospective and RCTs on exposure to Mediterranean diet and its food group components in relation to incident CVD.	2. A pooled risk analysis for single items of the Mediterranean diet: legumes (RR: 0.91; 95% CI: 0.83–0.98), fruits (RR: 0.88; 95% CI: 0.81–0.96), vegetables (RR: 0.87; 95% CI: 0.77–0.89), and olive oil (RR: 0.83; 95% CI: 0.77–0.89) showed a significant reduction in CVD risk with increasing consumption of individual components.
	3. Viguiliouk et al. (46)	3. Summary of findings from recent systematic reviews and meta-analyses of prospective studies and RCTs assessing the relationship between dietary pulse consumption and cardiometabolic health.	3. Prospective cohort studies of legume consumption concluded that at least 4 100-g servings/week was inversely associated with CHD risk (RR: 0.86; 95% CI: 0.78–0.94), but not with stroke or DM risk. Data from feeding studies showed that a daily serving of pulses slightly improves glycemic control and reduces LDL-C (0.17 mmol/l) and systolic BP (2.25 mm Hg).
	4. Kim et al. (48)	4. Meta-analysis of RCTs testing the effect of dietary pulses on adiposity measures.	4. Pulses of 1 serving/day compared with no pulses a day reduced body weight by a mean of 0.34 kg (95% CI: 0.04–0.63 kg) and body fat (nonsignificantly) by 0.34% (95% CI: 0.03%–0.71%), and no effect on waist circumference.
Coffee	1. Ding et al. (70)	1. A meta-analysis of 36 prospective cohort studies (n = 1,279,804).	1. Coffee consumption was inversely associated (p < 0.001) with CVD risk (CHD, stroke, heart failure, and CVD mortality), with lowest CVD risk at 3–5 cups/day; heavier coffee consumption was not associated with increased CVD risk. Coffee intake of 3.5 cups/day was associated with a 15% decrease in CVD.
	2. Park et al. (58)	2. A prospective cohort study (n = 186,000) of nonwhites followed for a mean of 16 yrs.	2. African Americans, Japanese Americans, Latinos, and whites who drank more than 4 cups of coffee/day showed an 18% lower risk of dying prematurely, compared to nondrinkers. Even a single cup of coffee daily reduced mortality 12% lower compared with nondrinkers.
	3. Gunter et al. (59)	3. A prospective cohort study (n = 521,000) of people enrolled in EPIC (European Prospective Investigation into Cancer and Nutrition) followed for a mean of 16 yrs.	3. Coffee drinkers in the highest intake quartile had a 7%–12% lower risk of dying prematurely compared with nondrinkers (p < 0.001), and also had lower rates of digestive diseases and stroke.
Tea	Li et al (72)	Prospective study of Chinese adults (n = 487,375) followed for 5 yrs.	Daily black tea consumption was associated with 10% reduction in major coronary events.
Energy drinks	Worthley et al. (94)	Uncontrolled experimental study (n = 50) of healthy subjects that evaluated the effects of energy drinks on platelet aggregation and endothelial function.	Energy drink consumption led to an increase in platelet aggregation with low and higher dose of adenosine (p < 0.003 and p < 0.070, respectively) and BP (p < 0.05) but no observed difference in endothelial function (p = 0.34).

Continued on the next page

Vegetable OM3. The principal OM3 derived from plants is ALA (18:3n-3), an essential fatty acid, which must be acquired from the diet. Sources of ALA include green leafy plants (ALA up to 80% of fatty acids); walnuts, canola oil, and soybean oil (ALA ~10% of total fatty acids); and flaxseeds/flaxseed oil (ALA ~50% of total fatty acids) (133,134). ALA is rapidly oxidized after intake and has a low rate of conversion to EPA/DHA (around 10% to EPA and 1% to DHA) (133).

Concerns about declining fish stocks have raised interest in a more sustainable and inexpensive OM3, such as ALA. ALA has some of the cardioprotective properties of its longer chain, marine-derived counterparts. In a recent meta-analysis of 33 observational studies, including dietary and biomarker studies,

TABLE 3 Continued

Nutrition/Food Item	Key Publication(s) on the Topic First Author (Ref. #)	Brief Summary of the Study	Key Conclusions
Mushrooms	1. Osonoi et al. (152)	1. Cross-sectional study (n = 726) of T2 DM outpatients were evaluated and analyzed for dietary patterns and relationship to CVD risk.	1. A plant-rich diet which included mushrooms was one of 3 dietary patterns correlated with a lower usage of diabetic medications and an overall healthier lifestyle.
	2. Keegan et al. (106)	2. Clinical study (n = 30) that compared the bioavailability of vitamin D2 in mushrooms to supplements containing D2 and D3 in healthy adults.	2. Mushrooms can increase and maintain blood levels of 25-hydroxyvitamin D in the healthy range, and is associated with a weakened post-prandial TG response. Ingestion of mushrooms is a worthy substitute for vitamin D.
	3. Poddar et al. (103)	3. RCT (n = 73) of obese adults comparing standard diet to a diet substituting mushrooms for red meat.	3. Mushrooms substituted for red meat diet led to an improved lipid profile and inflammatory markers. There was a lower caloric intake, BMI decreased, BP lowered, and more pounds were lost on this diet. Substituting mushrooms for red meat is a recommended strategy in prevention of CVD by decreasing CVD risk factors.
Fermented foods: kimchi, sauerkraut, tempeh, milk based kefir, yogurt, kombucha	1. Choi et al. (115)	1. RCT (n = 100) that studied the effect of the addition of kimchi 15 or 210 g/day to a controlled diet for 7 days on cholesterol, TGs, and fasting blood glucose.	1. Kimchi was found to decrease fasting blood glucose at both levels (15 g/day: −2.28%; $p = 0.002$; 210 mg/day: −6.96%; $p < 0.001$), TGs (15 g/day: −6.1 mg/dl; $p < 0.05$; 210 mg: −7.4 mg/dl, $p < 0.05$), and TC (15 g/day −6.8 mg/dl, $p < 0.001$; 210 g/day −8.9 mg/dl; $p < 0.001$). BP was not affected despite excess salt provided by kimchi.
	2. Anderson et al. (119)	2. Review of 2 studies. Study 1 was single-blinded and patients were randomly allocated to fermented milk (yogurt) containing Lactobacillus acidophilus L1 or containing Lactobacillus acidophilus ATCC 4311 for 3 weeks. Study 2 was a double-blind, placebo-controlled, cross-over study of yogurt containing L. acidophilus L1 or placebo. There was a 2-week washout between 2 4-week treatments.	2. Study 1 found a 2.4% ($p < 0.05$) reduction in cholesterol in those consuming yogurt with L. acidophilus L1. Study 2 found a reduction in cholesterol of 3.2% ($p < 0.05$) with L. acidophilus L1 in the first treatment period. In the second treatment period also using L. acidophilus L1, there were no significant changes in cholesterol. Comparing the 2 treatment periods there was a reduction of cholesterol by 2.9% ($p < 0.01$). Thus, consuming yogurt with L. acidophilus regularly may decrease the risk of CHD.
Omega-3 fatty acids	1. He et al. (128)	1. Meta-analysis of cohort studies of men and women (n=222,364) with mean follow-up period of 11.8 yrs on CHD mortality.	1. The pooled RRs for CHD death were 0.89 (95% CI: 0.79–1.01) for fish consumption 1–3 meals/month; 0.85 (95% CI: 0.76–0.96) once per week; 0.77 (95% CI: 0.66–0.89) 2–4 per week; and 0.62 (95% CI: 0.46–0.82) for ≥5 meals/week. Each 20-g/day increase in fish intake correlated with 7% reduced risk of CHD mortality ($p = 0.03$).
	2. Baker et al. (133)	2. Comprehensive review of the metabolism and health effects of vegetable n-3 PUFA ALA.	2. Effects of ALA on the lipid profile, BP, low-density lipoprotein oxidation, and hemostatic factors are inconsistent, although there is a suggestion of improved inflammatory status.
	3. Pan et al. (135)	3. Meta-analysis of prospective studies relating exposure to ALA and incident CVD.	3. The pooled RR of CVD for the comparison of the top with the bottom tertiles of ALA intake was 0.86 (95% CI: 0.77–0.97), with high heterogeneity. Among CVD subtypes, the association was only significant for fatal CHD (RR: 0.80; 95% CI: 0.65–0.98) and each 1-g/day increment of ALA intake was associated with a 10% lower risk of fatal CHD.
Vitamin B12/cobalamin	1. Lonn et al. (142)	1. RCT of folic acid, vitamin B6, and vitamin B12 vs. placebo in patients age ≥55 yrs with vascular disease or DM (n = 5,522). Average follow-up was 5 yrs.	1. No difference in death from CVD, MI, stroke (RR: 0.95; $p = 0.41$). Risk of stroke was reduced (RR: 0.75) but not risk for unstable angina hospitalization (RR: 1.24). There was an 18% decrease in homocysteine levels.
	2. Ebbing et al. (143)	2. RCT, 2×2 factorial design using folic acid + vitamin B12 + vitamin B6 (n = 772); folic acid + vitamin B12 (n = 772); vitamin B6 alone (n = 772); or placebo (n = 780) in patients undergoing coronary angiography for suspected CAD or aortic stenosis. Average follow-up was 38 months.	2. No difference in death, nonfatal MI, unstable angina hospitalizations, and nonfatal stroke in those receiving folic acid + B12 vs. not (HR: 1.09; $p = 0.36$). There was a 30% decrease in homocysteine levels.
	3. Bonaa et al. (144)	3. RCT, 2×2 factorial design, folic acid + vitamin B12 + vitamin B6; folic acid + vitamin B12; vitamin B6; or placebo inpatients who had MI within 7 days (n = 3,749). Average follow-up was 40 months.	3. No difference in recurrent MI, stroke, & sudden death due to CAD (folic acid + B12 RR: 1.08; $p = 0.31$). Folic acid + B6 + B12 trend toward increased CVD event risk (RR: 1.22; $p = 0.05$). 27% decrease in homocysteine levels.

ALA = alpha-linolenic acid; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; NHANES = National Health and Nutrition Examination Survey; RCT = randomized controlled trial; RR = risk ratio; T2 DM = type 2 diabetes mellitus; TG = triglyceride.

higher ALA intake was associated with a moderately lower risk of CVD, particularly fatal CHD (135). The pooled RR for the comparison of the top with the bottom tertiles of ALA intake was 0.86 (95% CI: 0.77 to 0.97), but there was high heterogeneity among studies. When restricting the analysis only to dietary intake studies, the RR was 0.90 (95% CI: 0.81 to 0.99). Assessment of the relation of dietary ALA with risk of CVD subtypes, including fatal CHD, nonfatal CHD, total CHD, and stroke, revealed that the association was only significant for fatal CHD (RR: 0.80; 95% CI: 0.65 to 0.98). Finally, in a dose-response analysis, each 1-g/day increment of ALA intake was associated with a 10% lower risk of fatal CHD. The aforementioned consortium of 19 observational studies also found higher plasma or adipose tissue levels of ALA to be associated with a reduced risk of MI and fatal CHD (127).

Two RCTs conducted in MI survivors have tested the effects of ALA on hard CVD endpoints: the Lyon Diet Heart study (136) and the Alpha-Omega trial (137). In particular, the Alpha-Omega trial demonstrated a trend toward lower CVD risk with 2-g/day ALA for 40 months compared with a combined control group receiving 400 mg/day EPA+DHA or placebo (RR: 0.91; 95% CI: 0.78 to 1.05). The Lyon Diet Heart Study, a randomized, controlled trial with free-living subjects, tested the effectiveness of a Mediterranean-style dietary pattern on composite measures of the coronary recurrence rate after a first myocardial infarction. The main finding reported was that subjects following the Mediterranean-style diet had a 50% to 70% lower risk of recurrent heart disease, as measured by 3 different combinations of outcome measures including: 1) cardiac death and nonfatal heart attacks; 2) the preceding plus unstable angina, stroke, heart failure, and pulmonary or peripheral embolism; and 3) all of these measures plus events that required hospitalization (138). To date, no primary prevention trials with ALA have been conducted.

OM3: BOTTOM LINE. Some evidence favors incorporating plant or marine-based OM3 daily into a heart-healthy diet, and probably in nonsupplement forms (139). There appear to be CVD benefits from either source of OM3, although some concerns regarding fish-based sources should be further examined.

VITAMIN B12. Vitamin B12 (cobalamin) is an essential micronutrient with deficiencies linked to severe hematological and neurological consequences (140). B12 supplementation is touted as having wide-ranging health effects: improved energy levels, memory, mood, CV health, and health of skin, hair, and nails.

Although it is clear that folic acid and vitamin B12 supplements lower homocysteine levels, results from several large prospective studies have not shown that these supplements decrease the risk of incident or recurrent CVD. In the Women's Antioxidant and Folic Acid Cardiovascular Study, 5,442 women with preexisting CVD or ≥3 coronary risk factors took a daily supplement containing vitamin B12, folic acid, and vitamin B6 or a placebo for 7.3 years (141). Treatment was not associated with a reduced risk of major CV events compared with placebo, despite lowered homocysteine levels. The HOPE 2 (Heart Outcomes Prevention Evaluation) trial found that daily treatment with folic acid, vitamin B6, and vitamin B12 for an average of 5 years reduced homocysteine levels and the risk of stroke, but not the risk of major CV events; moreover, a greater number of patients receiving active treatment were hospitalized for unstable angina (142).

In the WENBIT (Western Norway B Vitamin Intervention Trial), 3,096 patients undergoing coronary angiography were given daily supplements of vitamin B12 and folic acid with or without vitamin B6 for 1 year. Homocysteine levels were reduced by 30%, but treatment did not affect total mortality or the risk of major CV events during the 38-month follow-up, and was terminated early due to possible adverse effects (143). The NORVIT (Norwegian Vitamin Trial) (144) enrolled 3,749 men and women who experienced an acute MI in the prior 7 days. Although homocysteine levels were lowered by 27% with vitamin B12, there was no reduction in the primary endpoint of recurrent MI, stroke, and sudden death. The VISP (Vitamin Intervention for Stroke Prevention) trial (145) randomized 3,680 adults with recent stroke to a low or high fixed-dose combination of vitamins B12, B6, and folic acid. Moderate reduction of homocysteine levels in high-dose versus low-dose groups had no effect on vascular outcomes over 2 years of follow-up.

Many adults, particularly older adults, lack sufficient gastric acid to separate B12 from dietary protein, resulting in B12 malabsorption. Absorption is also impaired in diseases of the distal ileum (the site of absorption), such as inflammatory bowel disease, and by certain medications (e.g., metformin and acid-blockers). Therefore, supplementation is of particular importance for individuals older than age 50 years, in addition to anyone on a vegan diet (146).

Finally, it is important to note that too much B12, B6, or folate intake may have adverse effects, such as increased lung cancer in men, as noted in a recent paper (147).

VITAMIN B12 SUPPLEMENTATION: THE BOTTOM LINE. Multiple large studies do not support the use of supplemental vitamin B12 for prevention of CVD. Certain populations at risk of becoming deficient in

B12 should use supplements (the recommended daily allowance is 2.4 μg/day).

A LOOK TO THE FUTURE

In summary, the future health of the global population depends on a shift to healthier dietary patterns. However, in the search for the "perfect" dietary pattern and foods that provide "miracle" benefits, consumers are vulnerable to unsubstantiated health benefit claims. As clinicians, it is important to stay abreast of the current scientific evidence to provide meaningful and effective nutrition guidance to patients for ASCVD risk reduction. Available evidence (**Tables 2 and 3**) supports CV benefits of plant-based proteins, OM3 (from both marine and plant sources, although with some concerns regarding marine sources), vitamin B12 (but not in excess, and when dietary deficiencies are present), mushrooms, legumes of all sorts, coffee, tea, modest if any alcohol, fermented foods, and seaweed. The evidence to date suggests adverse CV outcomes with high intake of both red meat and added sugar, excessive vitamin B12, and any amounts of energy drinks. Finally, there is still debate over the effects of dairy products on CVD, although they remain the top source of saturated fat and sodium in the United States.

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REFERENCES

1. U.S. Department of Health and Human Services and U.S. Department of Agriculture. Dietary guidelines for Americans 2015-2020. 8th edition. December 2015. Available at: http://health.gov/dietaryguidelines/2015/guidelines. Accessed December 1, 2017.

2. Freeman AM, Morris PB, Barnard N, et al. Trending cardiovascular nutrition controversies. J Am Coll Cardiol 2017;69:1172–87.

3. Thorning TK, Raben A, Tholstrup T, Soedamah-Muthu SS, Givens I, Astrup A. Milk and dairy products: good or bad for human health? An assessment of the totality of scientific evidence. Food Nutr Res 2016;60:32527.

4. Drouin-Chartier JP, Brassard D, Tessier-Grenier M, et al. Systematic review of the association between dairy product consumption and risk of cardiovascular-related clinical outcomes. Adv Nutr 2016;7:1026–40.

5. Barnard ND, Willett WC, Ding EL. The misuse of meta-analysis in nutrition research. JAMA 2017;318:1435–6.

6. Chartres N, Fabbri A, Bero LA. Association of industry sponsorship with outcomes of nutrition studies: a systematic review and meta-analysis. JAMA Intern Med 2016;176:1769–77.

7. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63 25 Pt B:2960–84.

8. Qin LQ, Xu JY, Han SF, Zhang ZL, Zhao YY, Szeto IM. Dairy consumption and risk of cardiovascular disease: an updated meta-analysis of prospective cohort studies. Asia Pac J Clin Nutr 2015;24:90–100.

9. Alexander DD, Bylsma LC, Vargas AJ, et al. Dairy consumption and CVD: a systematic review and meta-analysis. Br J Nutr 2016;115:737–50.

10. Guo J, Astrup A, Lovegrove JA, Gijsbers L, Givens DI, Soedamah-Muthu SS. Milk and dairy consumption and risk of cardiovascular diseases and all-cause mortality: dose-response meta-analysis of prospective cohort studies. Eur J Epidemiol 2017;32:269–87.

11. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. N Engl J Med 1997;336:1117–24.

12. Chen M, Li Y, Sun Q, et al. Dairy fat and risk of cardiovascular disease in 3 cohorts of U.S. adults. Am J Clin Nutr 2016;104:1209–17.

13. Song M, Fung TT, Hu FB, et al. Association of animal and plant protein intake with all-cause and cause-specific mortality. JAMA Intern Med 2016;176:1453–63.

14. Michaëlsson K, Wolk A, Langenskiöld S, et al. Milk intake and risk of mortality and fractures in women and men: Cohort studies. BMJ 2014;349:g6015.

15. Buehring GC, Shen HM, Jensen HM, Jin DL, Hudes M, Block G. Exposure to bovine leukemia virus is associated with breast cancer: a case-control study. PLoS One 2015;10:e0134304.

16. McCann SE, Hays J, Baumgart CW, Weiss EH, Yao S, Ambrosone CB. Usual consumption of specific dairy foods is associated with breast cancer in the Roswell Park Cancer Institute Data Bank and Biorepository. Curr Dev Nutr 2017;1:e000422.

17. Qin B, Moorman PG, Alberg AJ, et al. Dairy, calcium, vitamin D and ovarian cancer risk in African-American women. Br J Cancer 2016;115:1122–30.

18. Yang M, Kenfield SA, Van Blarigan EL, et al. Dairy intake after prostate cancer diagnosis in relation to disease-specific and total mortality. Int J Cancer 2015;137:2462–9.

19. Lu W, Chen H, Niu Y, Wu H, Xia D, Wu Y. Dairy products intake and cancer mortality risk: a meta-analysis of 11 population-based cohort studies. Nutr J 2016;15:91.

20. Michaelsson K, Wolk A, Melhus H, Byberg L. Milk, fruit and vegetable, and total antioxidant intakes in relation to mortality rates: cohort studies in women and men. Am J Epidemiol 2017;185:345–61.

21. Feskanich D, Meyer HE, Fung TT, Bischoff-Ferrari HA, Willett WC. Milk and other dairy foods and risk of hip fracture in men and women. Osteoporos Int 2018;29:385–96.

22. Benatar JR, Sidhu K, Stewart RA. Effects of high and low fat dairy food on cardio-metabolic risk factors: a meta-analysis of randomized studies. PLoS One 2013;8:e76480.

23. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med 2011;364:2392–404.

24. de Goede J, Geleijnse JM, Ding EL, Soedamah-Muthu SS. Effect of cheese consumption on blood lipids: a systematic review and meta-analysis of randomized controlled trials. Nutr Rev 2015;73:259–75.

25. Huth PJ, Park KM. Influence of dairy product and milk fat consumption on cardiovascular disease risk: A review of the evidence. Adv Nutr 2012;3:266–85.

26. Drouin-Chartier JP, Côté JA, Labonté MÈ, et al. Comprehensive review of the impact of dairy foods and dairy fat on cardiometabolic risk. Adv Nutr 2016;7:1041–51.

27. Kearns CE, Schmidt LA, Glantz SA. Sugar industry and coronary heart disease research: A historical analysis of internal industry documents. JAMA Intern Med 2016;176:1680–5.

28. Nestle M. Food industry funding of nutrition research: The relevance of history for current debates. JAMA Intern Med 2016;176:1685–6.

29. Li Y, Hruby A, Bernstein AM, et al. Saturated fats compared with unsaturated fats and sources of carbohydrates in relation to risk of coronary heart disease: a prospective cohort study. J Am Coll Cardiol 2015;66:1538–48.

30. Malik VS, Hu FB. Fructose and cardiometabolic health: what the evidence from sugar-sweetened beverages tells us. J Am Coll Cardiol 2015;66:1615–24.

31. Bray GA, Popkin BM. Dietary sugar and body weight: have we reached a crisis in the epidemic of obesity and diabetes? Health be damned! Pour on the sugar. Diabetes Care 2014;37:950–6.

32. Nielsen SJ, Popkin BM. Changes in beverage intake between 1977 and 2001. Am J Prev Med 2004;27:205–10.

33. Welsh JA, Sharma AJ, Grellinger L, Vos MB. Consumption of added sugars is decreasing in the United States. Am J Clin Nutr 2011;94:726–34.

34. Powell ES, Smith-Taillie LP, Popkin BM. Added sugars intake across the distribution of us children and adult consumers: 1977–2012. J Acad Nutr Diet 2016;116:1543–50.e1.

35. DiNicolantonio JJ, Lucan SC, O'Keefe JH. The evidence for saturated fat and for sugar related to coronary heart disease. Prog Cardiovasc Dis 2016;58:464–72.

36. Stanhope KL, Bremer AA, Medici V, et al. Consumption of fructose and high fructose corn syrup increase postprandial triglycerides, ldl-cholesterol, and apolipoprotein-b in young men and women. J Clin Endocrinol Metab 2011;96:E1596–605.

37. Te Morenga LA, Howatson AJ, Jones RM, Mann J. Dietary sugars and cardiometabolic risk: Systematic review and meta-analyses of randomized controlled trials of the effects on blood pressure and lipids. Am J Clin Nutr 2014;100:65–79.

38. de Koning L, Malik VS, Kellogg MD, Rimm EB, Willett WC, Hu FB. Sweetened beverage consumption, incident coronary heart disease, and biomarkers of risk in men. Circulation 2012;125:1735–41, s1.

39. Yang Q, Zhang Z, Gregg EW, Flanders WD, Merritt R, Hu FB. Added sugar intake and cardiovascular diseases mortality among US adults. JAMA Intern Med 2014;174:516–24.

40. Micha R, Penalvo JL, Cudhea F, Imamura F, Rehm CD, Mozaffarian D. Association between dietary factors and mortality from heart disease, stroke, and type 2 diabetes in the United States. JAMA 2017;317:912–24.

41. World Health Organization. Guideline: Sugars Intake for Adults and Children. Geneva: World Health Organization, 2015.

42. U.S. Department of Health and Human Services. Scientific Report of the 2015 Dietary Guidelines Advisory Committee. Washington, DC: U.S. Government Printing Office, 2015.

43. Ros E, Hu FB. Consumption of plant seeds and cardiovascular health: epidemiological and clinical trial evidence. Circulation 2013;128:553–65.

44. Schwingshackl L, Schwedhelm C, Hoffmann G, et al. Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr 2017;105:1462–73.

45. Grosso G, Marventano S, Yang J, et al. A comprehensive meta-analysis on evidence of Mediterranean diet and cardiovascular disease: are individual components equal? Crit Rev Food Sci Nutr 2017;57:3218–32.

46. Viguiliouk E, Blanco Mejia S, Kendall CW, Sievenpiper JL. Can pulses play a role in improving cardiometabolic health? Evidence from systematic reviews and meta-analyses. Ann N Y Acad Sci 2017;1392:43–57.

47. Jayalath VH, de Souza RJ, Sievenpiper JL, et al. Effect of dietary pulses on blood pressure: a systematic review and meta-analysis of controlled feeding trials. Am J Hypertens 2014;27:56–64.

48. Kim SJ, de Souza RJ, Choo VL, et al. Effects of dietary pulse consumption on body weight: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr 2016;103:1213–23.

49. Li SS, Kendall CW, de Souza RJ, et al. Dietary pulses, satiety and food intake: a systematic review and meta-analysis of acute feeding trials. Obesity 2014;22:1773–80.

50. U.S. Department of Agriculture, Economic Research Service. Dried Beans. Washington, DC: U.S. Department of Agriculture, Economic Research Service, 2013.

51. Broom M. Trends in Pulse Consumption: Now and on the Horizon? Future of Pulse Production and Consumption. Sydney, Australia: Grains & Legumes Nutrition Council, 2016.

52. Mesas AE, Leon-Munoz LM, Rodriguez-Artalejo F, Lopez-Garcia E. The effect of coffee on blood pressure and cardiovascular disease in hypertensive individuals: a systematic review and meta-analysis. Am J Clin Nutr 2011;94:1113–26.

53. Steffen M, Kuhle C, Hensrud D, Erwin PJ, Murad MH. The effect of coffee consumption on blood pressure and the development of hypertension: a systematic review and meta-analysis. J Hypertens 2012;30:2245–54.

54. Winkelmayer WC, Stampfer MJ, Willett WC, Curhan GC. Habitual caffeine intake and the risk of hypertension in women. JAMA 2005;294:2330–5.

55. van Dam RM. Coffee and type 2 diabetes: From beans to beta-cells. Nutr Metab Cardiovasc Dis 2006;16:69–77.

56. Wedick NM, Brennan AM, Sun Q, Hu FB, Mantzoros CS, van Dam RM. Effects of caffeinated and decaffeinated coffee on biological risk factors for type 2 diabetes: a randomized controlled trial. Nutr J 2011;10:93.

57. van Dam RM, Hu FB. Coffee consumption and risk of type 2 diabetes: a systematic review. JAMA 2005;294:97–104.

58. Park SY, Freedman ND, Haiman CA, Le Marchand L, Wilkens LR, Setiawan VW. Association of coffee consumption with total and cause-specific mortality among nonwhite populations. Ann Intern Med 2017;167:228–35.

59. Gunter MJ, Murphy N, Cross AJ, et al. Coffee drinking and mortality in 10 European countries: a multinational cohort study. Ann Intern Med 2017;167:236–47.

60. Richardson T, Baker J, Thomas PW, Meckes C, Rozkovec A, Kerr D. Randomized control trial investigating the influence of coffee on heart rate variability in patients with ST-segment elevation myocardial infarction. QJM 2009;102:555–61.

61. Poole R, Kennedy OJ, Roderick P, Fallowfield JA, Hayes PC, Parkes J. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. BMJ 2017;359:j5024.

62. Urgert R, Katan MB. The cholesterol-raising factor from coffee beans. Annu Rev Nutr 1997;17:305–24.

63. Lopez-Garcia E, van Dam RM, Willett WC, et al. Coffee consumption and coronary heart disease in men and women: a prospective cohort study. Circulation 2006;113:2045–53.

64. Choi Y, Chang Y, Ryu S, et al. Coffee consumption and coronary artery calcium in young and middle-aged asymptomatic adults. Heart 2015;101:686–91.

65. Newcombe PF, Renton KW, Rautaharju PM, Spencer CA, Montague TJ. High-dose caffeine and cardiac rate and rhythm in normal subjects. Chest 1988;94:90–4.

66. Myers MG. Caffeine and cardiac arrhythmias. Ann Intern Med 1991;114:147–50.

67. Frost L, Vestergaard P. Caffeine and risk of atrial fibrillation or flutter: the Danish Diet, Cancer, and Health study. Am J Clin Nutr 2005;81:578–82.

68. Shen J, Johnson VM, Sullivan LM, et al. Dietary factors and incident atrial fibrillation: the Framingham Heart Study. Am J Clin Nutr 2011;93:261–6.

69. Greenberg JA, Dunbar CC, Schnoll R, Kokolis R, Kokolis S, Kassotis J. Caffeinated beverage intake and the risk of heart disease mortality in the elderly: a prospective analysis. Am J Clin Nutr 2007;85:392–8.

70. Ding M, Bhupathiraju SN, Satija A, van Dam RM, Hu FB. Long-term coffee consumption and risk of cardiovascular disease: a systematic review and a dose-response meta-analysis of prospective cohort studies. Circulation 2014;129:643–59.

71. Duffy SJ, Keaney JF Jr., Holbrook M, et al. Short- and long-term black tea consumption reverses endothelial dysfunction in patients with coronary artery disease. Circulation 2001;104:151–6.

72. Li X, Yu C, Guo Y, et al. Tea consumption and risk of ischaemic heart disease. Heart 2017;103:783–9.

73. Kuriyama S, Shimazu T, Ohmori K, et al. Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: The Ohsaki study. JAMA 2006;296:1255–65.

74. Bahorun T, Luximon-Ramma A, Neergheen-Bhujun VS, et al. The effect of black tea on risk factors of cardiovascular disease in a normal population. Prev Med 2012;54 Suppl:S98–102.

75. O'Keefe JH, Bhatti SK, Bajwa A, DiNicolantonio JJ, Lavie CJ. Alcohol and cardiovascular health: the dose

makes the poison…or the remedy. Mayo Clin Proc 2014;89:382–93.

76. Fernandez-Sola J. Cardiovascular risks and benefits of moderate and heavy alcohol consumption. Nat Rev Cardiol 2015;12:576–87.

77. Matsumoto C, Miedema MD, Ofman P, Gaziano JM, Sesso HD. An expanding knowledge of the mechanisms and effects of alcohol consumption on cardiovascular disease. J Cardiopulm Rehabil Prev 2014;34:159–71.

78. Ronksley PE, Brien SE, Turner BJ, Mukamal KJ, Ghali WA. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. BMJ 2011;342:d671.

79. Costanzo S, Di Castelnuovo A, Donati MB, Iacoviello L, de Gaetano G. Alcohol consumption and mortality in patients with cardiovascular disease: a meta-analysis. J Am Coll Cardiol 2010;55:1339–47.

80. Imhof A, Plamper I, Maier S, Trischler G, Koenig W. Effect of drinking on adiponectin in healthy men and women: A randomized intervention study of water, ethanol, red wine, and beer with or without alcohol. Diabetes Care 2009;32:1101–3.

81. Davies MJ, Baer DJ, Judd JT, Brown ED, Campbell WS, Taylor PR. Effects of moderate alcohol intake on fasting insulin and glucose concentrations and insulin sensitivity in postmenopausal women: a randomized controlled trial. JAMA 2002;287:2559–62.

82. Brinton EA. Effects of ethanol intake on lipoproteins and atherosclerosis. Curr Opin Lipidol 2010;21:346–51.

83. Salem RO, Laposata M. Effects of alcohol on hemostasis. Am J Clin Pathol 2005;123 Suppl:S96–105.

84. George A, Figueredo VM. Alcohol and arrhythmias: a comprehensive review. J Cardiovasc Med 2010;11:221–8.

85. Szabo G, Saha B. Alcohol's effect on host defense. Alcohol Res 2015;37:159–70.

86. Cao Y, Willett WC, Rimm EB, Stampfer MJ, Giovannucci EL. Light to moderate intake of alcohol, drinking patterns, and risk of cancer: results from two prospective US cohort studies. BMJ 2015;351:h4238.

87. Xi B, Veeranki SP, Zhao M, Ma C, Yan Y, Mi J. Relationship of alcohol consumption to all-cause, cardiovascular, and cancer-related mortality in us adults. J Am Coll Cardiol 2017;70:913–22.

88. Iriti M, Varoni EM. Cardioprotective effects of moderate red wine consumption: Polyphenols vs. Ethanol. J Appl Biomed 2014;12:193–202.

89. Higgins JP, Tuttle TD, Higgins CL. Energy beverages: content and safety. Mayo Clin Proc 2010;85:1033–41.

90. Seifert SM, Schaechter JL, Hershorin ER, Lipshultz SE. Health effects of energy drinks on children, adolescents, and young adults. Pediatrics 2011;127:511–28.

91. Somogyi LP. Caffeine Intake by the U.S. Population. Report Prepared for the Food and Drug Administration. Kensington, California: Oakridge National Laboratory, 2010.

92. Temple JL, Bernard C, Lipshultz SE, Czachor JD, Westphal JA, Mestre MA. The safety of ingested caffeine: a comprehensive review. Front Psychiatry 2017;8:80.

93. Kaoukis A, Panagopoulou V, Mojibian HR, Jacoby D. Reverse takotsubo cardiomyopathy associated with the consumption of an energy drink. Circulation 2012;125:1584–5.

94. Worthley MI, Prabhu A, De Sciscio P, Schultz C, Sanders P, Willoughby SR. Detrimental effects of energy drink consumption on platelet and endothelial function. Am J Med 2010;123:184–7.

95. Campbell B, Wilborn C, La Bounty P, et al. International Society of Sports Nutrition position stand: energy drinks. J Int Soc Sports Nutr 2013;10:1.

96. Committee on Nutrition and the Council on Sports Medicine and Fitness. Clinical report—sports drinks and energy drinks for children and adolescents: are they appropriate? Pediatrics 2011;2011:1182–9.

97. Peacock A, Droste N, Miller P. Alert and ready for action: Why it's time to ban energy drinks for under-18s [serial online]. October 2015. Available at: http://theconversation.com/alert-and-ready-for-action-why-its-time-to-ban-energy-drinks-for-under-18s-44765. Accessed December 1, 2017.

98. U.S. Food and Drug Administration. Guidance for Industry: Distinguishing Liquid Dietary Supplements from Beverages. Washington, DC: Office of Nutrition, Labeling and Dietary Supplements, 2014.

99. Guillamon E, Garcia-Lafuente A, Lozano M, et al. Edible mushrooms: role in the prevention of cardiovascular diseases. Fitoterapia 2010;81:715–23.

100. Rahman MA, Abdullah N, Aminudin N. Interpretation of mushroom as a common therapeutic agent for Alzheimer's disease and cardiovascular diseases. Crit Rev Biotechnol 2016;36:1131–42.

101. Martin KR. The bioactive agent ergothioneine, a key component of dietary mushrooms, inhibits monocyte binding to endothelial cells characteristic of early cardiovascular disease. J Med Food 2010;13:1340–6.

102. Jo Feeney M, Miller AM, Roupas P. Mushrooms—biologically distinct and nutritionally unique: exploring a "third food kingdom". Nutr Today 2014;49:301–7.

103. Poddar KH, Ames M, Hsin-Jen C, Feeney MJ, Wang Y, Cheskin LJ. Positive effect of mushrooms substituted for meat on body weight, body composition, and health parameters. A 1-year randomized clinical trial. Appetite 2013;71:379–87.

104. Calvo MS, Mehrotra A, Beelman RB, et al. A retrospective study in adults with metabolic syndrome: Diabetic risk factor response to daily consumption of agaricus bisporus (white button mushrooms). Plant Foods Hum Nutr 2016;71:245–51.

105. Stepien M, O'Mahony L, O'Sullivan A, et al. Effect of supplementation with vitamin D2-enhanced mushrooms on vitamin D status in healthy adults. J Nutr Sci 2013;2:e29.

106. Keegan RJH, Lu Z, Bogusz JM, Williams JE, Holick MF. Photobiology of vitamin D in mushrooms and its bioavailability in humans. Dermatoendocrinol 2013;5:165–76.

107. Kohn JB. Are mushrooms a significant source of vitamin D? J Acad Nutr Diet 2016;116:1520.

108. Khatun K, Mahtab H, Khanam PA, Sayeed MA, Khan KA. Oyster mushroom reduced blood glucose and cholesterol in diabetic subjects. Mymensingh Med J 2007;16:94–9.

109. Li J, Zou L, Chen W, et al. Dietary mushroom intake may reduce the risk of breast cancer: evidence from a meta-analysis of observational studies. PLoS One 2014;9:e93437.

110. Kozarski M, Klaus A, Jakovljevic D, et al. Antioxidants of edible mushrooms. Molecules 2015;20:19489–525.

111. de Mattos-Shipley KMJ, Ford KL, Alberti F, Banks AM, Bailey AM, Foster GD. The good, the bad and the tasty: the many roles of mushrooms. Stud Mycol 2016;85:125–57.

112. Dwivedi M, Kumar P, Laddha NC, Kemp EH. Induction of regulatory t cells: a role for probiotics and prebiotics to suppress autoimmunity. Autoimmun Rev 2016;15:379–92.

113. Ooi L-G, Liong M-T. Cholesterol-lowering effects of probiotics and prebiotics: a review of in vivo and in vitro findings. Int J Mol Sci 2010;11:2499–522.

114. Jones ML, Martoni CJ, Prakash S. Cholesterol lowering and inhibition of sterol absorption by lactobacillus reuteri ncimb 30242: a randomized controlled trial. Eur J Clin Nutr 2012;66:1234–41.

115. Choi IH, Noh JS, Han JS, Kim HJ, Han ES, Song YO. Kimchi, a fermented vegetable, improves serum lipid profiles in healthy young adults: randomized clinical trial. J Med Food 2013;16:223–9.

116. Kim EK, An SY, Lee MS, et al. Fermented kimchi reduces body weight and improves metabolic parameters in overweight and obese patients. Nutr Res 2011;31:436–43.

117. Song HJ, Lee H-J. Consumption of kimchi, a salt fermented vegetable, is not associated with hypertension prevalence. J Ethn Foods 2014;1:8–12.

118. Veiga P, Pons N, Agrawal A, et al. Changes of the human gut microbiome induced by a fermented milk product. Sci Rep 2014;4:6328.

119. Anderson JW, Gilliland SE. Effect of fermented milk (yogurt) containing lactobacillus acidophilus l1 on serum cholesterol in hypercholesterolemic humans. J Am Coll Nutr 1999;18:43–50.

120. Mohamadshahi M, Veissi M, Haidari F, Javid AZ, Mohammadi F, Shirbeigi E. Effects of probiotic yogurt consumption on lipid profile in type 2 diabetic patients: a randomized controlled clinical trial. J Res Med Sci 2014;19:531–6.

121. Wan-Loy C, Siew-Moi P. Marine algae as a potential source for anti-obesity agents. Mar Drugs 2016;14:222.

122. Abidov M, Ramazanov Z, Seifulla R, Grachev S. The effects of xanthigen in the weight

management of obese premenopausal women with non-alcoholic fatty liver disease and normal liver fat. Diabetes Obes Metab 2010;12:72–81.

123. Hernández-Corona DM, Martínez-Abundis E, González-Ortiz M. Effect of fucoidan administration on insulin secretion and insulin resistance in overweight or obese adults. J Med Food 2014;17:830–2.

124. Serban MC, Sahebkar A, Dragan S, et al. A systematic review and meta-analysis of the impact of spirulina supplementation on plasma lipid concentrations. Clin Nutr 2016;35:842–51.

125. Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. J Am Coll Cardiol 2011;58:2047–67.

126. Chowdhury R, Warnakula S, Kunutsor S, et al. Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. Ann Intern Med 2014;160:398–406.

127. Del Gobbo LC, Imamura F, Aslibekyan S, et al. O-3 polyunsaturated fatty acid biomarkers and coronary heart disease: pooling project of 19 cohort studies. JAMA Intern Med 2016;176:1155–66.

128. He K, Song Y, Daviglus ML, et al. Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. Circulation 2004;109:2705–11.

129. Zeisel SH, Warrier M. Trimethylamine n-oxide, the microbiome, and heart and kidney disease. Annu Rev Nutr 2017;37:157–81.

130. Tang WHW, Wang Z, Levison BS, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. N Engl J Med 2013;368:1575–84.

131. Siscovick DS, Barringer TA, Fretts AM, et al. Omega-3 polyunsaturated fatty acid (fish oil) supplementation and the prevention of clinical cardiovascular disease: a science advisory from the American Heart Association. Circulation 2018;137:e1–18.

132. Aung T, Halsey J, Kromhout D, et al. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: meta-analysis of 10 trials involving 77,917 individuals. JAMA Cardiol 2018;3:225–34.

133. Baker EJ, Miles EA, Burdge GC, Yaqoob P, Calder PC. Metabolism and functional effects of plant-derived omega-3 fatty acids in humans. Prog Lipid Res 2016;64:30–56.

134. Muir AD, Westcott ND. Flax: the Genus Linum. Boca Raton, FL: Taylor & Francis, 2003.

135. Pan A, Chen M, Chowdhury R, et al. Alpha-linolenic acid and risk of cardiovascular disease: a systematic review and meta-analysis. Am J Clin Nutr 2012;96:1262–73.

136. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation 1999;99:779–85.

137. Kromhout D, Giltay EJ, Geleijnse JM. N-3 fatty acids and cardiovascular events after myocardial infarction. N Engl J Med 2010;363:2015–26.

138. Kris-Etherton P, Eckel RH, Howard BV, et al. AHA science advisory: Lyon Diet Heart Study. Benefits of a Mediterranean-style, National Cholesterol Education Program/American Heart Association step I dietary pattern on cardiovascular disease. Circulation 2001;103:1823–5.

139. Sacks FM, Lichtenstein AH, Wu JHY, et al. Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association. Circulation 2017;136:e1–23.

140. Langan RC, Goodbred AJ. Vitamin B12 deficiency: recognition and management. Am Fam Physician 2017;96:384–9.

141. Albert CM, Cook NR, Gaziano JM, et al. Effect of folic acid and B vitamins on risk of cardiovascular events and total mortality among women at high risk for cardiovascular disease: a randomized trial. JAMA 2008;299:2027–36.

142. Lonn E, Yusuf S, Arnold MJ, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. N Engl J Med 2006;354:1567–77.

143. Ebbing M, Bleie O, Ueland PM, et al. Mortality and cardiovascular events in patients treated with homocysteine-lowering B vitamins after coronary angiography: a randomized controlled trial. JAMA 2008;300:795–804.

144. Bonaa KH, Njolstad I, Ueland PM, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. N Engl J Med 2006;354:1578–88.

145. Toole JF, Malinow MR, Chambless LE, et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention For Stroke Prevention (VISP) randomized controlled trial. JAMA 2004;291:565–75.

146. Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and its Panel on Folate, Other B Vitamins, and Choline. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. Washington, DC: National Academies Press, 1998.

147. Brasky TM, White E, Chen CL. Long-term, supplemental, one-carbon metabolism-related vitamin B use in relation to lung cancer risk in the vitamins and lifestyle (vital) cohort. J Clin Oncol 2017;35:3440–8.

148. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College Of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2889–934.

149. American Academy of Pediatrics Committee on School Health. Soft drinks in schools. Pediatrics 2004;113:152–4.

150. American Diabetes Association. 4. Lifestyle management. Diabetes Care 2017;40:S33–43.

151. U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion. Healthy People 2020. Objective nws-17.2 [serial online]. 2014. Available at: https://www.healthypeople.gov/2020/topics-objectives/objective/nws-172. Accessed December 1, 2017.

152. Osonoi Y, Mita T, Osonoi T, et al. Relationship between dietary patterns and risk factors for cardiovascular disease in patients with type 2 diabetes mellitus: a cross-sectional study. Nutr J 2016;15:15.

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