Deciphering the Riddles in Nutrition and Cardiovascular Disease

Amelia Carro[1] and Josefa María Panisello[2]

1. Instituto Corvilud, Asturias, Spain; 2. Fundación para el Fomento de la Salud (FUFOSA), Health Foundation, Madrid, Spain

Abstract

Cardiovascular disease is the leading global cause of death in Western countries, and its development is largely associated with unhealthy dietary patterns. A large body of scientific evidence has reported that nutrition might be the most preventive factor of cardiovascular disease death and could even reverse heart disease. Processes of chronic inflammation and oxidative distress share triggers that are modifiable by nutrition. This review aimed to identify potential targets (food patterns, single foods or individual nutrients) for cardiovascular disease prevention, and analyse the mechanisms implicated in their cardioprotective effects.

Keywords

Nutrition, cardiovascular disease, prevention, inflammation, diet, lifestyle

Disclosure: The authors have no conflicts of interest to declare.
Received: 22 June 2019 **Accepted:** 23 October 2019 **Citation:** *European Cardiology Review* 2019;14(3):141–50. **DOI:** https://doi.org/10.15420/ecr.2019.07
Correspondence: Amelia Carro, Instituto Corvilud, Travesía El Calvario N1, Bajo, 33430 Candás (Asturias), Spain. E: corvilud@gmail.com

Dietary Patterns

Several studies correlate healthy dietary patterns with lower plasma concentrations of pro-inflammatory markers.[1] These healthy dietary patterns support greater benefits than the potential effects of a single nutrient supplementation. The current body of evidence shows that healthy dietary patterns share similarities, shown in *Figure 1*.[2] These features fit with the report of the most recent workshop convened by the World Heart Federation, and three models are recommended by the Unites States Dietary Guidelines Advisory Committee: Mediterranean diet (MD), American healthy diet and vegetarian diet (VD).[3,4] The latter is a type of plant-based diet that restricts different types of animal foods (meat, poultry or fish), and has been associated with a lower risk of cardiovascular (CV) risk factors (obesity, hypertension, type 2 diabetes) and coronary heart disease (CHD).[5,6] However, VD, as a concept, focuses more on the exclusion of animal sources of food than the quality of plant foods; this raises some heterogeneity and deserves further research to assure the features of a heart healthy diet.[7] Thus, recent studies tried to cluster different subtypes of VD according to the frequency of intake of three food groups: healthy plant foods (whole grains, fruits, vegetables, nuts, legumes, coffee, tea), less healthy plant foods (fruit juices, refined grain, potatoes, sugar sweetened and artificially sweetened beverages, sweets and desserts) and animal foods (animal fat, dairy, eggs, fish or seafood, meat and miscellaneous animal foods) given their associations with chronic conditions.[8] Diets with higher intake of healthy plant foods and lower in animal foods were associated with a lower risk of incident CV disease (CVD), CVD mortality and all-cause mortality.[5–7] No true association was found with less healthy plant-based diets and CVD or all-cause mortality.[7] Therefore, health implications of diets high in refined carbohydrates and sugar, and low in fruits, vegetables and animal foods must be acknowledged when assessing individuals with a VD.

Other therapeutic diets, such as the Dietary Approaches to Stop Hypertension (DASH) and the Portfolio diets recommended in the Canadian Cardiovascular Society guidelines, also emphasise the principles of a healthy diet.[9,10]

The MD and the DASH diet are probably the best-studied dietary patterns in relation to CVD prevention. Both may improve downregulation of low-grade inflammation and better control of bodyweight, further controlling other risk factors, and ultimately are correlated with lower numbers of clinical events.[5,11]

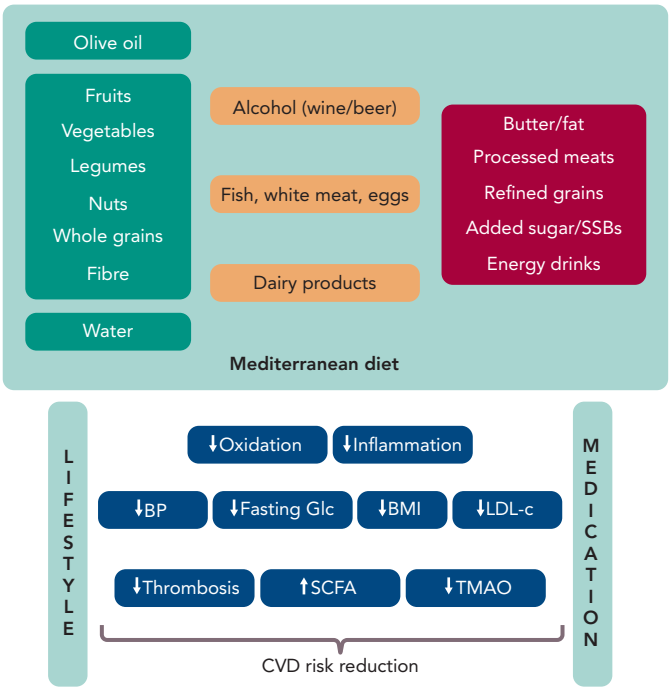
Mediterranean Diet

The MD is defined as the traditional dietary pattern found in the early 1960s in Greece, Southern Italy, Spain and other olive-growing countries of the Mediterranean basin.[12] It is a frugal diet that fulfils the definition of "healthy diet" (*Table 1*), with some distinctive attributes (*Figure 1*): olive oil the principal source of fat, moderate intake of wine (mainly wine during meals), fish, seafood, poultry, eggs and dairy products (cheese and yoghurt, preferred in the form of low fat), and low consumption of red meat.

All kinds of olive oil (virgin, extra virgin olive oil and refined olive oil) contain oleic acid as the main fat, but only unrefined olive oil (virgin and extra virgin olive oil) contain tocopherols, phytosterols, monounsaturated fatty acids (MUFA) and several bioactive polyphenols (hydroxytyrosol, tyrosol, oleocanthal, resveratrol), with postulated anti-atherogenic and anti-inflammatory properties.[13–15]

The evidence supporting CVD benefits is large, strong and consistent, in terms of clinically meaningful rate reductions of CHD, ischaemic stroke and total CVD. Until now, these benefits had been attributed to improvements in blood pressure, lipid profile, glucose metabolism,

Figure 1: Healthy Dietary Pattern



The Mediterranean diet (MD) fulfils basic principles of a "Healthy Dietary Pattern", with some distinctive features related to the nutrients included (i.e. olive oil, wine), but also extended to other lifestyle choices that are broadly referred as "Mediterranean Lifestyle Pattern". The graphic represents the MD with food items grouped according to recommended frequency intake. The green boxes show food items that should sustain the diet and provide the highest energy intake (every main meal). Water is included in this section, with a daily recommended intake of 1.5–2.0 l. As well as water, non-sugar-rich herbal infusions and broths (with low-fat and -salt content) may complete the requirements. Orange boxes include foods to be eaten in moderate amounts, such as: protein animal sources: fish (two or more weekly servings), white meat (two weekly servings) and eggs (two to four weekly servings); dairy products: cheese and yoghurt, preferred in the form of low-fat; and alcohol: moderate consumption of wine and other fermented beverages during meals (one glass per day for women and two glasses per day for men, as a generic reference). The red box represents unhealthy fat-rich foods (butter/fat, processed meat) and the sugary (added sugar, refined grains, candies, pastries and sugar-sweetened beverages; SSBs, such as sweetened fruit juices and soft drinks). These should be consumed in small amounts and left for special occasions. Medication is only considered if required for primary or secondary prevention purposes. Lifestyle: along with recommendations regarding the proportion and frequency of food consumption, the MD incorporates lifestyle and cultural elements aimed to acquire all the benefits from the MD, and to preserve the cultural heritage. Blue boxes exemplify mechanisms that confer the MD its ability to reduce cardiovascular risk. These elements embrace moderation, socialisation, culinary activities, physical activity, adequate rest, seasonality, and traditional, local, eco-friendly and biodiverse products. BMI = body mass index; BP = blood pressure; CVD = cardiovascular disease; Glc = glucose; LDL-c = low-density lipoprotein cholesterol; SCFA = short-chain fatty acids; TMAO = trimethylamine N-oxide.

arrhythmic risk or gut microbiome.[5] However, vascular anti-inflammatory effects have recently been hypothesised as a possible mechanism that links MD and low CVD prevalence (*Table 2*).[16–19]

This hypothesis was confirmed by the Prevención con Dieta Mediterránea (PREDIMED) findings on MD mechanisms: modulation of the expression of adhesion molecules in leukocytes; improvements in the circulating levels of soluble adhesion molecules, cytokines, chemokines and macrophage inflammatory proteins; and plaque stabilisation after 3 months, and 1, 3 and 5 years of intervention.[20] Epigenetic studies of the MD reinforce these results, with proven influence on the methylation status of peripheral white blood cell genes, interactions among MD and the expression of other molecules (cyclooxygenase-2, interleukin-6, apolipoprotein, cholesteryl ester transfer protein plasma), transcription factors and gene polymorphisms (*Table 2*).[21–23]

The authors of the PREDIMED study in 2013 recently retracted the original publication as a result of an error in the randomisation procedures affecting a portion of participants included.[24] The authors re-ran the analyses omitting 1,588 participants from 7,447, and published a corrected version that showed no significant changes in the results of the trial.[24,25] In both the original and republished study, the incidence of CVD in the MD groups was lowered by approximately 30% when compared with the control diet.[20,24,25] Therefore, the overall conclusion remains unchanged, and PREDIMED remains the largest dietary intervention trial to assess the effects of the MD on CVD prevention.

Dietary Approaches to Stop Hypertension Diet

The DASH model follows the "healthy diet" pattern (*Figure 1*), with critical emphasis on a low intake of sodium and refined grains.[26,27] Focusing on inflammatory markers and oxidative stress, several studies have shown the protective effect of the DASH diet on CVD (*Table 1*) mediated by significant reductions of high-sensitivity C-reactive protein concentrations. Cross-sectional analysis evaluating potential associations between dietary quality (DASH dietary quality score), adiposity, and biomarkers of glucose metabolism, lipid profile and inflammation reveal that a higher adherence to the DASH dietary pattern significantly improves adiposity measures, and lowers concentrations of pro-inflammatory, pro-thrombotic and pro-atherogenic markers.[28] Improvements in lipoprotein profile and glucose homeostasis are also achieved.

It has also been shown that a DASH diet increases plasma renin activity and serum aldosterone levels in response to blood pressure reductions.[29] The effect of sodium intake on blood pressure differs by genotype at the angiotensinogen, beta2-adrenergic receptor and kallikrein loci.[29,30] These findings have implications for understanding the mechanisms through which diet affects blood pressure, the heterogeneity of these effects, and the extent to which dietary and pharmacological interventions can modulate genetic predisposition.[29,30]

Individual Food Items

There are some specific dietary guidelines that are exclusively food based.[31–33] Comprehensive dietary modelling is undertaken to ensure nutrient reference values, including targets for sodium, and saturated and trans fat. This section develops some of the features of each of the individual food items and its possible relationship to CVD risk reduction.

Fruits and Vegetables

Daily consumption of multiple servings of both fruits and vegetables is strongly and widely recommended, since its total intake has been inversely associated with CVD risk, and seems to be the healthiest and most beneficial source of anti-oxidants for CVD risk reduction.[34] The benefits for subgroups have been less studied, and may vary considerably according to their phytochemical and micronutrient composition (*Table 3*).[35–37] Some of the anti-inflammatory mechanisms proposed for fruits and vegetables are summarised in *Table 2*. Anthocyanins (a subclass of flavonoids) found in blueberries, strawberries, raspberries, red cabbage, red radishes and eggplant have potent anti-inflammatory properties: free radical scavenging, endothelial nitric oxide (NO) regulation, endothelial function modulation and influence on glucose metabolism.[35–39]

Cruciferous vegetables have been associated with vascular benefits due to their potential to release nitrite via the enterosalivary nitrate–nitrite–NO pathway. Dietary nitrates are secreted by the salivary glands and reduced to nitrite via the action of commensal oral bacteria. Salivary nitrite levels can increase >1,000-fold greater

Table 1: "Healthy Dietary Pattern"

Principles	Main features
Plant-based and high consumption of vegetables, fruits, legumes, nuts, whole grain cereals and fish	Warrant high intake of fibre, anti-oxidants, vitamins, minerals, polyphenols, monounsaturated and polyunsaturated fatty acids
Carbohydrates of low glycaemic load	Keep blood sugar levels consistent, avoiding oscillations in glycaemic levels (and subsequent insulin releases)
Reduced consumption of salt, refined sugar, and saturated and trans fats	Mainly in the form of processed foods, red meats, refined cereals, starches, and sugar-added drinks and foods
Examples of "Healthy Dietary Patterns" Vegetarian diet* American healthy diet Mediterranean diet Dietary Approaches to Stop Hypertension (DASH) Portfolio Diet	

*A healthy dietary pattern fulfils basic principles as detailed. Examples of a "Healthy Dietary Pattern" are given. *Vegetarian Diet focuses on restriction of different types of animal foods and is mainly plant-based; it is important to emphasise, however, that some plant-based food items might include carbohydrates of high glycaemic load (fruit juices, refined grain, potatoes, sugar sweetened and artificially sweetened beverages, sweets and desserts) or even saturated fat. Therefore, it is advisable that plant-based food items of a Vegetarian Diet include a higher proportion of whole grains, fruits, vegetables, nuts, legumes, coffee and tea instead.*

Table 2: Proposed Mechanisms for the Anti-inflammatory Effects of Dietary Patterns and Individual Food Items

Dietary Pattern/Food Item	Pro-inflammatory Markers and Genes	Oxidative Stress Markers	Leukocyte Expression
MD[16–23]	sVCAM-1, sICAM-1, RANTES, MIP-1beta, TNF-alpha, TNFR-60, IL-1beta, IL-6, IL-7,IL-10, IL-12p70, IL13, IL-18, MMP-9,VEGF, CRP, TCF7L2, ApoA2, CETP, COX-2, MCP-1, LRP1	Lymphocytes: CD11a, CD49d, CD40 Monocytes: CD11a, CD11b, CD49d, CD40	MDA, oxLDL
DASH diet[28]	sICAM-1, IL-6, CRP, PAI-1		
Fruits,[35,38,39] vegetables,[35,38,39] legumes[48,49]	TNF-alpha, TNFR-60, IL-1beta, IL4, IL-6, gamma delta T cell, fibrinogen, sE-selectin		F2-isoprostanes,2,3 dinor-5,6-dihydro-15-F2t IsoP
Nuts[20,55–57]	CRP, IL-6, TNF-alpha, TNF-beta, TNF-R2, sICAM-1, fibrinogen, PF4, resistin		
Fermented beverages[75–79]	IL-1-alpha, IL-5, IL-6, IL-6r, IL-8, IL-10,IL-15, IL-18, CRP, MDC, sVCAM-1, sICAM-1, E selectin, fibrinogen, CD40 ligand, MCP-1, factor VII, PAI-1, IFN-gamma, RANTES, TNF-beta	Lymphocytes: LFA-1 monocytes: LFA-1, MAC-1, VLA-4, CCR2, CD36, CD15	SOD, MDA
Coffee[92,94] and tea[95–98] (polyphenols)	NF-kappa beta, sICAM-1, sE- and sP-selectin, IL-1beta, IL-18, CRP, SAA, CXCL5, CXCL7, CXCL8, CXCL12, CCL2, TNF-alpha, beta-thromboglobulin, RANTES, ApoB	Monocytes: VLA-4, CD40, CD36	oxLDL, 8-iso-prostaglandin F2-alpha, ROS, SOD, Nrf2
Omega-3 PUFA[125–127]	sVCAM-1, sICAM-1, sP-selectin, TNF-alpha, TNFR, IL-1beta, IL-6, MMP-7, MMP-9, CRP, PAI-1, SAA		T-lymphocytes
Fibre[19]	sVCAM-1, sICAM-1, TNF-alpha, TNFR2, IL-6, IL-18, CRP, PAI-1		
Anti-oxidants/vitamins[153,154]	IL-6, CRP, TNF-alpha, leptin, tHcy		
Polyphenol[92,94–98]	NF-kappa beta, sICAM-1, sE- and sP-selectin, IL-1beta, IL-18, CRP, SAA, CXCL5, CXCL7, CXCL8, CXCL12, CCL2, TNF-alpha, beta-thromboglobulin, RANTES, ApoB	Monocytes: VLA-4, CD40, CD36	oxLDL, 8-iso-prostaglandin F2alpha, ROS, SOD, Nrf2

ApoA2 = apolipoprotein A2; ApoB = apolipoprotein B; CCL2 = chemokine (C-C motif) ligand 2; CETP = cholesteryl ester transfer protein plasma; COX-2 = cyclooxygenase-2; CRP = C-reactive protein; CXCL = chemokine (C-X-C motif) ligand; DASH = Dietary Approaches to Stop Hypertension; LFA = lymphocyte function-associated antigen 1; IL = Interleukin; LRP1 = low-density lipoprotein receptor-related protein; MDC = macrophage-derived chemokine; MCP-1 = monocyte chemoattractant protein; MD = Mediterranean diet; MDA = malondialdehyde; oxLDL = oxidised LDL; MIP-1beta = macrophage inflammatory protein 1 beta; MMP-9 = metallopeptidase-9; Nrf2 = nuclear factor (erythroid-derived 2)-like 2; omega-3 PUFA = omega-3 polyunsaturated fatty acid; PAI-1 = plasminogen activator inhibitor 1; PF4 = platelet factor 4; RANTES = regulated on activation; SAA = serum amyloid A; sICAM-1 = soluble intercellular adhesion molecule 1; SOD = superoxide dismutase; sVCAM-1 = soluble vascular cell adhesion molecule; TCF7L2 = transcription factor 7-like 2; tHcy = total homocysteine; TNF = tumour necrosis factor; TNFR = tumour necrosis factor receptor; VEGF = vascular endothelial growth factor; VLA-4 = very late antigen-4.

than in the circulation.[40] Among leafy green vegetables, nitrate concentrations are most appreciable in spinach, arugula, mesclun, lettuce and Swiss chard.[41,42] The European Food Safety Authority has set the Acceptable Daily Intake for nitrate at 3.7 mg/kg (approximately 260 mg for a 70-kg adult).[41] A recently published systematic review and meta-analysis reported that intakes of dietary nitrate were significantly associated with a reduction in resting blood pressure, improved endothelial function, reduced arterial stiffness and reduced platelet aggregation.[43]

The amount of vegetable intake recommended in dietary guidelines varies globally, but is usually around five or six servings/day (375–450 g/day). For vegetable types, leafy green vegetables, cruciferous vegetables and tomatoes were inversely associated with CVD risk

Table 3: Classification of Vegetable Types with Nutrients and Phytochemicals Associated with Each Vegetable Type[35–37,39]

Vegetable classification					
Cruciferous	**Leafy green**	**Yellow-orange-red**	**Purple vegetables**	**Allium**	**Legumes**
• Cabbage • Cauliflower • Broccoli • Brussels sprouts • Red cabbage • Red radishes • Collard greens • Kale	• Lettuce • Spinach • Arugula • Mesclun • Swiss chard • Celery	• Tomato • Carrot • Pumpkin • Sweet potato • Yellow capsicum • Red capsicum	• Red cabbage • Red radishes • Eggplant	• Onion • Garlic • Leek	• Lentils • Peas • Chickpeas • Kidney beans • Soybeans • Green beans
• Organosulfur compounds (isothiocyanates, glucosinolates) • Vitamin E (tocopherols) • Vitamin C • Carotenoids (lutein, zeaxanthin, beta-carotene) • Flavanols (quercetin, isorharmnetin, kaempferol) • Flavanones (naringenin) • Selenium • Calcium	• Nitrate • Vitamin K (phylloquinone) • Vitamin E (alpha-tocopherol) • Vitamin C • Carotenoids (lutein, beta-carotene) • Flavanols (quercetin, isorharmnetin, kaempferol) • Folate • Iron • Zinc • Calcium	• Carotenoids (lycopene, alpha-carotene, beta-carotene, beta-cryptoxanthin)	• Flavanols (quercetin) • Folate (vitamin B9) • Carotenoids (vulgaxanthin) • Manganese • Potassium • Iron • Vitamin C	• Organosulfur compounds (allin, methiin, propiin, isoalliin, allicin) • Flavanols (quercetin, isorharmnetin, kaempferol) • Selenium	• Isoflavones • Saponins • Flavanols (quercetin) • Folate • Iron • Zinc • Calcium • Dietary fibre • Vitamin E • Vitamin B6 • Selenium • Lignans

in non-linear dose–response analyses. The greatest CVD benefits were observed at intakes of ≥200 g/day for cruciferous vegetable, ≥120 g/day for leafy green vegetables and ≥200 g/day for tomatoes.[44]

Daily recommendations on fruit intake range from 100 to 300 g (200 g/day). However, it must be taken in to account that the process of juicing concentrates calories, risking excess energy intake and loss of fibre. There are few studies evaluating the clinical benefits of vegetable juicing versus raw or cooked forms. Until comparative data become available, whole food consumption is preferred, with juicing primarily reserved for situations when daily intake of vegetables and fruits is inadequate. Guidance should be provided to maintain optimal overall caloric intake and to avoid the addition of sugars (e.g. honey) to minimise caloric overconsumption. In addition, there is no evidence of CV benefit with the addition of high-dose antioxidant dietary supplements if these intakes are warranted.

Legumes

Legumes are seeds with complex matrices rich in nutrients and chemicals, carrying a high caloric density that makes them an affordable and sustainable source of protein and fibre. Various effects on CV risk factors provide evidence for CV prevention. These foods have a low glycaemic index, and reduce glycaemia and postprandial insulinaemia, favouring diabetes prevention, especially in the context of a MD.[45] Legumes have a hypocholesterolaemic effect (lowering both LDL and triglycerides), but their presumed effect in reducing blood pressure has not been consistently proven.[46,47]

Legumes are a good source of protein, starch, isoflavones, vitamin B_6, folate and iron. The anti-inflammatory effects of this food group are frequently included with vegetables, which makes it difficult to separate its own mechanisms on pro-inflammatory/oxidative stress markers and leukocyte expression (*Table 2*). However, significant reductions of high-sensitivity C-reactive protein, interleukin-6 and tumour necrosis factor-alpha with a legume-based diet have been demonstrated, independent of caloric intake or weight change.[48,49]

Based on these beneficial properties, legumes should be part of any cardiometabolic healthy diet, with a daily intake of around 50–100 g (140–180 kcal/day).[50]

Nuts and Seeds

Nuts and seeds (almonds, hazelnuts, walnuts, pistachios, cashews, macadamias, pinions, peanuts etc.) are peculiar vegetables with a high fat content (usually exceeding 50% of energy) mainly containing unsaturated fatty acids (UFA), such as oleic MUFA (almonds, hazelnuts) or n-6 polyunsaturated linoleic and n-3 as alpha-linolenic acid (in nuts). Although peanuts are actually vegetables, their composition and UFA content assimilates them to nuts. Nuts and seeds contain other bioactive compounds: L-arginine, soluble fibre, vitamin E, phytosterols, polyphenols, anti-oxidants, potassium, calcium and magnesium. Numerous large prospective cohort studies have demonstrated reductions in CVD morbidity and mortality with the consumption of nuts and seeds.[51,52] Mechanisms proposed for favourable CVD outcomes are likely mediated by dose-dependent hypocholesterolaemic effects and improvements of glycaemic profile.[53,54] The PREDIMED study provided first-class evidence that regular nut consumption halves the incidence of diabetes, and reduces the incidence of CVD by 30%.[20] Additional benefits are derived from the role on oxidative stress, inflammation and vascular reactivity through modulation of inflammatory and oxidants mediators (*Table 2*).[20,55–57]

Although the benefits are accepted, there is no standard recommendation for nuts inclusion on dietary patterns. Following a MD, daily supplementation with a serving of mixed nuts (i.e. 15 g walnuts, 7.5 g almonds and 7.5 g hazelnuts) would be enough to get the desired CV effects. Caution must be taken at >75 g, because of the risk of excess caloric intake.

Grains and Tubers

Grains are the largest source of energy in almost all diets worldwide. The bran and germ layers present in whole grains are rich in fibre, lignans, micronutrients, fatty acids and other phytonutrients.[58]

Depletion of these nutrients during the milling process partially explains why whole grain consumption is generally related to higher satiety and a lower glycaemic response compared with refined grains.[59] High intake of whole grains has been associated with reduced risk of CHD disease, type 2 diabetes and overall mortality.[60] Refining grains, in contrast, causes major loss of nutrients and fibre, which has important health implications, including adverse metabolic effects, weight gain, increased risk of CVD and overall mortality.[60–62]

There are few data linking gluten and CHD. People with coeliac disease or gluten sensitivity might have inflammatory mechanisms more related to zonulin release into the gut than to gliadin, and these altered pathways could predispose to type 2 diabetes and even CHD.[63,64] However, there is no current evidence supporting a link between gluten consumption and CHD, and should not be restricted in people without coeliac disease or gluten sensitivity.[65]

Roots and tubers (the so-called starchy vegetables) are a good source of starch, which may help maintain a healthy gut.[66] Gut dysbiosis is associated with intestinal inflammation and has been linked to the development of CVD.[67] However, there is no evidence that restoring gut dysbiosis with tubers improves CV outcomes. Intake of potatoes, for instance, provides a large amount of rapidly absorbed carbohydrate (glycaemic load), and its daily consumption has been associated with increased risk of type 2 diabetes, hypertension, weight gain and even CHD (especially consumed in the form of "French fries").[68–71]

Evidence does not support strong recommendations on the specific proportion of energy intake from carbohydrates, but keeping this to <60% of energy appears desirable, and consumption of whole grains is emphasised. This would be about 232 g/day of whole grains, and 50 g/day of tubers and starchy vegetables (with a limit of 100 g/day of tubers and starchy vegetables).

Fish and Seafood

Fish intake has been associated with reduced risk of CVD, mainly attributed to the particular properties of omega-3 fatty acids (O3FA), which are abundant in fish composition.[72,73] O3FA are precursors of eicosanoids, a large component of the central nervous system, a structural element of every cell of the body and a regulator of cardiac rhythm. They are thought to reduce arrhythmias, thrombosis, inflammation and blood pressure, and favourably modify the lipid profile.[74] An average weekly intake of 2 g of O3FA in fish might reduce CVD risk by more than one-third.[72] Although O3FA from plant sources (specifically alpha-linolenic acid) have been associated with reduced risk of CVD disease and had been proposed as an alternative source to substitute fish, the quantity required is not clear.

Beverages

Alcohol

Alcoholic beverages contain ethanol (ethyl alcohol) and are classified by the elaboration process as: fermented (by alcohol fermentation; <15% alcohol content): red or white wine, beer or cider; and distillate (by alcohol distillation; 20–60% alcohol content): spirits, such as cognac, whiskey, gin, vodka and rum, and liqueurs flavoured with fruits, herbs or spices.

Fermented beverages are believed to provide a greater CV protection than distillate beverages, especially red wine. Its higher polyphenol content favourably modifies oxidation and inflammation parameters related to arteriosclerosis by different pathways: higher NO availability (improving endothelial function), increases in HDL cholesterol levels and anti-aggregation/profibrinolytic/anti-inflammation properties (*Table 2*).[75–79] Beer is another type of fermented beverage with moderate polyphenol content that has cardioprotective effects comparable to wine.[80,81] Both alcoholic and non-alcoholic beer improve inflammatory biomarkers profile, homocysteine and folic acid levels (*Table 2*).

Alcohol intake and CVD risk show a "U-shaped" relationship, with both abstainers and heavy drinkers carrying a higher risk than moderate drinkers.[82,83] Adverse effects of (often heavy) alcohol consumption include a higher risk of atrial fibrillation, non-ischaemic dilated cardiomyopathy and long-term weight gain.[84–86] In addition, alcohol is causally linked to upper aerodigestive tract cancers (oral cavity, pharynx, larynx, oesophagus), and those of the colon, liver and female breast. Associations exist for many other types of cancer, but the precise role of alcohol requires further research for it to be fully disentangled from ecological and lifestyle factors.[87]

By definition, a standard drink contains 14 g of ethanol (17 g of pure alcohol). This equates to 350 ml of beer (5% ethanol), 150 ml of table wine (12% ethanol), or 45 ml of hard liquor or distilled spirits (40% ethanol).[88] Although the exact nadir of risk depends on sex, age, ethnicity and baseline disease, it seems that consuming one or two daily drinks derives the lowest risk (2 for men; 1–1.5 for women).[89,90] This would be the daily intake recommendation, mainly in the form of fermented beverages.

Coffee

Coffee is one of the most widely consumed beverages in the world, representing the liquid extract of coffee beans. It contains many active compounds responsible for its bitter taste, and conferring anti0oxidant and anti-inflammatory actions.

Several mechanisms contribute to the sustained CV health effects of coffee. However, the response of each individual component varies, and might interfere with others in a complex relationship. Various genetic polymorphisms affecting caffeine metabolism (i.e. cytochrome P450 1A2 variants), receptor-mediated effects (i.e. adenosine receptors) or non-receptor mediated effects (e.g. low catechol-O-methyltransferase activity) may influence an individual's response to caffeine. An increased risk of CHD or MI has been reported only among individuals with a genotype associated with slow caffeine metabolism (CYP1A2*1F instead of CYP1A2*1A), or low catechol-O-methyltransferase activity genotype (low catecholamine metabolism).[91] The infusion of coffee maintains a high concentration of potassium, magnesium, vitamin E, niacin, polyphenols (mainly chlorogenic acid), micronutrients, lignans and phytochemicals. Chlorogenic and caffeic acids improve the anti-oxidative status of the body by slowing down the process of inflammation, which protects from the hazardous effect of free radicals and against endothelial damage. There is no scientific association with blood pressure elevation and, in turn, it actually lowers diabetes risk in a dose-dependent manner.[92]

Unlike filtered coffee, some components present in unfiltered coffee (cafestol and kahweol) raise serum lipids.[93] Whether these components are involved in the deposition of LDL cholesterol is still debated. Usually, consumption of three or four daily cups of coffee leads to a small increase in HDL cholesterol. The effect on LDL is more complex, since the resistance of LDL to oxidative modification increments significantly after drinking coffee, but the LDL concentration does not (or at least,

not significantly).[94] Therefore, regular consumption of coffee (3–5 cups/day, which corresponds to a coffee polyphenol intake of 101–337 mg/day) can be recommended based on its ability to lower CVD risk.[93]

Tea

Tea contains a significant amount of flavonoids and polyphenols, considered the most abundant dietary anti-oxidants present, and responsible for a wide range of health effects in the prevention of CVD.[95] Polyphenols delay progression of atherosclerosis through several mechanisms: regulation of signalling–transcription pathways (including downregulation of pro-inflammatory cytokines) and anti-oxidant systems (enhanced NO production), prevention of leukocyte migration/plaque infiltration, and reduction of adhesion molecules, among others (Table 2).[96] Both short- and long-term tea consumption have shown to improve endothelium-dependent flow-mediated dilation, reverse endothelial vasomotor dysfunction in CHD patients and are associated with favourable changes on lipid profile.[97–99] These effects translate into a lower risk of developing CHD and major cardiac events, even all-cause mortality.[100,101]

The evidence for a favourable CVD profile is based on regular tea consumption (3–5 cups/day) without added sugars, sweeteners or milks and creams (both animal and plant-based), and that should be the proper way to tackle any recommendation on this beverage.

Dairy Products

A growing body of nutritional science highlights the complex mechanisms and pleiotropic pathways of cardiometabolic effects of dairy products (i.e. milk, yogurt and cheese) that may be mediated by specific proteins (whey and casein proteins), amino acids (leucine, isoleucine and valine), medium-chain and odd-chain saturated fats, UFA, branched-chain fats, natural trans fats, probiotics, vitamin K_1/K_2, and calcium, or by processing methods (fermentation/homogenisation). These intricate processes translate into divergent conclusions regarding CVD: although systematic reviews and meta-analyses show either neutral or a favourable association between dairy intake and CVD-related outcomes, other studies associate dairy fat with a unfavourable risk profile that can be reversed by replacing fat from dairy products with polyunsaturated fatty acid (PUFA) or vegetable fat.[102–108] In cohorts utilising objective biomarkers, higher blood levels of dairy fatty acids are consistently associated with a lower incidence of diabetes and neutral/favourable CVD risk profile. Reduced fat dairy products remain a convenient source of some essential vitamins and minerals, and high-quality protein. Obtaining these compounds should not be routinely based on supplements, since fermentation processes and probiotics are a relevant component in the biological pathways and clinical effects of these foods.[109] In fact, the VITamin D and OmegA-3 TriaL (VITAL) trial has recently shown that diet supplementation with non-dietary vitamin D did not result in a lower incidence of invasive cancer or CV events than a placebo, which highlights the relevance of metabolic pathways in the effects observed with dairy products.[110]

Although further investigation is required, based on available evidence, the empiric recommendation on reduced-fat in place of regular- and high-fat dairy is adequate, and is included in MD and DASH dietary patterns (average 250 mg/daily, yielding 150 kcal of caloric intake).

Eggs

The high cholesterol concentrations found in eggs (200–230 mg/egg; 350–385 mg/100 g) led to the widespread recommendation of limiting egg intake in fear of subsequent increases in total and LDL cholesterol.[111] However, eggs are rich in amino acids and several micronutrients that might interplay for the net effect on cholesterol levels and its clinical impact. Clinical studies reveal that cholesterol increases are discrete, with interindividual variability, and are coupled with slight elevations in HDL cholesterol that favour the development of large and low-atherogenic LDL particles.[112] In fact, even daily egg consumption is not clearly associated with incident CVD in general populations and might reduce stroke risk.[113–115]

However, US dietary guidelines raised controversy because of apparently contradictory statements, saying that 'cholesterol is not a nutrient of concern for overconsumption', but that 'individuals should eat as little dietary cholesterol as possible'.[7]

A recent study involving pooled individual data from six prospective US cohorts found that egg consumption was associated with an increased incidence of CVD and death.[116] However, the association was possibly biased and inaccurately proven. A recent meta-analysis and systematic review found no association between egg intake and CHD or total mortality, but, in contrast, lower risk of mortality from stroke.[117] Egg consumption has been also associated with hypertension, type 2 diabetes and markers of glucose homeostasis.[117,118]

The debate on the role of eggs for CVD prevention would remain largely moot until further data (including the genetic basis of cholesterol intake on CVD risk) are clearly defined. In the meantime, the importance of following evidence-based dietary recommendations, such as limiting intake of cholesterol-rich foods, should not be dismissed. Cardiometabolic effects can be derived from the consumption of up to two or three eggs per week, even in people with diabetes.

Oils, Butter and Fats

Primary types of dietary fat include saturated fat (SFA), UFA (including MUFA and PUFA) and trans fatty acids. Only dietary trans fatty acids intake demonstrates a consistent and strong association with adverse CVD outcomes. SFA have received widespread controversy, as the increases of total and LDL cholesterol levels undoubtedly translate into either neutral or harmful CVD outcomes in different clinical trials and metanalyses.[119–122] It must be acknowledged that SFA are diverse compounds with variable effects on CHD risk depending on many factors apart from the dietary SFA intake, such as the SFA status, biomarkers and the carbon length of the SFA.[123] Genetic factors contribute to the risk of CHD related to the dietary intake of C-18 fatty acid. It is advisable to replace long-chain fatty acids (LCFA) with PUFA, MUFA, short-chain fatty acids, whole grains and plant proteins.[123,124]

Mechanisms for the benefit with long-chain O3FA derived from fish oil might include improvements in the lipid and lipoprotein profile, oxidation, thrombosis, platelet aggregation, endothelial function, blood viscosity, membrane fluidity and plaque stability, modulation of concentration/expression of pro-inflammatory markers (adhesion molecules, cytokines etc.), and immune cells (*Table 2*).[125–127]

Noteworthy, benefits of the supplementation with these fatty acids remain to be confirmed.[128,129] Although icosapent ethyl administration in patients with elevated triglyceride demonstrated significant reduction in CVD outcomes, the addition of O3FA did not result in a lower incidence of major CV events or cancer than placebo

in a primary prevention trial.[110,130] In addition, it is not possible to recommend the safest amount of dietary consumption of SFA, especially LCFA, at this time, but studies suggest it should be well below 9% of total caloric intake.[123]

Coconut oil is 92% SFA, predominantly lauric acid C12:0 and myristic acid (C14:0). Since only 4% of coconut oil has short-chain fatty acids (C-10 or less fatty acids), it acts mostly as a LCFA, with direct portal vein absorption and is highly soluble in water.[131] However, there is a lack of prospective studies on CV, and the current literature raises mixed effects on serum lipids and the content of LCFA. In addition, replacement of coconut oil with PUFA and MUFA seems to reduce CHD risk.[64] Therefore, this yet scarce evidence does not currently support coconut oil use for the prevention or treatment of CVD, and general recommendations on SFA intake (limited to <9% of total energy intake) should prevail.[7,123]

Meat

The intake of meat has increased in industrialised countries, and actually constitutes the basic component of meals. Although general meat consumption has been reported to be associated with all-cause and specific-cause mortality, the type of meat considered (red, white, processed) might redefine these associations. Red meat and processed meat may increase the risk of all-cause and CV mortality by means of several components that boost CV alterations.[132,133] Various red meat-associated agents have been invoked, including SFA, high salt intake, trimethylamine N-oxide generation by microbiota and environmental pollutants contaminating red meat, none of which are specific to red meat. For instance, it has been demonstrated that residues of organochlorine pesticides are present in red meat at concentrations close to the WHO maximum recommendations. Epidemiological evidence and systematic reviews support an association of pesticide exposure with CVD and CV mortality (MI, cerebrovascular disease). These associations might be mediated via oxidative stress and inflammation pathways.[134]

Other human-specific hypotheses associated with red meat are also plausible, such as infectious agents (viruses) or xenoautoantigens (triggered by metabolic incorporation of a non-human sialic acid N-glycolylneuraminic acid into the tissues of red meat consumers).[133] N-glycolylneuraminic acid incorporation from red meat can induce xenosialitis in vascular endothelium, and may contribute to red meat-induced aggravation of atherosclerosis and CVD. Despite all this circumstantial evidence, further research is required to confirm that this process is actually pro-atherogenic *in vivo* and thus a major causative factor in the development of CVD in humans.[134]

Very little has been reported about the impact of white meat intake on health; the interpretation of such effects is an arduous task, as individuals consuming more white meat are, at the same time, consuming less red meat. Findings obtained from meta-analyses are weak, and do not report increments on all-cause or CV mortality with 100 g daily consumption.[135,136] Therefore, this could be a reasonable recommendation until more studies assessing the effect of white meat consumption on mortality are conducted, and there is no current evidence to support the choice of white over red meat in terms of CV risk reduction.

Added Sugar and Sugar-sweetened Beverages

The first associations between excess intake of added sugars, metabolic abnormalities and CV risk surfaced in the 1950s, but were eclipsed until recently (2014) by the belief that an excess intake of SFA was the key dietary factor.

Sweeteners are mainly being consumed as sugar substitutes that can be classified as nutritive sweeteners (polyols or sugar alcohols) and non-nutritive substitutes. Although almost 75% of packaged foods contain added sugars, sugar-sweetened beverages (SSBs; soda, sweet teas, fruit drinks) account for half of all added sugar intake.[137–139] The effects of non-nutritive substitutes, both artificial sweeteners (acesulfame K, aspartame, cyclamate, saccharin, neotame, advantame and sucralose) and natural sweeteners (NSSs; thaumatin, steviol glucosides, monellin, neohesperidin dihydrochalcone and glycyrrhizin) are conflicting.[140] NSSs interfere with glucose and energy homeostasis; alter leptin levels; adversely modify lipid profile, inflammatory factors, circulation and composition of gut microbiota; and decrease satiety, consequently increasing the risk of CHD, MI, cerebrovascular accident and vascular death.[64,137,140–146]

While some studies report an association between NSS use and reduced risk of overweight, obesity and type 2 diabetes, other studies suggest that NSS use could increase all of them, and the risk of metabolic syndrome, CHD and cancer.[64] This association might be influenced by gene–SSB interactions.[137] In particular, intake of SSBs can exacerbate the effects of chromosome 9p21 variants (i.e. rs4977574), considered the most robust genetic markers on CHD.[147] The clinical and epidemiological data available at present are insufficient to make definitive conclusions regarding the benefits of non-nutritive substitutes in displacing caloric sweeteners as related to energy balance, maintenance or decrease in bodyweight and other cardiometabolic risk factors.

Based on the previously mentioned evidence, numerous expert bodies have now made recommendations to limit dietary added sugar intake to <10% of calories, and preferably <100 calories daily for women and <150 calories daily for men. Clinicians should recommend 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 nutrition labelling for added sugars.[148,149]

Other Nutrients and Bioactive Compounds

It is important to focus on the potential benefits of the intake of specific nutrients to avoid possible deficiencies of these nutrients, which can lead to the development of atherosclerotic disease.

Fibre

The health benefits of dietary fibre intake are indisputable, while a deficiency of fibre intake is associated with CVD development.[150] The implicated mechanisms include decreased glucose/cholesterol absorption, downregulation of expression of oxidative stress-related cytokines or the inflammatory response mediated by gut microbiota exposed to fibre.[19] The influence of long-term fibre intake on gut microbiota responsiveness to specific interventions is now becoming apparent. Increased fibre intake has been shown to improve certain metabolic parameters associated with obesity and its comorbidities (glucose homeostasis, serum cholesterol levels, blood pressure), particularly in conjunction with energy-controlled dietary regimes.[151] The association between dietary fibre intake and risk of CHD has been studied through meta-analysis showing a significant dose–response relationship, especially for fibre from cereals and fruits.[152]

Bioactive Compounds

Recent research has identified the bioactive compounds that contribute to the beneficial effects of foods rich in anti-oxidants (beta-carotene, vitamin C, vitamin E, selenium) and their potential mechanism: reducing endothelial cells damage, improving the production of NO and inhibiting oxidation of LDL cholesterol (*Table 2*).[153,154]

Although the supplement industry began to promote the benefits of anti-oxidant supplements long before scientific evidence was available, recent multiple subsequent trials have reported either neutral or negative results for vitamin E, beta-carotene, O3FA, vitamin D or multivitamin supplementation.[110,155–160] Thus, although foods rich in anti-oxidants at physiological levels appear to be have health benefits, further investigation will be necessary to better define the role of anti-oxidant supplements in health promotion.[161,162]

Polyphenols

Polyphenols are the most abundant dietary anti-oxidants present in most plant origin foods and beverages, which possess a wide range of health effects in the prevention of CVD.[95] The most relevant food sources have been previously described (fruit and vegetables, red wine, black tea, coffee, extra virgin olive oil, nuts), and their potential anti-inflammatory role has been summarised.[163]

Conclusion

We defined a healthy dietary pattern taking into consideration nutritional adequacy as recommended by most dietary guidelines. A focus exclusively on food groups does not incorporate added fats, sugar and other constituents, and the interplay of intermediate risk factors within inflammation processes. The healthy dietary pattern we proposed allows for flexible, global application of these criteria (*Table 1*), with foods and amounts tailored to the preferences and cultures of different populations. ■

1. Centritto F, Iacoviello L, di Giuseppe R, et al. Dietary patterns, cardiovascular risk factors and C-reactive protein in a healthy Italian population. *Nutr Metab Cardiovasc Dis* 2009;19:697–706. https://doi.org/10.1016/j.numecd.2008.11.009; PMID: 19303267.
2. Mozaffarian D. Dietary and policy priorities for cardiovascular disease, diabetes, and obesity: A comprehensive review. *Circulation* 2016;133:187–225. https://doi.org/10.1161/CIRCULATIONAHA.115.018585; PMID: 26746178.
3. Anand SS, Hawkes C, de Souza RJ, et al. Food consumption and its impact on cardiovascular disease: importance of solutions focused on the globalized food system: a report from the workshop convened by the World Heart Federation. *J Am Coll Cardiol* 2015;66:1590–614. https://doi.org/10.1016/j.jacc.2015.07.050; PMID: 26429085.
4. US Department of Health and Human Services & US Department of Agriculture. *2015–2020 Dietary Guidelines for Americans*, 8th ed. Washington, DC: USHHS, 2015. Available at: https://health.gov/dietaryguidelines/2015/resources/2015-2020_Dietary_Guidelines.pdf (accessed 1 September 2019).
5. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report from the American Heart Association. *Circulation* 2017;35:e146–e603. https://doi.org/10.1161/CIR.0000000000000485; PMID: 28122885.
6. Ravera A, Carubelli V, Sciatti E, et al. Nutrition and cardiovascular disease: Finding the perfect recipe for cardiovascular health. *Nutrients* 2016;8:363. https://doi.org/10.3390/nu8060363; PMID: 27314382.
7. International Food Policy Research Institute. *2017 Global Food Policy Report*. Washington, DC: International Food Policy Research Institute, 2017. https://doi.org/10.2499/9780896292550.
8. Kim H, Caulfield LE, Garcia-Larsen V, et al. Plant-based diets are associated with a lower risk of incident cardiovascular disease, cardiovascular disease mortality, and all-cause mortality in a general population of middle-aged adults. *JAMA* 2019;8:e012865. https://doi.org/10.1161/JAHA.119.012865; PMID: 31387433.
9. Jenkins DJ, Jones PJ, Lamarche B, et al. Effect of a dietary portfolio of cholesterol lowering foods given at 2 levels of intensity of dietary advice on serum lipids in hyperlipidemia: a randomized controlled trial. *JAMA* 2011;306:831–9. https://doi.org/10.1001/jama.2011.1202; PMID: 21862744.
10. Saneei P, Salehi-Abargouei A, Esmaillzadeh A, et al. Influence of Dietary Approaches to Stop Hypertension (DASH) diet on blood pressure: a systematic review and meta-analysis on randomized controlled trials. *Nutr Metab Cardiovasc Dis* 2014;24:1253–61. https://doi.org/10.1016/j.numecd.2014.06.008; PMID: 25149893.
11. Silveira BKS, Oliveira TMS, Andrade PA, et al. Dietary pattern and macronutrients profile on the variation of inflammatory biomarkers: Scientific Update. *Cardiol Res Pract* 2018; 2018:4762575. https://doi.org/10.1155/2018/4762575; PMID: 29725543.
12. Trichopoulou A, Lagiou P. Healthy traditional Mediterranean diet: an expression of culture, history, and lifestyle. *Nutr Rev* 1997;55:383–9. https://doi.org/10.1111/j.1753-4887.1997.tb01578.x; PMID: 9420448.
13. Schwingshackl L, Hoffmann G. Mediterranean dietary pattern, inflammation and endothelial function: a systematic review and meta-analysis of intervention trials. *Nutr Metab Cardiovasc Dis* 2014;24:929–39. https://doi.org/10.1016/j.numecd.2014.03.003; PMID: 24787907.
14. Guasch-Ferré M, Hu FB, Martínez González MA, et al. Olive oil intake and risk of cardiovascular disease and mortality in the PREDIMED Study. *BMC Med* 2014;12:78. https://doi.org/10.1186/1741-7015-12-78 PMID: 24886626.
15. Guo X, Tresserra-Rimbau A, Estruch R, et al. Effects of polyphenol, measured by a biomarker of total polyphenols in urine, on cardiovascular risk factors after a long-term follow-up in the PREDIMED study. *Oxid Med Cell Longev* 2016;2016:2572606. https://doi.org/10.1155/2016/2572606 PMID: 26881019.
16. Esposito K, Ciotola M, Giugliano D. Mediterranean diet, endothelial function and vascular inflammatory markers. *Public Health Nutr* 2006; 9:1073–6. https://doi.org/10.1017/S1368980007668529; PMID: 17378943.
17. Llorente-Cortés V, Estruch R, Mena MP, et al. Effect of Mediterranean diet on the expression of pro-atherogenic genes in a population at high cardiovascular risk. *Atherosclerosis* 2010; 208:442–50. https://doi.org/10.1016/j.atherosclerosis.2009.08.004; PMID: 19712933.
18. Casas R, Sacanella E, Urpí-Sardà M, et al. The effects of the mediterranean diet on biomarkers of vascular wall inflammation and plaque vulnerability in subjects with high risk for cardiovascular disease. A randomized trial. *PLoS ONE* 2014; 9:e100084. https://doi.org/10.1371/journal.pone.0100084; PMID: 24925270.
19. Casas R, Urpi-Sardà M, Sacanella E, et al. Anti-Inflammatory Effects of the Mediterranean Diet in the Early and Late Stages of Atheroma Plaque Development. *Mediat Inflamm* 2017; 2017:3674390. https://doi.org/10.1155/2017/3674390; PMID: 28484308.
20. Estruch R, Ros E, Salas-Salvadó J, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *N Engl J Med* 2013; 368:1279. https://doi.org/10.1056/NEJMoa1200303; PMID: 23432189.
21. Arpón A, Milagro FI, Razquin C et al. Impact of consuming extra-virgin olive oil or nuts within a Mediterranean diet on DNA methylation in peripheral white blood cells within the PREDIMED-Navarra randomized controlled trial: A role for dietary lipids. *Nutrients* 2017;10:15. https://doi.org/10.3390/nu10010015; PMID: 29295516.
22. Corella D, Carrasco P, Fitó M, et al. Gene-environment interactions of CETP gene variation in a high cardiovascular risk Mediterranean population. *J Lipid Res* 2010;51:2798–807. https://doi.org/10.1194/jlr.P005199; PMID: 20581105.
23. Corella D, Carrasco P, Sorlí JV, et al. Mediterranean diet reduces the adverse effect of the TCF7L2-rs7903146 polymorphism on cardiovascular risk factors and stroke incidence: A randomized controlled trial in a high-cardiovascular-risk population. *Diabetes Care* 2013;36:3803–11. https://doi.org/10.2337/dc13-0955; PMID: 23942586.
24. Estruch R, Ros E, Salas-Salvadó J, et al. Retraction and Republication: Primary Prevention of Cardiovascular Disease with a Mediterranean Diet. *N Engl J Med* 2013;368:1279–90. *N Engl J Med* 2018;378:2441–2. https://doi.org/10.1056/NEJMc1806491; PMID: 29897867.
25. Estruch R, Ros E, Salas-Salvadó J, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *N Engl J Med* 2018; 378:e34. https://doi.org/10.1056/NEHMoa1800389; PMID: 29897866.
26. Rai SK, Fung TT, Lu N, et al. The Dietary Approaches to Stop Hypertension (DASH) diet, Western diet, and risk of gout in men: Prospective cohort study. *BMJ* 2017;357:j1794. https://doi.org/10.1136/bmj.j1794; PMID: 28487277.
27. Soltani S, Chitsazi MJ, Salehi-Abargouei, A. The effect of dietary approaches to stop hypertension (DASH) on serum inflammatory markers: A systematic review and meta-analysis of randomized trials. *Clin Nutr* 2018;37:542–50. https://doi.org/10.1016/j.clnu.2017.02.018; PMID: 28302405.
28. Phillips CM, Harrington JM, Perry IJ. Relationship between dietary quality, determined by DASH score, and cardiometabolic health biomarkers: A cross-sectional analysis in adults. *Clin Nutr* 2019;38:1620–8. https://doi.org/10.1016/j.clnu.2018.08.028; PMID: 30219609.
29. Houston M. The role of nutrition and nutraceutical supplements in the treatment of hypertension. *World J Cardiol* 2014;6:38–66. https://doi.org/10.4330/wjc.v6.i2.38; PMID: 24575172.
30. Lin PH, Allen JD, Li YJ, et al. Blood Pressure-Lowering Mechanisms of the DASH Dietary Pattern. *J Nutr Metab* 2012;2012:472396. https://doi.org/10.1155/2012/472396; PMID: 22496969.
31. National Health and Medical Research Council. *Australian Dietary Guidelines*. Canberra, Australia: National Health and Medical Research Council (NHMRC), 2013.
32. Cobiac LJ, Scarborough P, Kaur A, et al. The Eatwell Guide: Modelling the Health Implications of Incorporating New Sugar and Fibre Guidelines. *PLoS One*. 2016;11(12):e0167859. https://doi.org/10.1371/journal.pone.0167859; PMID: 27997546.
33. Health Canada. *Eating Well with Canada's Food Guide - First Nations, Inuit and Métis.* Ottawa: Health Canada, 2019. Available at: https://www.canada.ca/en/health-canada/services/food-nutrition/reports-publications/eating-well-canada-food-guide-first-nations-inuit-metis.html (accessed 27 March 2019).
34. Hosseini B, Berthon BS, Saedisomeolia A, et al. Effects of fruit and vegetable consumption on inflammatory biomarkers and immune cell populations: A systematic literature review and meta-analysis. *Am J Clin Nutr* 2018;108:136–55. https://doi.org/10.1093/ajcn/nqy082; PMID: 29931038.
35. Bazzano LA, Serdula MK, Liu S. Dietary intake of fruits and vegetables and risk of cardiovascular disease. *Curr Atheroscler Rep* 2003;5:492–9. https://doi.org/10.1007/s11883-003-0040-z; PMID: 14525683.
36. Liu RH. Health-promoting components of fruits and vegetables in the diet. *Adv Nutr* 2013;4:384S–92S. https://doi.org/10.3945/an.112.003517; PMID: 23674808.
37. Murphy MM, Barraj LM, Spungen JH, et al. Global assessment of select phytonutrient intakes by level of fruit and vegetable consumption. *Br J Nutr* 2014;112:1004–18. https://doi.org/10.1017/S0007114514001937; PMID: 25108700.
38. Wu X, Beecher GR, Holden JM, et al. Concentrations of anthocyanins in common foods in the United States and estimation of normal consumption. *J Agric Food Chem* 2006;54:4069–75. https://doi.org/10.1021/jf060300l; PMID: 16719536.
39. Wedick NM, Pan A, Cassidy A, et al. Dietary flavonoid intakes and risk of type 2 diabetes in US men and women. *Am J Clin Nutr* 2012;95:925–33. https://doi.org/10.3945/ajcn.111.028894; PMID: 22357723.
40. DeMartino AW, Kim-Shapiro DB, Patel RP4, et al. Nitrite and nitrate chemical biology and signalling. *Br J Pharmacol* 2019;176:228–45. https://doi.org/10.1111/bph.14484; PMID: 30152056.
41. Stanaway L, Rutherfurd-Markwick K, Page R, et al. Acute Supplementation with Nitrate-Rich Beetroot Juice Causes a Greater Increase in Plasma Nitrite and Reduction in Blood Pressure of Older Compared to Younger Adults. *Nutrients* 2019;11:1683. https://doi.org/10.3390/nu11071683; PMID: 31336633.
42. Bondonno CP, Blekkenhorst LC, Liu AH, et al. Vegetable-derived bioactive nitrate and cardiovascular health. *Mol Aspects Med* 2018;61:83–91. https://doi.org/10.1016/j.mam.2017.08.001; PMID: 28802834.
43. Jackson JK, Patterson AJ, MacDonald-Wicks LK, et al. The role of inorganic nitrate and nitrite in cardiovascular disease risk factors: a systematic review and meta-analysis of human evidence. *Nutr Rev* 2018; 76:348–71. https://doi.org/10.1093/nutrit/nuy005; PMID: 29506204.
44. Aune D, Giovannucci E, Boffetta P, et al. Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality: A systematic review and dose-response meta analysis of prospective studies. *Int J Epidemiol* 2017;46:1029–56. https://doi.org/10.1093/ije/dyw319;

PMID: 28338764.
45. Becerra-Tomás N, Díaz-López A, Rosique-Esteban N, et al. PREDIMED Study Investigators. Legume consumption is inversely associated with type 2 diabetes incidence in adults: A prospective assessment from the PREDIMED study. *Clin Nutr* 2018;37:906–13. https://doi.org/10.1016/j.clnu.2017.03.015; PMID: 28392166.
46. U.S. Department of Agriculture, Economic Research Service. Dried Beans. Washington, DC: U.S. Department of Agriculture, Economic Research Service, 2013. www.ers.usda.gov/webdocs/publications/39541/49186_vgs-354-sa1.pdf?v=41912 (accessed 31 October 2019).
47. Sala-Vila A, Estruch R, Ros E. New insights into the role of nutrition in CVD prevention. *Curr Cardiol Rep* 2015;17:26. https://doi.org/10.1007/s11886-015-0583-y; PMID: 25894796.
48. Hosseinpour-Niazi S, Mirmiran P, Fallah-Ghohroudi A, et al. Non-soya legume-based therapeutic lifestyle change diet reduces inflammatory status in diabetic patients: a randomised cross-over clinical trial. *Br J Nutr* 2015;114:213–9. https://doi.org/10.1017/S0007114515001725; PMID: 26077375.
49. Salehi-Abargouei A, Saraf-Bank S, Bellissimo N, et al. Effects of non-soy legume consumption on C-reactive protein: a systematic review and meta-analysis. *Nutrition* 2015;31:631–9. https://doi.org/10.1016/j.nut.2014.10.018; PMID: 25837205.
50. Broom M. *Trends in Pulse Consumption: Now and on the Horizon? Future of Pulse Production and Consumption*. Sydney, Australia: Grains & Legumes Nutrition Council, 2016.
51. Guasch-Ferré M, Liu X, Malik VS, et al. Nut Consumption and Risk of Cardiovascular Disease. *J Am Coll Cardiol* 2017; 70:2519–32. https://doi.org/10.1016/j.jacc.2017.09.035; PMID: 29145952.
52. Aune D, Keum N, Giovannucci E, et al. Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: A systematic review and dose-response meta analysis of prospective studies. *BMC Med* 2016;14:207. https://doi.org/10.1186/s12916-016-0730-3; PMID: 27916000.
53. Sabate J, Oda K, Ros E. Nut consumption and blood lipid levels: a pooled analysis of 25 intervention trials: A pooled analysis of 25 intervention trials. *Arch Intern Med* 2010;170:82xs://doi.org/10.1001/archinternmed.2010.79; PMID: 20458092.
54. Del Gobbo LC, Falk MC, Feldman R, et al. Effects of tree nuts on blood lipids, apolipoproteins, and blood pressure: Systematic review, meta-analysis, and dose- response of 61 controlled intervention trials. *Am J Clin Nutr* 2015;102:1347–56. https://doi.org/10.3945/ajcn.115.110965; PMID: 26561616.
55. Yu Z, Malik VS, Keum N, et al. Associations between nut consumption and inflammatory biomarkers. *Am J Clin Nutr* 2016;104:722–8. https://doi.org/10.3945/ajcn.116.134205; PMID: 27465378.
56. Neale EP, Tapsell LC, Guan V, et al. The effect of nut consumption on markers of inflammation and endothelial function: A systematic review and meta-analysis of randomised controlled trials. *BMJ Open* 2017;7:e016863. https://doi.org/10.1136/bmjopen-2017-016863; PMID: 29170286.
57. Xiao Y, Xia J, Ke Y, et al. Effects of nut consumption on selected inflammatory markers: A systematic review and meta-analysis of randomized controlled trials. Nutrition. 2018;54: 129–143. https://doi.org/10.1016/j.nut.2018.02.017 PMID: 29852452.
58. Okarter N, Liu RH. Health benefits of whole grain phytochemicals. *Crit Rev Food Sci Nutr* 2010;50:193–208. https://doi.org/10.1080/10408390802248734; PMID: 20301011.
59. Holt SH, Brand-Miller JC, Stitt PA. The effects of equal-energy portions of different breads on blood glucose levels, feelings of fullness and subsequent food intake. *J Am Diet Assoc* 2001;101:767–73. https://doi.org/10.1016/S0002-8223(01)00192-4; PMID: 11478473.
60. Zong G, Gao A, Hu FB, Sun Q. Whole grain intake and mortality from all causes, cardiovascular disease, and cancer: a meta-analysis of prospective cohort studies. *Circulation* 2016;133:2370–80. https://doi.org/10.1161/CIRCULATIONAHA.115.021101; PMID: 27297341.
61. Mozaffarian D, Hao T, Rimm EB, et al. Changes in diet and lifestyle and long-term weight gain in women and men. *N Engl J Med* 2011;364:2392–404. https://doi.org/10.1056/NEJMoa1014296; PMID: 21696306.
62. Hu FB. Are refined carbohydrates worse than saturated fat? *Am J Clin Nutr* 2010;91:1541–2. https://doi.org/10.3945/ajcn.2010.29622; PMID: 20410095.
63. Sturgeon C, Fasano A. Zonulin, a regulator of epithelial and endothelial barrier functions, and its involvement in chronic inflammatory diseases. *Tissue Barriers* 2016;4:e1251384. https://doi.org/10.1080/21688370.2016.1251384; PMID: 28123927.
64. Houston M, Minich D, Sinatra ST, et al. Recent Science and Clinical Application of Nutrition to Coronary Heart Disease. *J Am Coll Nutr* 2018;37:169–87. https://doi.org/10.1080/07315724.2017.1381053; PMID: 29313752.
65. Lebwohl B, Cao Y, Zong G, et al. Long term gluten consumption in adults without celiac disease and risk of coronary heart disease: prospective cohort study. *BMJ* 2017;357:j1892. https://doi.org/10.1136/bmj.j1892; PMID: 28465308.
66. Birt DF, Boylston T, Hendrich S, et al. Resistant starch: Promise for improving human health. *Adv Nutr* 2013;4: 587–601. https://doi.org/10.3945/an.113.004325; PMID: 24228189.
67. Battson ML, Lee DM, Weir TL, et al. The gut microbiota as a novel regulator of cardiovascular function and disease. *J Nutr Biochem* 2017;56:1–15. https://doi.org/10.1016/j.jnutbio.2017.12.010; PMID: 29427903.
68. Muraki I, Rimm EB, Willett WC, et al. Potato consumption and risk of type 2 diabetes: results from three prospective cohort studies. *Diabetes Care* 2016;39:376–84. https://doi.org/10.2337/dc15-0547; PMID: 26681722.
69. Borgi L, Rimm EB, Willett WC, et al. Potato intake and incidence of hypertension: results from three prospective US cohort studies. *BMJ* 2016;353:i2351. https://doi.org/10.1136/bmj.i2351; PMID: 27189229.
70. Bertoia ML, Mukamal KJ, Cahill LE, et al. Changes in intake of fruits and vegetables and weight change in united states men and women followed for up to 24 years: analysis from three prospective cohort studies. *PLoS Med* 2015;12:e1001878. https://doi.org/10.1371/journal.pmed.1001878; PMID: 26394033.
71. Borch D, Juul-Hindsgaul N, Veller M, et al. Potatoes and risk of obesity, type 2 diabetes, and cardiovascular disease in apparently healthy adults: a systematic review of clinical intervention and observational studies. *Am J Clin Nutr* 2016;104:489–98. https://doi.org/10.3945/ajcn.116.132332; PMID: 27413134.
72. Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits. *JAMA* 2006;296:1885–99. https://doi.org/10.1001/jama.296.15.1885; PMID: 17047219.
73. Zheng J, Huang T, Yu Y, et al. Fish consumption and CHD mortality: an updated meta-analysis of seventeen cohort studies. *Public Health Nutr* 2012;15:725–37. https://doi.org/10.1017/S1368980011002254; PMID: 21914258.
74. Galli C, Rise P. Fish consumption, omega 3 fatty acids and cardiovascular disease. The science and the clinical trials. *Nutr Health* 2009;20:11–20. https://doi.org/10.1177/026010600902000102; PMID: 19326716.
75. Haseeb S, Alexander B, Baranchuk A. Wine and cardiovascular health: A comprehensive review. *Circulation* 2017;136:1434–48. https://doi.org/10.1161/CIRCULATIONAHA.117.030387; PMID: 28993373.
76. Haseeb S, Alexander B, Santi RL, et al. What's in wine? A clinician's perspective. *Trends Cardiovasc Med* 2019;29:97–106. https://doi.org/10.1016/j.tcm.2018.06.010; PMID: 30104174.
77. Janssen I, Landay AL, Ruppert K, et al Moderate wine consumption is associated with lower hemostatic and inflammatory risk factors over 8 years: The study of women's health across the nation (SWAN). *Nutr Aging* 2014;2:91–9. https://doi.org/10.3233/NUA-130034; PMID: 25705320.
78. Estruch R, Sacanella E, Badia E, et al. Different effects of red wine and gin consumption on inflammatory biomarkers of atherosclerosis: A prospective randomized crossover trial. Effects of wine on inflammatory markers. *Atherosclerosis* 2004;175:117–23. https://doi.org/10.1016/j.atherosclerosis.2004.03.006; PMID: 15186955.
79. Estruch R, Sacanella E, Mota F, et al. Moderate consumption of red wine, but not gin, decreases erythrocyte superoxide dismutase activity: A randomized cross-over trial. *Nutr Metab Cardiovasc Dis* 2011; 21:46–53. https://doi.org/10.1016/j.numecd.2009.07.006; PMID: 19819677.
80. Costanzo S, Di Castelnuovo A, Donati MB, et al. Wine, beer or spirit drinking in relation to fatal and non-fatal cardiovascular events: A meta-analysis. *Eur J Epidemiol* 2011;26:833–50. https://doi.org/10.1007/s10654-011-9631-0; PMID: 22076059.
81. de Gaetano G, Costanzo S, Di Castelnuovo A, et al. Effects of moderate beer consumption on health and disease: A consensus document. *Nutr Metab Cardiovasc Dis* 2016;26:443–67. https://doi.org/10.1016/j.numecd.2016.03.007; PMID: 27118108.
82. Mukamal K, Lazo M. Alcohol and cardiovascular disease. *BMJ* 2017;356:j1340. https://doi.org/10.1136/bmj.j1340; PMID: 28330843.
83. Ronksley PE, Brien SE, Turner BJ, et al. Association of alcohol consumption with selected cardiovascular disease outcomes. A systematic review and meta analysis. *BMJ* 2011;342: d671. https://doi.org/10.1136/bmj.d671; PMID: 21343207.
84. Larson SC, Drca N, Wolk A. Alcohol consumption and risk of atrial fibrillation: a prospective study and dose-response meta-analysis. *J Am Coll Cardiol* 2014; 64:281–9.https://doi.org/10.1016/j.jacc.2014.03.048; PMID: 25034065.
85. Laonigro I, Correale M, Di Biase M, et al. Alcohol abuse and heart failure. *Eur J Heart Fail* 2009;11:453–62. https://doi.org/10.1093/eurjhf/hfp037; PMID: 19336433.
86. Núñez-Cordoba JM, Valencia-Serrano F, Toledo E, et al. The Mediterranean diet and incidence of hypertension: the Seguimiento Universidad de Navarra (SUN) Study. *Am J Epidemiol* 2009;169:339–46. https://doi.org/10.1093/aje/kwn335; PMID: 19037007.
87. LoConte NK, Brewster AM, Kaur JS, et al. Alcohol and Cancer: A Statement of the American Society of Clinical Oncology. *J Clin Oncol* 2018;36:83–93. https://doi.org/10.1200/JCO.2017.76.1155; PMID: 29112463.
88. O'Keefe JH, Bhatti SK, Bajwa A, et al. Alcohol and cardiovascular health: the dose makes the poison… or the remedy. *Mayo Clin Proc* 2014;89:382–93. https://doi.org/10.1016/j.mayocp.2013.11.005; PMID: 24582196.
89. Zhao J, Stockwell T, Roemer A, et al. Alcohol consumption and mortality from coronary heart disease: an updated metaanalysis of cohort studies. *J Stud Alcohol Drugs* 2017;78:375–86. https://doi.org/10.15288/jsad.2017.78.375; PMID: 28499102.
90. Mukamal K, Lazo M. Alcohol and cardiovascular disease. *BMJ* 2017;356: j1340. https://doi.org/10.1136/bmj.j1340; PMID: 28330843.
91. Turnbull D, Rodricks JV, Mariano GF, et al. Caffeine and cardiovascular health. *Regul Toxicol Pharmacol* 2017; 89:165–85. https://doi.org/10.1016/j.yrtph.2017.07.025; PMID: 28756014.
92. Cornelis MC, El-Sohemy A. Coffee, caffeine, and coronary heart disease. *Curr Opin Lipidol* 2007;18:13–9. https://doi.org/10.1097/MOL.0b013e3280127b04; PMID: 17218826.
93. Butt MS, Sultan MT. Coffee and its consumption: benefits and risks. *Crit Rev Food Sci Nutr* 2011;51:363–73. https://doi.org/10.1080/10408390903586412; PMID: 21432699.
94. Yukawa GS, Mune M, Otani H, et al. Effects of coffee consumption on oxidative susceptibility of low-density lipoproteins and serum lipid levels in humans. *Biochemistry (Mosc)* 2004;69:70–4. https://doi.org/10.1023/B:BIRY.0000016354.05438.0f; PMID: 14972021.
95. Mozaffarian D, Wu JHY. Flavonoids, Dairy Foods and Cardiovascular and Metabolic Health: A review of emerging biologic pathways. *Circ Res* 2018;122:369–84. https://doi.org/10.1161/CIRCRESAHA.117.309008; PMID: 29348256.
96. Bahramsoltani R, Ebrahimi F, Farzaei MH, et al. Dietary polyphenols for atherosclerosis: A comprehensive review and future perspectives. *Crit Rev Food Sci Nutr* 2019;59:114–32. https://doi.org/10.1080/10408398.2017.1360244; PMID: 28812379.
97. Witkowska AM, Waśkiewicz A, Zujko ME, et al. Dietary polyphenol intake but not the dietary total antioxidant capacity is inversely related to cardiovascular disease in postmenopausal polish women: Results of WOBASZ and WOBASZ II Studies. *Oxid Med Cell Longev* 2017; 2017:5982809. https://doi.org/10.1155/2017/5982809; PMID: 28713488.
98. Chiva-Blanch G, Badimon L. Effects of polyphenol intake on metabolic syndrome: Current Evidences from Human Trials. *Oxid Med Cell Longev* 2017;2017:5812401. https://doi.org/10.1155/2017/5812401 PMID: 28894509.
99. 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. https://doi.org/10.1016/j.ypmed.2011.12.009; PMID: 22198621.
100. Li X, Yu C, Guo Y, et al. Tea consumption and risk of ischaemic heart disease. *Heart* 2017;103:783–9. https://doi.org/10.1136/heartjnl-2016-310462; PMID: 28077466.
101. 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. https://doi.org/10.1001/jama.296.10.1255; PMID: 16968850.
102. Qin LQ, Xu JY, Han SF, et al. Dairy consumption and risk of cardiovascular disease: an updated meta-analysis of prospective cohort studies. *Asia Pac J Clin Nutr* 2015;24:90–100. https://doi.org/10.6133/apjcn.2015.24.1.09; PMID: 25740747.
103. 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. https://doi.org/10.1017/S0007114515005000; PMID: 26786887.
104. Guo J, Astrup A, Lovegrove JA, et al. Milk and dairy consumption and risk of cardiovascular diseases and all-cause mortality: dose-response metaanalysis of prospective cohort studies. *Eur J Epidemiol* 2017;32:269–87. https://doi.org/10.1007/s10654-017-0243-1; PMID: 28374228.
105. Gholami F, Khoramdad M, Esmailnasab N, et al. The effect of dairy consumption on the prevention of cardiovascular diseases: A meta-analysis of prospective studies. *J Cardiovasc Thorac Res* 2017;9:1–11. https://doi.org/10.15171/jcvtr.2017.01; PMID: 28451082.
106. 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. https://doi.org/10.3945/an.115.011403; PMID: 28140321.
107. Chen M, Li Y, Sun Q, Pan A, et al. Dairy fat and risk of cardiovascular disease in 3 cohorts of U.S. adults. *Am J Clin Nutr* 2016;104:1209–17. https://doi.org/10.3945/ajcn.116.134460; PMID: 27557656.
108. Colditz GA, Manson JE, Hankinson SE. The Nurses' Health Study: 20-year contribution to the understanding of health among women. *J Womens Health* 1997;6:49–62. https://doi.org/10.1089/jwh.1997.6.49; PMID: 9065374.
109. Soedamah-Muthu SS, de Goede J. Dairy Consumption and Cardiometabolic Diseases: Systematic Review and Updated Meta-Analyses of Prospective Cohort Studies. *Curr Nutr Rep* 2018;7:171–82. https://doi.org/10.1007/s13668-018-0253-y; PMID: 30406514.
110. Manson JE, Cook NR, Lee IM, et al; VITAL Research Group. Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. *N Engl J Med* 2019;380:33–44. https://doi.org/10.1056/NEJMoa1809944; PMID: 30415629.
111. Krauss RM, Eckel RH, Howard B, et al. AHA dietary guidelines: revision 2000: a statement for healthcare professionals from the nutrition committee of the American Heart Association. *Circulation* 2000;102:2284–99. https://doi.org/10.1161/01.CIR.102.18.2284; PMID: 11056107.
112. Fuller NR, Caterson ID, Sainsbury A, et al. The effect of a high-egg diet on cardiovascular risk factors in people with type 2 diabetes: The Diabetes and Egg (DIABEGG) study a 3-mo randomized controlled trial. *Am J Clin Nutr* 2015;101:705–13. https://doi.org/10.3945/ajcn.114.096925;

PMID: 25833969.
113. Shin JY, Xun P, Nakamura Y, et al. Egg consumption in relation to risk of cardiovascular disease and diabetes: a systematic review and meta-analysis. *Am J Clin Nutr* 2013; 98:146–59. https://doi.org/10.3945/ajcn.112.051318; PMID: 23676423.
114. Rong Y, Chen L, Zhu T, et al. Egg consumption and risk of coronary heart disease and stroke: dose response meta-analysis of prospective cohort studies. *BMJ* 2013;346:e8539. https://doi.org/10.1136/bmj.e8539; PMID: 23295181.
115. Alexander DD, Miller PE, Vargas AJ, et al. Meta- analysis of egg consumption and risk of coronary heart disease and stroke. *J Am Coll Nutr* 2016;35:704–16. https://doi.org/10.1080/07315724.2016.1152928; PMID: 27710205.
116. Zhong VW, Van Horn L, Cornelis MC, et al. Associations of Dietary Cholesterol or Egg Consumption With Incident Cardiovascular Disease and Mortality. *JAMA* 2019;321:1081–95. https://doi.org/10.1001/jama.2018.15246; PMID: 30874756.
117. Mazidi M, Katsiki N, Mikhailidis DP, et al. Egg Consumption and Risk of Total and Cause-Specific Mortality: An Individual-Based Cohort Study and Pooling Prospective Studies on Behalf of the Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group. *J Am Coll Nutr* 2019;38:552–63. https://doi.org/10.1080/07315724.2018.1534620; PMID: 31173548.
118. Way X, Son M, Meram C, et al. Mechanism and Potential of Egg Consumption and Egg Bioactive Components on Type-2 Diabetes. *Nutrients* 2019:11: 357. https://doi.org/10.3390/nu11020357; PMID: 30744071.
119. Astrup A, Dyerberg J, Elwood P, et al. The role of reducing intakes of saturated fat in the preventions of cardiovascular disease. Where does the evidence stand in 2010? *Am J Clin Nutr* 2011; 93:684–8. https://doi.org/10.3945/ajcn.110.004622; PMID: 21270379.
120. 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. https://doi.org/10.7326/M13-1788; PMID: 24723079.
121. Siri-Tarino PW, Sun Q, Hu FB, et al. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. *Am J Clin Nutr* 2010;91:502–9. https://doi.org/10.3945/ajcn.2009.27725; PMID: 20071648.
122. Bier DM. Saturated Fats and Cardiovascular Disease: Interpretations Not as Simple as They Once Were. *Crit Rev Food Sci Nutr* 2016;56:1943–6. https://doi.org/10.1080/10408398.2014.998332; PMID: 25774535.
123. Houston MC. The Role of Saturated Fats in Coronary Heart Disease. *J Heart Stroke* 2017;2:1025–6.
124. Mente A, Dehghan M, Rangarajan S, et al. Prospective Urban Rural Epidemiology (PURE) study investigators. Association of dietary nutrients with blood lipids and blood pressure in 18 countries: a cross-sectional analysis from the PURE study. *Lancet Diabetes Endocrinol* 2017;5:774–87. https://doi.org/10.1016/S2213-8587(17)30283-8; PMID: 28864143.
125. Calder PC. The role of marine omega-3 (n-3) fatty acids in inflammatory processes, atherosclerosis and plaque stability. *Mol Nutr Food Res* 2012;56:1073–80. https://doi.org/10.1002/mnfr.201100710; PMID: 22760980.
126. Fredman G, Tabas I. Boosting Inflammation Resolution in Atherosclerosis: The Next Frontier for Therapy. *Am J Pathol* 2017;187:1211–21. https://doi.org/10.1016/j.ajpath.2017.01.018; PMID: 28527709.
127. Bennett M, Gilroy DW. Lipid Mediators in Inflammation. *Microbiol Spectr* 2016;4. https://doi.org/10.1128/microbiolspec.MCHD-0035-2016; PMID: 27837747.
128. Aung T, Halsey J, Kromhout D, et al. Omega-3 Treatment Trialists' Collaboration. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: meta-analysis of 10 trials involving 77917 individuals. *JAMA Cardiol* 2018;3:225–34. https://doi.org/10.1001/jamacardio.2017.5205; PMID: 29387889.
129. Siscovick DS, Barringres TA, Fretts AM, et al. Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Epidemiology and Prevention; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology. Omega-3 polyunsaturated fatty acid (fish oil) supplementation and the prevention of clinical cardiovascular disease. A science advisory from the American Heart Association. *Circulation* 2017;135:e867–84. https://doi.org/10.1161/CIR.0000000000000482; PMID: 28289069.
130. Bhatt DL, Steg PG, Miller M, et al. REDUCE-IT Investigators. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *New Eng J Med* 2019;380:11–22. https://doi.org/10.1056/NEJMoa1812792; PMID: 30415628.
131. Wallace TC. Health Effects of Coconut Oil-A Narrative Review of Current Evidence. *J Am Coll Nutr* 2019;38:97–107. https://doi.org/10.1080/07315724.2018.1497562; PMID: 30395784.
132. Micha R, Wallace SK, Mozaffarian D. Red and processed meat consumption and risk of incident coronary heart disease, stroke, and diabetes mellitus: a systematic review and meta-analysis. *Circulation* 2010;121:2271–83. https://doi.org/10.1161/CIRCULATIONAHA.109.924977; PMID: 20479151.
133. Alisson-Silva F, Kawanishi K, Varki A. Human risk of diseases associated with red meat intake: Analysis of current theories and proposed role for metabolic incorporation of a non-human sialic acid. *Mol Aspects Med* 2016;51:16–30. https://doi.org/10.1016/j.mam.2016.07.002; PMID: 27421909.
134. Mostafalou S, Abdollahi M. Pesticides: an update of human exposure and toxicity. *Arch Toxicol* 2017;91:549–99. https://doi.org/10.1007/s00204-016-1849-x; PMID: 27722929.
135. Abete I, Romaguera D, Vieira AR, et al. Association between total, processed, red and white meat consumption and all-cause, CVD and IHD mortality: a meta analysis of cohort studies. *Br J Nutrit* 2014;112:762–75. https://doi.org/10.1017/S000711451400124X; PMID: 24932617.
136. Bergeron N, Chiu S, Williams PT, et al. Effects of red meat, white meat, and nonmeat protein sources on atherogenic lipoprotein measures in the context of low compared with high saturated fat intake: a randomized controlled trial. *Am J Clin Nutr* 2019;pii:nqz035. https://doi.org/10.1093/ajcn/nqz035; PMID: 31161217; epub ahead of press.
137. Malik VS, Hu FB. Sugar-Sweetened Beverages and Cardiometabolic Health: An Update of the Evidence. *Nutrients* 2019;11:pii:E1840. https://doi.org/10.3390/nu11081840; PMID: 31398911.
138. 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. https://doi.org/10.2337/dc13-2085; PMID: 24652725.
139. James P, Seward MW, James O'Malley A, et al. Changes in the food environment over time: examining 40 years of data in the Framingham Heart Study. *Int J Behav Nutr Phys Act* 2017;14:84. https://doi.org/10.1186/s12966-017-0537-4; PMID: 28646894.
140. Toews I, Lohner S, Küllenberg de Gaudry D, et al. Association between intake of non-sugar sweeteners and health outcomes: systematic review and meta-analyses of randomised and non-randomised controlled trials and observational studies. *BMJ* 2019;364:k4718. https://doi.org/10.1136/bmj.k4718; PMID: 30602577.
141. de Koning L, Malik VS, Kellogg MD, et al. Sweetened beverage consumption, incident coronary heart disease, and biomarkers of risk in men. *Circulation* 2012;125 Suppl:1735–41. https://doi.org/10.1161/CIRCULATIONAHA.111.067017; PMID: 22412070.
142. Ruiz-Ojeda FJ, Plaza-Díaz J, Sáez-Lara MJ, et al. Effects of Sweeteners on the Gut Microbiota: A Review of Experimental Studies and Clinical Trials. *Adv Nutr* 2019;10 Suppl:S31–S48. https://doi.org/10.1093/advances/nmy037; PMID: 30721958.
143. Azad MB, Abou-Setta AM, Bhupendrasinh F, et al. Nonnutritive sweeteners and cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials and prospective cohort studies. *CMAJ* 2017; 189:E929–E939. https://doi.org/10.1503/cmaj.161390; PMID: 28716847.
144. Mossavar-Rahmani Y, Kamensky V, Manson JE, et al. Artificially Sweetened Beverages and Stroke, Coronary Heart Disease, and All-Cause Mortality in the Women's Health Initiative. *Stroke* 2019;50:555–62. https://doi.org/10.1161/STROKEAHA.118.023100; PMID: 30802187.
145. Pase MP, Himali JJ, Beiser AS, et al. Sugar- and Artificially Sweetened Beverages and the Risks of Incident Stroke and Dementia: A Prospective Cohort Study. *Stroke* 2017;48:1139–46. https://doi.org/10.1161/STROKEAHA.116.016027; PMID: 28428346.
146. Gardener H, Elkind MSV. Artificial Sweeteners, Real Risks. *Stroke* 2019;50:549–51. https://doi.org/10.1161/STROKEAHA.119.024456; PMID: 30760171.
147. Zheng Y, Li Y, Huang T, Cheng HL, et al. Sugar-sweetened beverage intake, chromosome 9p21 variants, and risk of myocardial infarction in Hispanics. *Am J Clin Nutr* 2016;103:1179–84. https://doi.org/10.3945/ajcn.115.107177; PMID: 26961926.
148. World Health Organization. *Guideline: Sugars Intake for Adults and Children*. Geneva: World Health Organization, 2015.
149. Micha R, Penalvo JL, Cudhea F, et al. Association between dietary factors and mortality from heart disease, stroke, and type 2 diabetes in the United States. *JAMA* 2017;317:912–24. https://doi.org/10.1001/jama.2017.0947; PMID: 28267855.
150. Yang Y, Zhao LG, Wu QJ, et al . Association between dietary fiber and lower risk of all-cause mortality: a meta-analysis of cohort studies. *Am J Epidemiol* 2015;181:83–91. https://doi.org/10.1093/aje/kwu257; PMID: 25552267.
151. Bozzetto L, Costabile G, Della Pepa G, et al. Dietary Fibre as a Unifying Remedy for the Whole Spectrum of Obesity-Associated Cardiovascular Risk. *Nutrients* 2018;10:pii:E943. https://doi.org/10.3390/nu10070943; PMID: 30037123.
152. Wu Y, Qian Y, Pan Y, et al. Association between dietary fiber intake and risk of coronary heart disease: A meta-analysis. *Clin Nutr* 2015;34:603–11. https://doi.org/10.1016/j.clnu.2014.05.009; PMID: 24929874.
153. Papas AM. Diet and antioxidant status. *Food Chem Toxicol* 1999;37:999–1007. https://doi.org/10.1016/S0278-6915(99)00088-5; PMID: 10541457.
154. Heitzer T, Schlinzig T, Krohn K, et al. Endothelial dysfunction, oxidative stress, and risk of cardiovascular events in patients with coronary artery disease. *Circulation* 2001;104:2673–8. https://doi.org/10.1161/hc4601.099485; PMID: 11723017.
155. Bailey RL, Gahche JJ, Lentino CV, et al. Dietary supplement use in the United States, 2003–2006. *J Nutr* 2011;141:261–6. https://doi.org/10.3945/jn.110.133025; PMID: 21178089.
156. Chun OK, Floegel A, Chung SJ, et al. Estimation of antioxidant intakes from diet and supplements in U.S. adults. *J Nutr* 2010;140:317–24. https://doi.org/10.3945/jn.109.114413; PMID: 20032488.
157. GISSI-Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infaro miocardico). Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI- Prevenzione trial. *Lancet* 1999;354:447–55. https://doi.org/10.1016/S0140-6736(99)07072-5.
158. Hennekens CH, Buring JE, Manson JE, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med* 1996;334:1145–9. https://doi.org/10.1056/NEJM199605023341801; PMID: 8602179.
159. Lawson KA, Wright ME, Subar A, et al. Multivitamin use and risk of prostate cancer in the National Institutes of Health-AARP Diet and Health Study. *J Natl Cancer Inst* 2007;99:754–64. https://doi.org/10.1093/jnci/djk177; PMID: 17505071.
160. Vivekananthan DP, Penn MS, Sapp SK, et al. Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials. *Lancet* 2003;361:2017–23. https://doi.org/10.1016/S0140-6736(03)13637-9; PMID: 12814711.
161. Moyer MW. The myth of antioxidants. *Sci Am* 2013;308:62–7. https://doi.org/10.1038/scientificamerican0213-62; PMID: 23367786.
162. Hasnain BI, Mooradian AD. Recent trials of antioxidant therapy: what should we be telling our patients? *Cleve Clin J Med* 2004;71:327–34. https://doi.org/10.3949/ccjm.71.4.327; PMID: 15117174.
163. Bahramsoltani R, Ebrahimi F, Farzaei MH, et al. Dietary polyphenols for atherosclerosis: A comprehensive review and future perspectives. *Crit Rev Food Sci Nutr* 2019;59:114–132. https://doi.org/10.1080/10408398.2017.1360244; PMID: 28812379.