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REVIEW

Recent Science and Clinical Application of Nutrition to Coronary Heart Disease

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ABSTRACT

One of the greatest threats to mortality in industrialized societies continues to be coronary heart disease (CHD). Moreover, the ability to decrease the incidence of CHD has reached a limit utilizing traditional diagnostic evaluations and prevention and treatment strategies for the top five cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidemia, obesity, and smoking). It is well known that about 80% of CHD can be prevented with optimal nutrition, coupled with exercise, weight management, mild alcohol intake, and smoking cessation. Among all of these factors, optimal nutrition provides the basic foundation for prevention and treatment of CHD. Numerous prospective nutrition clinical trials have shown dramatic reductions in the incidence of CHD. As nutritional science and nutrigenomics research continues, our ability to adjust the best nutrition with an individualized approach is emerging. This article reviews the role of nutrition in the prevention and treatment of CHD and myocardial infarction (MI).

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Introduction

Cardiovascular disease (CVD) remains the number one cause of morbidity and mortality in the United States (1,2). The annual cost (direct and indirect) of treating CVD is approximately US$320 billion (2). One in every three deaths is due to CVD, with more than 2200 US citizens dying from stroke or MI daily (2–5). Clinical studies suggest that a limit has been reached in the ability to reduce coronary heart disease (CHD) by relying on the top five CHD risk factors as presently defined. These are hypertension, dyslipidemia, diabetes mellitus, obesity, and smoking cessation (1). More than 400 CHD risk factors have been defined (2). Approximately 80% of CHD can be prevented by optimal nutrition, regular aerobic and resistance exercise, ideal body weight and body composition, mild alcohol intake, and not smoking (1). There are numerous insults to the cardiovascular system, but there are only three finite vascular responses, which are inflammation, oxidative stress, and vascular immune dysfunction, which lead to the atherosclerotic process and plaque formation, CHD, and myocardial infarction (MI) (Figure 1).

Background of nutrition and coronary heart disease: Pathophysiology and vascular function

Revolutionizing the treatment of coronary heart disease and interrupting the finite pathways

The interaction of the various insults with cell membranes and the endothelial vascular receptors (pattern recognition receptors (PRR), nod like receptors (NLR), toll-like receptors (TLR), and caveolae (which contain endothelial nitric oxide synthase [eNOS] and nitric oxide [NO]) determine the cellular internal signaling and vascular responses (2,6–8) (Figure 2). Chronic insults of any type induce the inflammatory, oxidative stress, and immune responses, which become dysregulated and produce damage to the vascular system. In this scenario, the blood vessel becomes an "innocent bystander" to the pathogenic mechanisms, which eventually leads to functional and structural cardiovascular injury with CHD (2). Numerous scientifically validated nutritional or dietary components and nutraceutical supplements have great promise to reduce the vascular damage (4,8). These are discussed in detail in the treatment section.

Atherosclerosis and endothelial dysfunction

Atherosclerosis and endothelial dysfunction (the earliest vascular abnormality) are postprandial diseases that begin early in life (9–12) (Figure 3). The consumption of excessive sodium chloride (NaCl), refined carbohydrates (CHO), sugars, starches, trans fatty acids (TFA), and some, but not all, saturated fatty acids (SFA) will promote glucotoxicity, triglyceride toxicity, vascular metabolic endotoxemia, inflammation, oxidative stress, and vascular immune dysfunction that may persist long after the initial insult. This may also result in an exaggerated response (metabolic memory) with repeated or chronic nutritional insults, (6,9–12).

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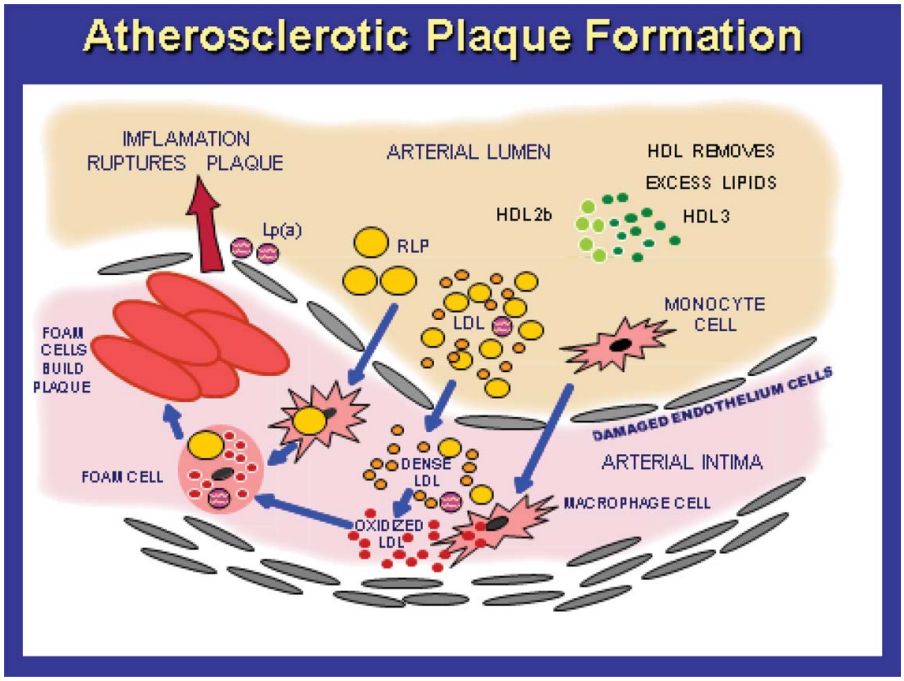

Figure 1. The pathogenesis atherosclerotic plaque formation.

Nutrition and CHD

Targeted nutrition in combination with other lifestyle changes is a foundational recommendation for the reduction of CHD. National and international nutritional guidelines are still evolving as new science and nutrigenomic studies are published. There are many recent clinical trials that provide new information in this quest to improve CHD outcomes related to nutrition (13,14) (Table 1).

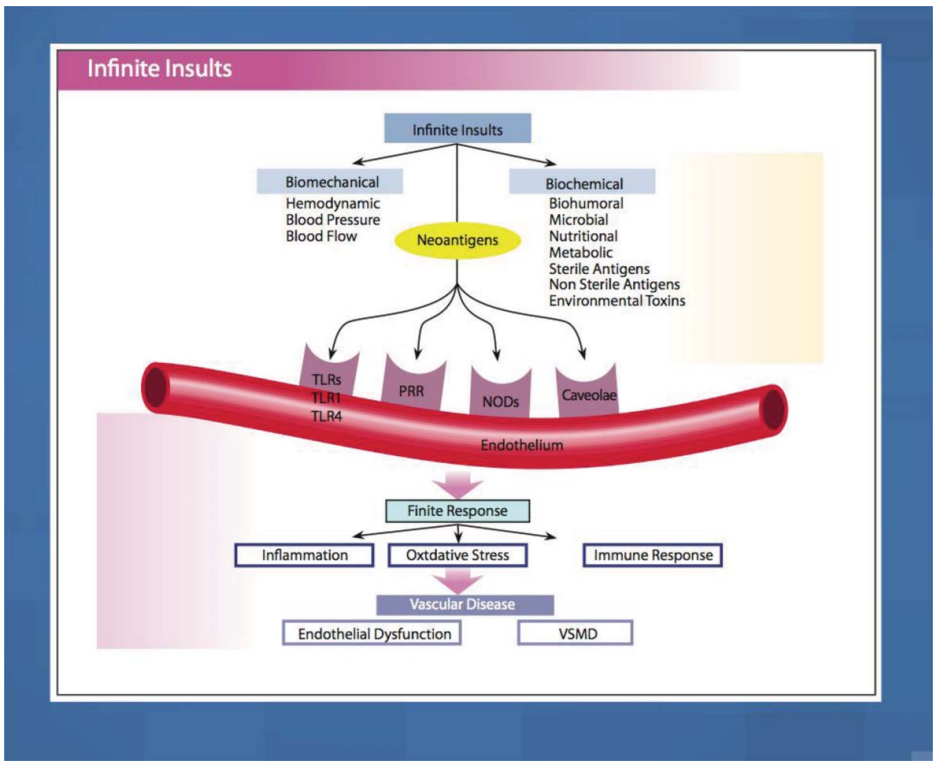

Figure 2. Biochemical and biomechanical insults that interact with vascular receptors (pattern recognition receptors, PRR, NOD-like receptors [NLR], toll-like receptors [TLR], and caveolae) to induce the three finite responses of vascular inflammation, oxidative stress, and vascular immune dysfunction, which lead to endothelial dysfunction and VSM and cardiac dysfunction.

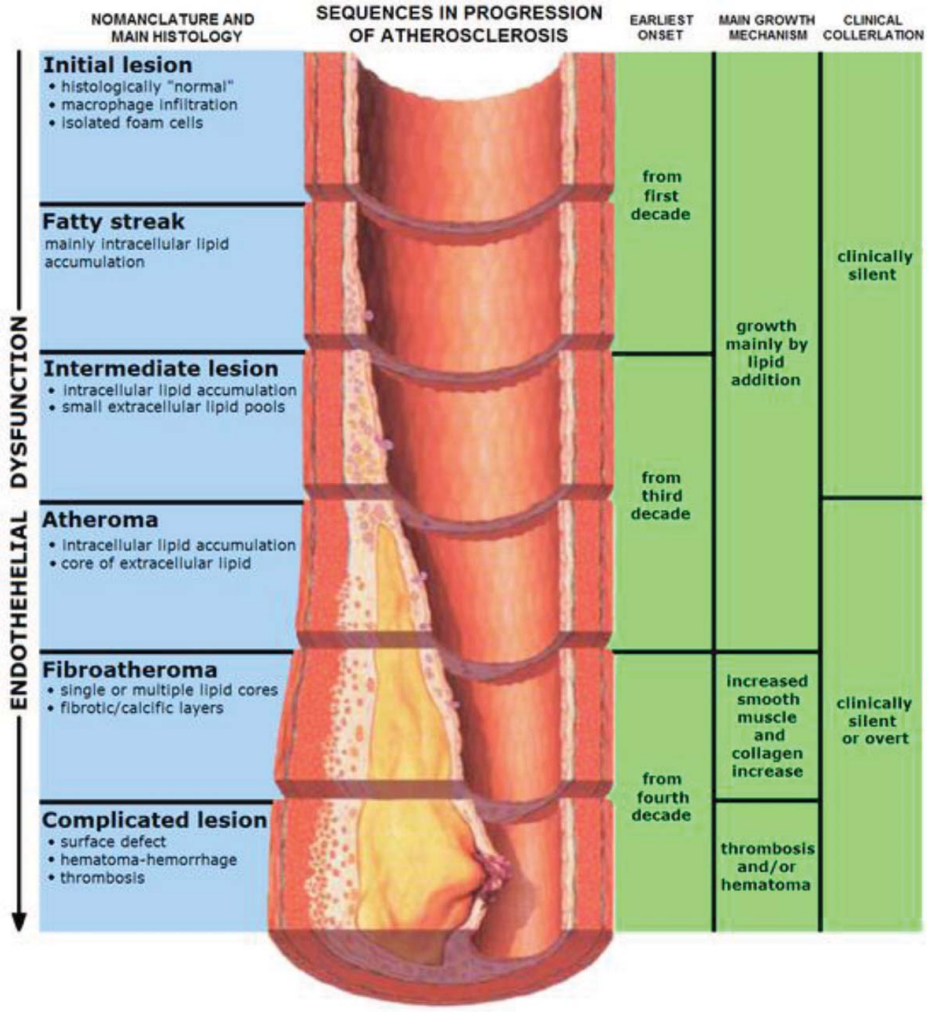

Figure 3. Atherosclerosis progression. The initial lesion progresses to a fatty streak, then intermediate lesion, atheroma, fibroatheroma (a complicated lesion prone to rupture), and thrombosis

Specific diets and coronary heart disease

Mediterranean diet (TMD: Traditional Mediterranean diet)

In the 4.8-year primary prevention (PREDIMED diet), the rates of major cardiovascular events from myocardial infarction (MI), cerebrovascular accidents (CVA), or total cardiovascular (CV) deaths were reduced by 28% with nuts and 30% with extra-virgin olive oil (EVOO) (16). The reduction in CVA was 39% overall ($p < 0.003$), with a 33% reduction from EVOO and a 46% reduction from nuts. The reduction in MI was 23% overall ($p = 0.25$), with a 20% reduction with EVOO and a 26% reduction from nuts. Total CV deaths were reduced by 17% ($p = 0.8$) (15–18). New onset type 2 diabetes mellitus (T2DM) was decreased by 40% with EVOO and 18% with mixed nuts (18). This reduction was associated with decreases in high-sensitivity C-reactive protein (HSCRP) and interleukin (IL-6).

The high content of nitrate (NO_3) that is converted to nitrite (NO_2) (average of 400 mg per day), the increased amounts of omega-3 fatty acids, good omega-6 fatty acids, and polyphenols such as quercetin, resveratrol, and catechins, in grapes and wine, provide many of the beneficial outcomes in CHD (17). Secondary prevention post MI in the Lyon Heart study (19) demonstrated significant reductions in all events including cardiac death, nonfatal MI, unstable angina, CVA, congestive heart failure (CHF), and hospitalization at 4 years using the Mediterranean style diet supplemented with alpha-linolenic acid (ALA) compared to a prudent Western diet. Compared to the control, the Mediterranean-style diet with ALA demonstrated a 73% lower risk of cardiac death and nonfatal MI during the study period (19). Olive oil was associated with a decreased risk of overall mortality and a significant reduction in CVD mortality in a large Mediterranean cohort of 40,622 subjects (20). For each increase in olive oil by 10 grams there was a 13% decrease in CV mortality. In the highest quartile of olive oil intake, there was a 44% decrease in CV mortality (20).

One of the mechanisms by which the TMD, particularly if supplemented with extra-virgin olive oil at 50 grams per day, can exert CV health benefits is through changes in the transcriptomic response of genes related to cardiovascular risk that include genes for atherosclerosis, inflammation, oxidative stress vascular immune dysfunction, T2DM, and hypertension (16,17,21–23). This includes genes such as ADR-B2 (adrenergic beta 2 receptor),

Table 1. Summary of Nutrition, Nutrients, and Daily Intake.

Nutrient	Daily intake
Diets that benefit cardiovascular health:	
Mediterranean diet and MD + ALA	
DASH 1 and 2	
Vegetarian diet	
• Potential for nutrient deficiencies, including vitamin B12, vitamin D, omega-3 fatty acids, iron, calcium, carnitine, zinc, and protein	
Paleolithic diet	
Caloric restriction and intermittent fasting	
Low AGEs	
Alkaline diet	
• No definitive results but appears in line with DASH and TMD	
Fats:	Less than 35% total caloric intake
SFA	< 7%–9% of total diet
• LCFA and MCFA have variable effects, with LCFA having a higher risk; SCFA are neutral	Replace with PUFA or MUFA
Coconut oil	
• No recommendation for prevention or treatment of CHD or CVD, but it is a possible substitute for high glycemic carbohydrates in low amounts	
Trans fat	Avoid trans fat
PUFA:	Omega-3 to omega-6 ratio at 4:1
Omega-3 fatty acids	>1 gram of EPA + DHA per day
• Opt for balanced formulation with DHA, EPA, GLA, and gamma-delta tocopherols	1.1 gram/day for women 1.6 gram/day for men ~2% total daily calories
MUFA (178):	50 grams/day
Extra virgin olive oil	
Diet elements:	
Animal protein	
• Avoid processed red meat	
• Aim for lean cuts	
Fish	1–2 servings/week
• Choose fish with high omega-3 content and low mercury levels	20 grams/day
Nuts	>5 servings/week; 28 grams/day
Vegetables and fruits	200–800 grams/day
• Dark leafy greens have the strongest effect on CHD risk	
Milk and milk products	
• Intake has an inverse association with CVD	
Eggs	*6–12 eggs per week as part of a healthy cardiovascular diet*
• No association with increased risk, except possibly for diabetics	
Special recommendation for diabetics	
Refined carbohydrates, sugar, and sugar substitutes	Reduce or eliminate from diet
Alcohol	1–2 drinks/day for women 2–4 drinks/day for men
Isolated nutrients and neutraceutical supplements	
Curcumin	
Cinnamaldehyde (cinnamon)	
Sulforaphane (broccoli)	
Resveratrol	
Luteolin	
Quercetin	
Caffeine:	Caffeinated coffee for
• Different effect on fast metabolizers compared to slow metabolizers	slow metabolizers: 59 and younger <2–3 cups Older than 59 <1 cup
Soy protein	15 to 30 grams/day
Whey protein	20 grams/day
Gluten	
• No link even in those with celiac disease	
• Choose 100% whole grains	
Sodium	Low sodium to potassium ratio
Potassium	4.7 grams/day, preferably from food
Magnesium	

IL7R (interleukin 7 receptor), IFN gamma (interferon), MCP1 (monocyte chemotactic protein), TNFα (tumor necrosis factor alpha), interleukin 6 (IL-6), and hsCRP (high-sensitivity C-reactive protein (16,17,20–23). In summary, the TMD has been shown to have the following effects (15–17,21–23):

- Lowers blood pressure.
- Improves serum lipids: lowers total cholesterol (TC), low-density lipoprotein (LDL), triglycerides (TG), increases high-density lipoprotein (HDL), and lowers oxidized LDL (oxLDL) and lipoprotein a (Lpa). In addition, the TMD improves LDL size and decreases the LDL particle number (LDL P) to a less atherogenic profile.

- Improves T2DM and dysglycemia.
- Improves oxidative defense and reduces oxidative stress: F-2 isoprostanes and 8-oxo-2′-deoxyguanosine (8OHDG)
- Reduces inflammation: lowers hsCRP, IL6, soluble vascular cell adhesion molecule (sl-VCAM,) and soluble cell adhesion molecule (sI-CAM).
- Reduces thrombosis and factor VII after meals.
- Decreases brain natriuretic peptide (BNP).
- Increases nitrates/nitrites.
- Improves membrane fluidity.
- Reduces MI, CHD, and CVA.
- Reduces homocysteine.

Dietary approaches to stop hypertension (DASH) diets (DASH 1 and 2)

The DASH diets reduce blood pressure (BP) and CHD. Both DASH 1 and DASH 2 diets emphasize increased daily intake of fruits, vegetables, whole grains, beans, fiber, low-fat dairy products, poultry, fish, and seeds and nuts, but limiting red meat, sweets, and sugar-containing beverages. The intake of potassium, magnesium, and calcium is increased but with a variable restriction in dietary sodium (24,25). The DASH diets evaluated borderline or stage 1 hypertension (<160/80–95 mm Hg) in 379 subjects who were drug free over 8 weeks. A control diet was prescribed for 3 weeks and then the study subjects were randomized to the control diet, a fruit and vegetable diet with 8 and 5 servings, or a combined fruit and vegetable diet with 10 servings and low fat dairy. The contents of sodium, potassium, magnesium, calcium, and fiber were the same in the 2 diets. The control diet had less potassium, magnesium, and calcium by 50%, less fiber by 22 grams, and only 4 servings of fruit and vegetables but was otherwise the same as the other. Both DASH diets reduced blood pressure within 4 weeks by approximately 10/5 mm Hg. The blood pressure remained stable as long as there was good adherence to the diets. The results of the various types of DASH I and DASH II diets are:

1. DASH I overall combination diet vs control diet: 5/3 mm Hg.
2. DASH I hypertensive patients. Combination diet vs control diet: 10.7/5.2 mm Hg.
3. DASH II overall combination vs low-sodium DASH diet: 8.9/ 4.5 mmHg vs control high-sodium diet.
4. DASH II hypertensive patients. Combination low-sodium DASH 11.5/6.8 mmHg.in the diet vs control high-sodium diet.

Limiting refined carbohyrates, despite an increased dietary saturated fatty acids (SFA), improves the lipid profile with both of the DASH diets

The DASH diets are as effective in BP reduction as one antihypertensive medication and also decrease hsCRP and serum lipids. In the Nurses' Health Study (NHS), adherence to the DASH dietary pattern was associated with a lower risk of CHD by 14% in those with the highest adherence to the diet (26). The effect of DASH-like diets that provided different amounts of protein from lean beef was evaluated in a recent clinical trial (26A). The diets that were included were DASH 28 grams of beef/day; beef in an optimal lean diet (BOLD) 113 grams of beef/day; and beef in an optimal lean diet plus additional protein (BOLD+) 153 grams of beef/day. During a 5-week randomized, crossover study design, 36 normotensive participants (SBP, 116 ± 3.6 mm Hg) were fed four isocaloric diets: HAD (33% total fat, 12% saturated fatty acids (SFA),17% protein (PRO), 20 g beef/day), DASH (27% total fat, 6% SFA, 18% PRO, 28 g beef/day), BOLD (28% total fat, 6% SFA, 19% PRO, 113 g beef/ day), and BOLD+ (28% total fat, 6% SFA, 27% PRO, 153 g beef/ day). SBP decreased ($p < 0.05$) in subjects on the BOLD+ diet (111.4 ± 1.9 mm Hg) versus HAD (115.7 ± 1.9). There were no significant effects of the DASH and BOLD diets on SBP. Augmentation index (AI) was significantly reduced in subjects on the BOLD diet (–4.1%). There were no significant effects of the diets on DBP or endothelial function (as measured by peripheral arterial tonometry). A moderate protein DASH-like diet including lean beef decreased SBP in normotensive individuals (26A).

The DASH diets provide various mechanisms for the improvement in all the cardiovascular risk factors and CHD risk including:

1. Increased nitric oxide and increased plasma nitrate.
2. Natriuresis.
3. Decrease oxidative stress and increased oxidative defense.
4. Reduced urinary F2-isoprostanes.
5. Improved endothelial function.
6. Decreased pulse wave velocity (PWV) and augmentation index (AI) with reduced arterial stiffness.

Dietary fats

Omega 3 fatty acids (PUFA)

The role of fats in CHD has been evaluated in numerous clinical trials (27–74). A large meta-analysis of omega-3 FA (30) reviewed 18 randomized controlled trials (RCTs) (93,000 subjects) and 16 prospective cohort studies (732,000 subjects) and examined EPA + DHA (eicosapentaenoic acid and docosahexaenoic acid) from foods or supplements and the relationship to CHD, MI, sudden cardiac death, coronary death, and angina in primary and secondary prevention. Among RCTs, there was a non-statistically significant 6% reduction in CHD risk with EPA + DHA. Subgroup analyses of data from RCTs indicated a statistically significant 14 % to 16% CHD risk reduction with EPA + DHA among higher risk populations including participants with elevated triglyceride levels over 150 mg/dL and elevated low-density lipoprotein cholesterol above 130 mg/dL. Meta-analysis of data from prospective cohort studies resulted in 18% significant reduction of CHD for higher intakes of EPA + DHA over 1 gram per day and risk of any CHD event. The sudden cardiac death (SCD) rate was reduced 47%. The greatest reduction in CHD (25%) occurred in those with high TG of more than 150 mg/dL and doses of omega 3 FA of more than 1 gram per day. These results and others indicate that EPA + DHA may be associated with a reduction in CHD risk, with the greatest benefit observed among higher risk populations in RCTs and those taking higher doses of EPA and DHA. Omega-3 FA reduce ventricular arrhythmias (60) and decrease cardiovascular and total mortality (61). Omega 3 FA are typically found in cold-water fish such as salmon, mackerel, and others,

as well as plant-based products like algae, flax, chia, and hemp seeds, but as fatty fish eat algae, they serve as a supply for these essential fats. Omega 3 fatty acids decrease MI and CHD 18% more with concomitant use of statins (64), reduce stent restenosis (62), reduce post MI mortality (65) coronary artery bypass graft (CABG occlusion) (66,67), plaque formation (68,69), coronary artery calcification (68,69), and atherosclerosis (68,69), improve the lipid profile (10,70), lower glucose, improve insulin resistance (71–73), and reduce blood pressure (2,4,11,74). The dose prescribed will depend on the condition being treated, as well as age, body weight, and use of concomitant medications and other nutritional supplements. It is best to use a balanced formulation with DHA, EPA, gamma linolenic acid (GLA), and gamma-delta tocopherols. This will prevent oxidation in the cell membranes and reduce depletions of the EPA and DHA by GLA or vice versa (10,70,74).

Monounsaturated fats

The effects of *cis*-monounsaturated fatty acids (*cis*-MUFA) on the risk of CHD and on CHD mortality have not been firmly established (75). In addition, dietary recommendations for cis-MUFA from various organizations do not agree. The effects of cis-MUFA on serum lipids, lipoproteins and endothelial vascular function are favorable (75–77). There are no randomized controlled trials with CHD events as endpoints, but several large prospective cohort studies have been published on the relationship between cis-MUFA and CHD risk (15–18,43,52,76–78). Partial replacement of SFA with MUFA improves the blood lipid and lipoprotein profile and reduces the risk of CHD (76). The Nurses' Health Study and the Health Professionals Follow-up Study followed more than 84,000 patients for 24 to 30 years (52). Replacing 5% of energy from SFA with equivalent energy intake from MUFA was associated with a 15% lower risk of CHD (hazard ratio (HR): 0.85, 95% CI: 0.74 to 0.97; $p = 0.02$) (52). Isocaloric replacement of 1% energy from 12:0–18:0 SFA combined showed an HR of CHD for MUFA of 0.94 (0.91 to 0.97; $p < 0.001$), and for 16:0 the HR was .90 (0.83 to 0.97; $p = 0.01$) (43). A recent review of the literature of randomized controlled clinical trials that used a 4-step cost-of-illness analysis estimated the success rate, disease biomarker reduction, disease incidence reduction, and cost savings of incorporating MUFA into the diet (77). Improvements were seen in CHD biomarkers incidence of CHD and T2 DM, in addition to annualized health care and societal cost savings for the daily MUFA intake (77).

In the 4.8-year primary prevention (PREDIMED diet), the rates of major cardiovascular events from myocardial infarction (MI), cerebrovascular accidents (CVA), or total CV deaths were reduced by 28% with nuts and 30% with extra-virgin olive oil (EVOO) (16). In a prospective study of Dutch patients with cardiac disease (Alpha Omega Cohort) (78), the risk of CVD and CHD mortality was evaluated over 7 years and the sum of SFAs and TFAs was theoretically replaced by PUFAs or *cis*-MUFAs in a group of drug-treated patients with a history of myocardial infarction. In continuous analyses, replacement of SFAs and TFAs with MUFAs (per 5% of energy) was associated with significantly lower risks of CVD mortality (HR 0.75) and CHD mortality (HR 0.70) (78). Nutrition guidelines for dietary fats are now shifting to recommend higher intakes of MUFA such as EVOO and nuts (15–18,75–78).

Saturated fatty acids

Clinical trials offer conflicting conclusions regarding the role of SFA in the risk of CHD. This has led to confusion in the lay public that is exacerbated by recently published national best-sellers and conflicting nutrition recommendations by national and international committees (18,27,31–59). The source of the confusion lies within the complexity, accuracy, and the coordination of the results and conclusions in basic science, clinical epidemiology, and prospective clinical trials. Some of the misconceptions and improper interpretations are related to the source of the SFA, carbon length absorption, the replacement nutrient(s), the genotypic expression to dietary SFAs, metabolism, and the composition and chemical expressions within the microbiome (31–35).

SFA also have variable effects on serum lipids and lipid subfractions, hepatic LDL receptor activity, nonalcoholic liver disease (NAFLD), thrombosis, release of tissue plasminogen activator, macrophage foam cell formation and growth, toll-like receptors (TLR 2 and TLR 4) interactions, nuclear factor (NF-kB) cytokine gene expression, NADPH oxidase, detoxification of radical oxygen species (ROS), activity of catalase, glutathione peroxidase (GPx), superoxide dismutase (SOD 1), thioredoxin reductase (TxNRD1), and the genetic ability to desaturate SFA to monounsaturated fatty acids (MUFA) (31–41). Stearate (C-18) has minimal effect on CHD risk or serum lipids due to its rapid desaturation to MUFA by stearoyl-CoA Δ-9-desaturase (SCD), which is genetically determined (31–33). The dietary SFA intake may not correlate with the measured SFA content in serum cholesterol esters and erythrocytes, resulting in a discrepancy in the ability to accurately predict CHD risk based on the "real" SFA status of an individual (31,36–38). High SFA content in serum cholesterol esters and erythrocytes, not high SFA intake, more accurately predicts CHD risk (36). Endogenous SFA synthesis, especially that of palmitic acid (16:0) from carbohydrates, contributes to the SFA status. Increased dietary intake of refined carbohydrates with low dietary consumption of SFA spares SFA due to the de novo synthesis of SFA from refined carbohydrate. A diet with reduced carbohydrate intake allows SFA to be utilized directly for energy production. Long-chain fatty acids (LCFA) enhance gastrointestinal growth of gram-negative bacteria (GNB) and lipopolysaccharide (LPS) uptake, inflammation and immune activation of T-cells, which will increase gastrointestinal permeability, and the risk of endotoxemia and infection from a variety of pathobionts at a dysfunctional microbial–epithelial interface (31,36–40).

Published clinical trials and reviews have provided more accurate insights into the relationship of SFA and CHD (27,42–49). A meta-analysis of 32 trials with more than 600,000 subjects included 17 observational studies of fatty acid (FA) biomarkers, 32 observational studies of FA intake, and 27 randomized controlled clinical trials (RCCT) of FA supplementation (27). The results of this meta-analysis are at variance

with other studies, perhaps due to the heterogeneity of the populations, selection bias, quality of studies selected, self-reporting of diet, and other confounders due to unmeasured dietary factors and other lifestyle factors. Despite the size of this meta-analysis, the results and conclusions drawn need to be interpreted with caution.

The largest meta-analysis of three large cohort studies (Health Professionals Follow-Up Study [HPFS], the Nurses' Health Study [NHS 1], and the NHS-2), utilizing a 5% isocaloric (ISC) energy replacement of SFA with polyunsaturated fatty acids (PUFA) or vegetable fat, was associated with a 24% and 10% reduction in CHD risk, respectively (43). The reduction in CHD with ISC energy replacement of SFA with PUFA, monounsaturated (MUFA), trans fatty acids (TFA), omega-6 FA, whole grains, vegetable or plant proteins, refined carbohydrates, high-fructose corn syrup, or starches depends on the percent of energy that is substituted (43,44). Replacement of 1% of energy from SFAs with PUFAs lowers LDL cholesterol, which predicts a 2–8% reduction in CHD (43).

SFA intake and CHD were positively associated in the prospective, longitudinal cohort studies of more than 115,000 men and women in the HPFS and the NHS over a 34- to 38-year follow-up (44). SFAs were mostly lauric acid (12:0), myristic acid (14:0), palmitic acid (16:0), and stearic acid (18:0) at 9.0–11.3% of energy intake. Comparing the highest versus the lowest groups of individual SFA intakes, CHD increased 7% for 12:0, 13% for 14:0, 18% for 16:0, 18% for 18:0, and 18% for all 4 SFAs combined ($p = 0.05$ to 0.001). The reduction in CHD after 1% energy ISC replacement of SFA 12:0–18:0 was 8% for PUFA, 5% for MUFA, 6% for whole grains, and 7% for plant proteins (45).

The PREvención con DIeta MEDiterránea (PREDIMED) was a 6-year prospective study of 7038 subjects with a high CVD risk that included MI, CVA, or death from CV causes (48). The dietary consumption of SFA and TFA from the highest to the lowest quintiles increased overall CVD by 81% and 67%, respectively. The intake of PUFAs and MUFAs reduced the risk of CVD and death. The ISC replacement of SFAs or TFA with MUFAs and PUFAs reduced CVD (48). SFA from processed foods increased CVD (48).

Conclusions and summary on SFA (31–59)

SFA are diverse compounds cannot be "lumped" into a single category and have variable effects on CHD. It is prudent to replace long-chain fatty acids (LCFA) with PUFA, MUFA, short-chain fatty acids (SCFA) , whole grains, plant proteins, and perhaps medium-chain fatty acids (MCFA). The daily recommended grams per day or percent of SFA relative to total fat or total calories cannot be accurately determined at this time. Some studies suggest that the SFA dietary intake should be well below 9% of the total caloric intake. The overall relationship of the human diet to CHD should include the totality of our nutrition and avoid reductionist evaluations of single macronutrients. New nutritional guidelines should promote dietary patterns that improve CHD based on validated science. Refined carbohydrates, high-fructose corn syrup, starches, and TFA increase the risk of CHD. Omega-6 FA appear to be neutral or to improve CHD risk, whereas omega-3 FA (PUFA), MUFA, fermented foods, fiber, fruits, and vegetables and the PREDIMED diet reduce CHD and CVD.

Conclusions are:

1. Dietary SFA intake is associated with an increased CHD risk, and reducing dietary SFA in isocaloric (ISC) replacement with PUFA, MUFA, omega-6 FA, whole grains, and plant proteins decreases CHD risk.
2. The source of the SFA is associated with the risk for CHD. Dietary intake of meat and animal fat have the greatest risk with a range of 6%–48%.
3. LCFA are the most likely SFA associated with CHD risk. SCFA are not associated with CHD risk, but additional studies are needed to confirm this.
4. The carbon chain number of the SFA, as odd or even, may be associated with CHD risk.
5. Replacement of SFA with PUFA reduces CHD risk.
6. Replacement of SFA with MUFA reduces CHD risk
7. Replacement of SFA with omega-6 FA decreases CHD risk.
8. Replacement of SFA with refined CHO increases CHD risk.

Trans fatty acids

A study of 126,233 participants from the NHS and the HPFS analyzed the relationship between choices of dietary fats and overall mortality (79). During the follow-up, 33,304 deaths were documented. Dietary TFA had the most significant adverse impact on health. Every 2% higher intake of TFA was associated with a 16% higher chance of premature death and a 25% increase in CHD death and nonfatal MI during the study period (79). A panel of experts in cardiovascular nutrition recently reported on trending controversies and provided some recommendations regarding fat intake (80) The overall recommendations were to reduce omega-6 fatty acids, increase omega-3 fatty acids and the ratio of omega-3 to omega-6 fatty acids, and reduce SFA, in addition to the elimination of TFA. The cardiovascular adverse effects of industrialized produced TFAs are shown here (81,82):

1. Dyslipidemia
   a. Increase TC 8%.
   b. Increase LDL-C9%.
   c. Increase TG and VLDL 9%.
   d. Lower HDL-C 2%–3%.
   e. Increase TC/HDL ratio 11%.
   f. Increase apolipoprotein B 8%.
   g. Increase lipoprotein (a) (Lp(a)) 4%.
2. Increase in adipose tissue TFA levels.
3. Increase in TG and phospholipid TFA levels.
4. Increase insulin resistance, glucose, and T2DM risk.
5. Increase thrombogenic risk and plaque vulnerability.
6. Increase risk of CHD and MI.
7. Increase risk of primary cardiac arrhythmias and sudden death.
8. Increase in all-cause mortality by 25% from lowest to highest quintile.
9. Increase of 2% in energy in total TFA intake results in 25% increase in CHD (CHD death and nonfatal MI).
10. Hypertension.

11. Endothelial dysfunction.
12. Obesity.
13. Increased inflammation.

Coconut oil

Coconut oil has been inappropriately promoted for a reduction in CHD and other CV events, with no evidence to support it in human clinical trials. In a meta-analysis of 21 studies with 8 clinical trials and 13 observational studies, coconut oil increased TC and LDL more than PUFA, but less than butter, increased HDL, and increased TG, with no change in TC/HDL ratio. There was no change in CV events (83–85). Coconut oil is 92% SFA, mostly lauric acid C12:0 (MCFA) and myrisitc acid (C14:0), which acts mostly like an LCFA. MCFA have rapid absorption, hepatic uptake, and immediate oxidation for energy production (84). Both lauric and myristic acid increase LDL-C similar to other MCFA and LCFA, but increase HDL-C more (85). MCT (medium-chain triglycerides) that are C-10 or less have direct portal vein absorption and are more water soluble. Only 4% of coconut oil is MCT of C-10 or less fatty acids. Coconut oil should not be recommended at this time for prevention or treatment of CHD or CVD due to the lack of prospective studies on CV outcomes, the mixed effects on serum lipids, the content of LCFA, and the fact that replacement of coconut oil with PUFA and MUFA reduces CHD risk.

Milk, milk products, and peptides

Recent clinical studies indicate that milk, milk peptides, and milk products reduce blood pressure, CHD, DM, CVA, and atherosclerosis (86–88). In a recent meta-analysis of 27 studies there was an inverse association between total dairy intake and CVD (RR = 0.90, 95% CI: 0.81–0.99), while no association was observed between total dairy intake and CHD (87). Milk and milk products improve insulin resistance, improve postprandial hyperglycemia, lower BP, increase nitric oxide, improve endothelial function, and decrease inflammation and oxidative stress (86,88). All of these effects may reduce the risk of CHD (86–88). Milk proteins, both caseins and whey proteins, and buttermilk with MFGM (milk fat globule membrane) are a rich sources of angiotensin-converting enzyme (ACE) inhibitory peptides that significantly reduce blood pressure (86–88). Val-Pro-Pro (VPP) and Ile-Pro-Pro (IPP) from *Lactobacillus helveticus* in fermented milk given at 12 grams per day reduces blood pressure about 11.2/6.5 mm Hg. The pooled data from the meta-analysis indicate an average reduction in blood pressure of 4.8/2.2 mm Hg with milk peptides (86–88).

Whey protein

Several studies show that chronic intake of several grams (typically 20 grams) of whey protein significantly reduces blood pressure (89–92), decreases TG and cholesterol levels (93), and lowers inflammation in patients with CVD (94,95). These benefits may come from chronic consumption rather than a single dose (96). The type of whey protein may impact results. Clinical trial data indicate that whey protein must be hydrolyzed to ACE inhibitor peptides for it to have antihypertensive properties (97–101). In addition, certain whey protein preparations may result in a relatively higher insulin response relative to other protein sources (102,103), which may or may not be beneficial in some patient populations.

Eggs

The effect of eggs on serum cholesterol and CHD risk has been a contentious argument over the past few decades, but recent studies have provided scientific guidance. A retrospective review of 17 studies with 556 subjects found that for each 100 mg of dietary cholesterol per day in eggs, the total cholesterol (TC) increased 2.2 mg%, low-density cholesterol (LDL-C) increased 1.9 mg%, high-density cholesterol (HDL-C) increased 0.3 mg%, and the TC/HDL ratio increased 0.2 units (104). A 50-gram egg contains about 200 mg of cholesterol, 6 grams of protein, and 5 grams of fat (36% SFA, 48% MUFA, and 16 % PUFA) (104).

Subjects with metabolic syndrome or type 2 diabetes mellitus (T2DM) consuming 3 whole eggs per day on a carbohydrate-restricted diet of less than 30% energy compared to an egg substitute had reductions in tumor necrosis alpha TNF alpha and triglycerides (TG), increases in HDL-C with no change in TC, LDL, or other inflammatory markers, and a lower risk T2DM or its progression (105,106). In the HPS and NHS studies with almost 18,000 subjects followed for 8–14 years there was no evidence of any significant association between egg consumption and risk for CHD with the possible exception of T2DM (107). However, in another study, egg consumption was not associated with any CVD outcome in individuals with T2DM (108). In a prospective cohort study over 13 years of 37,766 men (Cohort of Swedish Men) and 32,805 women (Swedish Mammography Cohort) who were free of CVD, egg consumption was assessed at baseline with a food-frequency questionnaire (108). There was no statistically significant association between egg consumption and risk of myocardial infarction (MI) in either men or women. In the Kuopio Ischaemic Heart Disease Risk Factor Study of 1032 men, egg or cholesterol intakes were not associated with increased CHD risk, even in ApoE4 carriers (109). A meta-analysis of 22 independent cohorts from 16 studies, including participants ranging in number from 1600 to 90,735 and a follow-up time from 5.8 to 20.0 years, evaluated the role of egg consumption on CHD risk (110). Comparison of the highest category (≥1 egg/d) of egg consumption with the lowest (<1 egg/week or none) resulted in a pooled hazard ratio (HR) of 0.96 (0.88, 1.05) for overall CVD, 0.97 (0.86, 1.09) for ischemic heart disease, and for ischemic heart disease mortality the HR was 0.98 (0.77, 1.24). A more recent meta-analysis concluded that consumption of up to one egg daily does not appear to be associated with the risk of CHD (110A). These meta analyses suggest that egg consumption is not associated with the risk of CVD and cardiac mortality in the general population. However, egg consumption may be associated with an increased incidence of T2DM among the general population and CVD comorbidity among diabetic patients of up to 42% for CHD mortality. Nevertheless, results

from randomized controlled trials suggest that consumption of 6 to 12 eggs per week, in the context of a diet that is consistent with guidelines on cardiovascular health promotion, has no adverse effect on major CHD risk factors in individuals at risk for developing diabetes or in those with T2DM. However, heterogeneities in study design, population included, and interventions prevent firm conclusions from being drawn.

Refined carbohydrates, sugars, and sugar substitutes

Refined carbohydrates are associated with an increased risk of CHD in prospective clinical trials and cohort studies (31,52,111–113). Sugars, refined carbohydrates, high-fructose corn syrup (HFCS), and starches confer significant risk for dyslipidemia, nonalcoholic fatty liver disease (NAFLD), and CHD compared to omega-3 FA, MUFA, fermented foods, fiber, fruits and vegetables, dairy, and the TMD and DASH 2 diets (113) A prospective study of 117,366 Chinese women and men (40–74 years of age) without history of diabetes, CHD, or stroke examined intakes of carbohydrates and staple grains, glycemic index, and glycemic load in relation to CHD using validated food frequency questionnaires over a median of 7.6 years (111). Carbohydrate intake (70% from white rice and 17% from refined wheat products) accounted for about 68% of the total energy intake. Carbohydrate intake and CHD were highly associated with hazard ratios for the lowest to highest quartiles of carbohydrate intake, respectively, which were 1.00, 1.38, 2.03, and 2.88 (95% confidence interval: 1.44, 5.78; p for trend = 0.001). The combined hazard ratios comparing the highest quartile with the lowest were 1.80 (95% confidence interval: 1.01, 3.17) for refined grains and 1.87 (95% confidence interval: 1.00, 3.53) for glycemic load (both p for trend = 0.03). Prior to this Chinese study, Keller at al. (112) performed a review of intervention and longitudinal studies on the intake of sugar-sweetened beverages related to changes in blood pressure, lipids, glucose, or CVD events such as stroke or myocardial infarction. Two of four prospective studies noted direct associations between sugar-sweetened beverages consumption and CHD. All included studies examining vascular risk factors found direct associations between sugar-sweetened consumption and change in blood pressure, lipids, and glucose (112). In the NHS and HPFUS, carbohyrates from refined starches and added sugars were positively associated with the risk of CHD (HR;1.10, 95% CI:1.00 to 2.1; p trend = 0.04) (52). Replacing SFA with carbohydrates from refined starches and added sugars was not significantly associated with CHD risk ($p > 0.10$) (52). The National Health and Nutrition Examination Survey (NHANES, 1988–1994 [III], 1999–2004, 2005–2010) evaluated the association of added sugar intake with CVD mortality during a median follow-up period of 14.6 years (112A). Age-, sex-, and race/ethnicity-adjusted HRs of CVD mortality across quintiles of the percentage of daily calories consumed from added sugar were 1.00 (reference), 1.09 (95% CI, 1.05–1.13), 1.23 (1.12–1.34), 1.49 (1.24–1.78), and 2.43 (1.63–3.62; $p < .001$), respectively. Adjusted HRs were 1.30 (95% CI, 1.09–1.55) and 2.75 (1.40–5.42; $p = .004$), respectively, comparing participants who consumed 10.0% to 24.9% or 25.0% or more calories from added sugar with those who consumed less than 10.0% of calories from added sugar (112A).

In a population-based cohort study of 39,786 subjects older than 18 years, daily diet soft drink consumption increased the risk of total CVA by 21% and the risk of all vascular events by 43%, which includes ischemic CVA, CHD, MI, and vascular death (114). The Japan Public Health Center study showed both sugar-sweetened and low-calorie sodas significantly increased the risk of stroke by 16% per one serving a day and CHD by 20% per one serving a day (115). Sugar substitutes increase the risk for obesity, weight gain, metabolic syndrome, T2DM, and CHD. The sugar substitutes interfere with learned responses that normally contribute to glucose and energy homeostasis, negatively alter the microbiome, alter leptin levels, and decrease satiety (116,117).

Advanced glycation end products (AGEs)

Food preparation needs to be discussed in relationship to nutrition and cardiovascular health. Advanced glycation end products (AGEs) are a group of oxidant and inflammatory compounds known to play a role in the pathogenesis of chronic diseases including CVD. They are formed during what is known as the Maillard reaction when reducing sugars and free amino groups of proteins, lipids, or nucleic acids come together through metabolism in cooking in the presence of heat. Several modern cooking methods, including industrial heat processing, grilling, broiling, roasting, searing, and frying, significantly increase dietary AGE formation and exposure (118). A low-AGE diet may decrease endogenously circulating AGE levels, impair endothelial function, lower inflammatory mediators, and reduce atherosclerosis development (119,120). A 6-week human intervention study in diabetics fed a low-AGE diet demonstrated a marked reduction in inflammation and oxidative stress compared to a standard diet (121). Dietary intake of AGEs can be reduced by avoiding foods known to be high in AGEs such as full-fat cheeses, meats, and highly processed foods, while increasing the consumption of fish, grains, low-fat milk products, fruits, and vegetables. Boiling, poaching, and stewing, as well as steaming and slower cooking at a lower heat, can reduce dietary AGE exposure (118).

Protein

Vegetarian diets and plant-based nutrition

Vegetarian diets significantly reduce CVD, CHD, and the coronary artery calcium score (CAC) that is proportional to the dietary intake (112–125). In the European Prospective Investigation into Cancer and Nutrition (EPIC) Study of 44,561 subjects in England and Scotland followed for 11.6 years, the body mass index (BMI), lipids, and blood pressure were all reduced in the vegetarian group and there was a 32% lower incidence of CHD after adjustment for other CHD risk factors (122). A study of 96,469 Seventh-Day Adventist men and women from 2002–2007 demonstrated a 12% decrease in total mortality, 15% in vegans, 9% in lacto-ovo vegetarians, 19% in pesco-vegetarians, and 8% in semi-vegetarians, which was primarily related to decreases in CVD (123). The CAC is also reduced with chronic dietary intake of fruits and vegetables (124).

A meta-analysis of nine cohort studies of 222,081 men and women found the overall reduction in CHD risk was 4% for each additional portion of fruit and vegetable intake per day ($p = 0.0027$) and 7% for each additional serving of fruit ($p = 0.0001$) (125). The association between vegetable intake and CHD risk was heterogeneous ($p = 0.0043$), more marked for cardiovascular mortality (0.74, $p < 0.0001$) than for fatal and nonfatal MI (0.95, $p = 0.0058$) (125). Dark green leafy vegetables had the most dramatic reduction in CHD risk. In a meta-analysis of 95 studies, for fruits and vegetables combined, the overall relative risk (RR) per 200 grams/day was 0.92 (95% confidence interval [CI]: 0.90–0.94) for coronary heart disease 0.84 (95% CI: 0.76–0.92), and for cardiovascular disease 0.97 (95% CI: 0.95–0.99) Similar associations were observed for fruits and vegetables separately. Reductions in risk were observed for up to 800 grams/day for all outcomes. Inverse associations were observed between CHD risk and the intake of apples and pears, citrus fruits, green leafy vegetables, cruciferous vegetables, and salads (126). Some vegetarian diets may be deficient in many nutrients and require supplemental B12, vitamin D, omega-3 fatty acids, iron, calcium, carnitine, zinc, and some high-quality amino acids and protein (127). Other studies suggest several other problems such as decreased sulfur amino acid intake with a low elemental sulfur, increased homocysteine and oxidative stress, and lower cysteine (33% of controls) and glutathione (63% of controls). In addition, lean muscle mass was 10% lower and there may be an increased risk of subclinical malnutrition and CVD (127).

Animal-protein diets

Recent studies show either no correlation or an inverse correlation of grass-fed beef, wild game, organically fed animals, and other sources of protein with CHD (128–133). The Paleolithic diet has also shown reductions in total mortality of 23% and CV mortality of 22% in a cohort study of 21,423 subjects (128). All meat (including red meat, fish, seafood, poultry) had an inverse relationship to CVD mortality in men in Asian countries (130). Other meta-analysis showed no association between red meat consumption and CHD but found that processed red meat increased risk of hypertension, total mortality, CHD, and T2DM risk (128–133). A recently published study of more than half a million subjects answering food questionnaires that were followed for 16 years did identify a significant association between all forms of red meat consumption, all-cause mortality, and cardiovascular mortality (https://www.ncbi.nlm.nih.gov/pubmed/28487287). In the BOLD (Beef in an Optimal Lean Diet Study) trial, a low dietary SFA intake heart healthy diet containing lean beef elicits a favorable effect on CHD, serum lipids, and lipoproteins that is comparable to the DASH diet (129). This may be related to certain amino acids in meat vs vegetables, such as the lysine and arginine content.

Soy protein

A meta-analysis by Anderson and Bush (134) found that soy protein intake at 15 to 30 grams daily had favorable impacts on LDL cholesterol, HDL cholesterol, and TG compared with non-soy controls. Data indicate that soy protein reduces LDL cholesterol and increases HDL cholesterol compared with milk protein (135) Despite the positive studies, there has been debate about the inclusion of soy protein in the diet and whether the health claim on soy protein and heart health should be reconsidered (136,137). Most likely, the variability in results may also be due to the heterogeneity of available soy products and their degree of processing, resulting in a variety of by-products formed such as fermentation complexes.

Fish

Studies largely support fish consumption for cardiovascular health (138–153). Park et al. (138) found that eating fish 1–2 times weekly, especially higher omega-3 fatty acid-containing fish, reduces risk of coronary death by 36% and total mortality by 17%. They advised eating a variety of seafood with limited intake of high mercury-containing fish with greater fish consumption (≥5 servings/week). Meta-analysis findings confirmed positive results for heart health and fish consumption: Li et al. (140) reported that fish intake reduces the risk of congestive heart failure by 6% for each 20 grams of daily fish. Chowdhury et al. (142) identified a similar, yet moderate, inverse association between fish consumption and cerebrovascular risk. Gender differences may also be responsible, as a large prospective trial with 20,069 men and women followed over 8–13 years (143) found that increased fish intakes were associated with reduced stroke incidence in women while that same association was absent for men. Active ingredients in bonito and other cold-water fish may contribute to their cardioprotective qualities, such as the presence of ACE inhibitory peptides (144–146). Intake of sardine muscle protein, which contains valyl–tyrosine (Val–Tyr), by mildly hypertensive volunteers led to 9.7/5.3 mm Hg reduction in blood pressure in 1 week (147).

It is important to consider the type of fish and their relative methylmercury levels, as well as the degree to which individuals can transport mercury based on polymorphisms for the metallothionein protein (148). Methylmercury has detrimental effects that increase the risk of CHD, myocardial infarction, and hypertension (149–152). However, the benefits of fish consumption likely outweigh the risks from the potential toxins it contains (153).

Dietary acid load and protein

Diet-induced "low-grade" metabolic acidosis is thought to play an important role in the development of cardiovascular disease, hypertension, dyslipidemia, and obesity (154,155). Vegetables, fruits, and alkali-rich beverages (red wine and coffee) are considered alkaline, while fats and oils are neutral. Meats, especially red meat, has a high acid load but also dairy products and cereal grains are acid-producing (154,155). Dietary acid load can be improved by increasing intake of fruits and vegetables and decreasing excessively high dietary animal protein intake (156). A 10-day intervention with an alkaline Paleolithic-style diet led to a marked increase in potassium levels and improvements in vascular reactivity, blood pressure, glucose tolerance, insulin sensitivity, and lipid profiles (157). While the definitive effects of dietary acid load on cardiovascular health are not yet clear,

it is apparent that such dietary changes are in line with the DASH and TMD.

Specific dietary and nutritional components and caloric restriction

Several dietary and nutritional components have been shown to interrupt the inflammatory vascular receptors, such as pattern recognition receptors PRR, the nucleotide-binding oligomerization domain (NOD)-like receptors (NOD-like receptors, NLRs), NOD, and toll-like receptors (TLRs) (8). These include:

- Curcurmin (turmeric) blocks TLR 4, NOD 1, and NOD 2.
- Cinnamaldehyde (cinnamon) blocks TLR 4.
- Sulforaphane (broccoli) blocks TLR 4.
- Resveratrol (nutritional supplement, red wine, grapes) blocks TLR 1.
- Epigallocatechin gallate (EGCG) (green tea) blocks TLR 1.
- Luteolin (celery, green pepper, rosemary, carrots, oregano, oranges, olives) blocks TLR 1.
- Quercetin (tea, apples, onion, tomatoes, capers) blocks TLR 1.

These interactions between food groups or supplements with the vascular membrane receptors may initiate improved vascular responses, and decreased vascular inflammation, oxidative stress, and vascular immune responses that reduce CHD risk.

A prospective study of 42 subjects over 2 years showed a significant reduction in progression of CHD as assessed by coronary artery calcium (CAC) compared to historical controls using a phytonutrient concentrate containing a high content of fruit and vegetable extracts. The change in the CAC score was significantly less in the treated patients vs the control patients (19.6% vs 34.7% increase, respectively, $p < 0.009$), a 15.1% difference (158).

Caffeine

The cytochrome P-450–CYP1A2 genotype modifies the association between caffeinated coffee intake and the risk of hypertension, CVD, CHD, and MI in a linear relationship (159–166). Caffeine is exclusively metabolized by CYP1A2 to paraxanthine, theobromine, and theophylline (159). The gene lies on chromosome 15q24.1 and the SNP is rs7762551 A to C (159). The C SNP decreases enzymatic activity (159). Caffeine also blocks vasodilating adenosine receptors (166). The rapid metabolizers of caffeinated coffee IA/IA allele have average BP reduction of 10/7 mm Hg and reduce risk of MI by 17%–52% (164). This SNP represents about 40%–45% of the population (159–164). The slow metabolizers of caffeine IF/IF or IA/IF allele have higher BP of 8.1/5.7 mm Hg lasting >3 hours after consumption, tachycardia, increased aortic stiffness, higher pulse wave velocity, vascular inflammation, and increased catecholamines (159–164). Hypertension risk is increased (1.72 to 3.00 RR) (160). Based on age and consumption, the risk of MI will vary. At age 59 years there was a 36% increase in MI with 2–3 cups/day and a 64% increase with 4 cups/day or more. Under the age of 59 years, MI increased by 24% (1 cup/day), 67% (2 cups/day), and 233% (4 or more cups/day) (164,165). This SNP represents about 55–60% of the population.

Caloric restriction

Caloric restriction refers to reduction of energy intake at the individualized level that is sufficient to maintain a slightly low to normal body weight (i.e., body mass index < 21 kg/m^2) without causing malnutrition (167). Findings from long-term calorie restriction in animal models have revealed improvements in metabolic health, offsetting chronic disease and consequently extending life span (168).

Animal studies on caloric restriction have identified cardiovascular benefits, including reductions in oxidative stress and inflammation in the heart and vasculature, beneficial effects on endothelial function and arterial stiffness, protection against atherosclerosis, and less detrimental age-related changes in the heart (169). Limited evidence from human data suggests some of these effects translate to human caloric restriction (170). Alternate-day or intermittent fasting (ADF) is another similar approach with cardiovascular benefit. Typically, ADF involves consuming 25% of energy needs on the fast day and ad libitum food intake on the following day (171). Results indicate weight loss and improvements in cardiometabolic health such as reductions in aortic vascular smooth muscle cell proliferation, C-reactive protein, adiponectin, leptin, total cholesterol, LDL cholesterol, triacylglycerol concentrations, and systolic blood pressure and increases in LDL particle size in a relatively short time period (172). Caloric restriction could be implemented by constructing a personalized diet based on nutrient-dense, low-energy foods such as vegetables, fruits, whole grains, nuts, fish, low-fat dairy products, and lean meats (173).

Alcohol

The connection between alcohol consumption and CHD is based on a U-shaped curve such that overconsumption or underconsumption is not as likely to reduce CHD as the base of the U-shaped curved curve that is associated with the lowest risk of CHD (174–176). A drink in most research studies is 14 grams of ethanol or 0.6 fluid ounces of pure alcohol. This equates to a 12-ounce beer, a 5-ounce glass of table wine, or 1.5 ounces of hard liquor (174). “Light to moderate” drinking (defined as 1 drink/day for women, 2 drinks/day for men) is associated with lower rates of total mortality, CHD morbidity and mortality, diabetes mellitus, heart failure, and strokes, especially in people over 50 years of age (174–176). This was confirmed in an analysis of studies combining data on more than 1 million people and overall death rates, where the U-shaped curve was best at 1 to 2 drinks per day for women and 2 to 4 drinks per day for men (175). There are many beneficial effects of alcohol, including enhancing insulin action, raising HDL cholesterol, reducing inflammation, and improving arterial function. Red wine in particular is rich in polyphenols, with antioxidant, anti-inflammatory, and antiplatelet actions (174,175).

In a recent review and meta-analysis of alcohol consumption and cardiovascular disease, light to moderate alcohol

consumption (176) reduced the risk for CHD 29% and all-cause mortality was reduced by 13%. Pinot noir is generally credited with having the highest concentration of the potent polyphenol resveratrol, and the grape cannonau from the island of Sardinia, Italy, has been associated with the exceptional longevity in those communities (174–176).

Gluten

About 1% of the public has celiac disease and perhaps another 6–7% have verified gluten sensitivity with dramatic changes in the appearance of their gastrointestinal tract (177). A key consequence of the damage to the intestinal wall lining is that the normally tight junctions that bind cells lining the gastrointestinal (GI) tract become loose. When these junctions are loose, the contents of the GI tract can enter the wall of the bowels and then enter into the bloodstream. Many studies have shown that after a fatty meal, a wave of inflammation and endotoxins enter the bloodstream and may remain present for hours (6,9,10). When gliadin, a component of gluten-containing foods like bread, is present in the intestines of those with celiac or gluten sensitivity, a newly discovered protein called zonulin is released into the gut (177). Zonulin is now thought to have a potential role not only in celiac disease but also Type 1 diabetes, obesity, and other immune illnesses (177). Zonulin has been shown to be the "crowbar" that opens tight junctions and leads to autoimmune responses such as a leaky GI tract (177). The ability to measure blood levels of zonulin may revolutionize our understanding of GI, autoimmune, and other systemic diseases. A pharmaceutical molecule that is a zonulin blocker (AT-1001) is being developed to determine whether it can enable a patient with celiac disease to consume wheat products without damage.

There are few data linking gluten and CHD. In an analysis of patients who had suffered an MI in Sweden, those with celiac disease had outcomes similar to those without celiac disease (178). There are case reports of cardiomyopathy being associated with gluten sensitivities that respond to withdrawal foods (179). In another case report, a review of gluten antibodies and proven celiac disease was reported in 9 additional cases of cardiomyopathy (180).

Generally, 100% whole grains, as opposed to processed white-flour-based foods, are to be encouraged to patients with CHD. A meta-analysis that examined whole grain consumption and the risk of developing CHD and MI in more than 400,000 participants found that the highest consumption of whole grains reduced the risk by about 25% (181). The authors indicated that whole-grain foods contain fiber, vitamins, minerals, phytoestrogens, and phenolic compounds, and have a favorable effect on measures of cholesterol, blood glucose, inflammation, and arterial function. In a 26-year follow-up of 64,714 women in the NHS and 45,303 men in the HPFS, dietary gluten intake was not associated with risk of CHD (fatal or nonfatal MI) (182). After adjustment for known risk factors, participants in the highest fifth of estimated gluten intake had a multivariable hazard ratio for coronary heart disease of 0.95 (95% confidence interval 0.88 to 1.02; p for trend = 0.29). After additional adjustment for intake of whole grains the multivariate hazard ratio was 1.00 (0.92 to 1.09; p for trend = 0.77). In contrast, after additional adjustment for intake of refined grains the estimated gluten consumption was associated with a lower risk of coronary heart disease (multivariate hazard ratio 0.85, 0.77 to 0.93; p for trend = 0.002) (182).

Nuts

Nuts are high in MUFA and PUFA but may also contain some omega-6 FA. The beneficial effects of nut consumption on cardiovascular disease, CV deaths, CHD, and MI was well documented in the PrimiMED trial, with a reduction in total CV death of 28% with nut consumption (15–18). In the Adventist Health Study that examined obesity and metabolic syndrome in more than 800 people, there was a strong inverse relationship between tree nut consumption and developing both medical conditions (183). Other studies suggest that eating tree nuts does not lead to weight gain and the high concentration of fiber and nutrients offsets the calories consumed. Nuts may reduce CHD deaths and all-cause mortality as well (15–18,184). In a larger analysis of the Adventist Health Study, residents over age 84 years old and consuming nuts >5 times a week had a 20% reduction in total mortality and 40% reduction in CHD mortality (184) The impact of including nuts in the diet has been analyzed in a recent large meta-analysis (185). The habit of eating 28 grams of nuts/day reduced the risk for CHD by 0.71, for stroke by 0.93, for all cardiovascular disease, and 0.79 for all-cause mortality. It was estimated that 4 million deaths a year could be avoided worldwide by eating one handful of nuts. In even more recent analysis of dietary habits and outcome, inadequate nut intake was associated with increased cardiometabolic deaths, as was the consumption of excess salt, excess sugar, sweetened beverages, inadequate vegetables, and processed meats (186). In a study of 40 subjects comparing a walnut-enriched diet to a control diet over 8 weeks, the walnut diet reduced total cholesterol and apolipoprotein B (187). Walnuts also significantly improve endothelial function (188).

Dietary sodium, potassium, magnesium, and calcium

Increased dietary sodium is associated with an increased risk of hypertension, CHD, MI, CHF, CVA, renal insufficiency, and proteinuria (189–195). Approximately 75 million people in the United States and up to 1 billion worldwide have been diagnosed with hypertension (189–195). Up to 50% of cardiovascular-related deaths result from hypertension.

The sodium–potassium ratio may be more important than the actual dietary sodium and potassium intake and the association with CHD (189). A number of population studies demonstrated that higher dietary potassium, as rated by urinary excretion or dietary recall, was generally associated with lower blood pressure and CHD regardless of the level of sodium intake (189–195). According to a report of the Institute of Medicine, adult recommendations are to consume at least 4.7 grams of potassium daily to control blood pressure and reduce dietary sodium intake to about 1.5 to 2 grams per day (2,4,189–195). The potassium/sodium ratio should be greater than 2.5 to 3.0 (2,4,189–195). Foods high in potassium include bran, mushrooms, macadamia nuts and almonds, dark leafy greens, avocados, apricots, fruits, and acorn squash.

The sodium to potassium ratio was evaluated recently in a South Korean study (190). The study population was constructed by pooling the Korean National Health and Nutrition Examination Surveys between 2010 and 2014. The study groups were divided into quartiles based on the sodium to potassium ratio. The quartiles with the higher sodium to potassium ratio had greater hypertension prevalence rates. Significantly higher systolic and diastolic blood pressure was observed in the second quartiles compared to the first quartiles. A strong association was also detected between the sodium to potassium ratio and blood pressure even at a low level of sodium to potassium ratio.

The role of dietary magnesium in cardiovascular health is important and supported by many studies. It is estimated that nearly half the U.S. population is consuming less than the recommended amount of magnesium in their diets, and magnesium deficiency is a commonly overlooked risk factor for cardiovascular disease (191). The lower the dietery intake of magnesium, the greater is the risk of succumbing to cardiovascular disease. Magnesium supplementation can be therapeutic for a range of cardiovascular issues including arrhythmias, hypertension, atherosclerosis, and endothelial dysfunction. Magnesium is critical for tissues that have electrical or mechanical activity, such as nerves, muscles (including the heart), and blood vessels (191). In a 6-month study of patients with known ischemic heart disease, magnesium supplementation led to an impressive decrease in angina attacks and a decrease in the use of antianginal drugs such as nitroglycerin by improving endothelial function (192). In patients on dialysis, magnesium supplements had improved arterial remodeling and elasticity (193).

In a recent analysis of a group of hypertensive women randomized to magnesium supplements or placebo, no change in measurements of carotid intimal medial thickening (IMT) occurred in the group given magnesium, while the carotid IMT worsened over 6 months in the placebo group (194). There was also an improvement in flow-mediated dilation in the magnesium-treated group. In another study, researchers investigated the relationship between dietary magnesium intake and mortality from cardiovascular disease in a sample of Asian adults (195). Dietary intake in 58,615 healthy Japanese aged 40–79 years in the Japan Collaborative Cohort (JACC) Study was assessed by food frequency questionnaires with a median of 14.7-year follow-up. Overall, there were 2690 deaths from cardiovascular disease, comprising 1227 deaths from strokes and 557 deaths from CHD. Dietary magnesium intake was inversely associated with mortality from hemorrhagic stroke in men and with mortality from total and ischemic strokes, CHD, CHF, and total cardiovascular disease in women. Increased dietary magnesium intake was associated with reduced mortality from cardiovascular disease in the population. The 2015 Dietary Guidelines Advisory Committee indicated that magnesium represents a "shortfall nutrient" and its consumption is too low relative to the Estimate Average Requirement (EAR) for the U.S. population (196). In some areas the consumption is only 50% of the EAR and can exist despite the present normal serum magnesium levels. Improved reference ranges and diagnostic testing such a red blood cell magnesium is needed with validation of optimal health and health outcomes. Chronic magnesium deficiency can lead to many chronic diseases, including hypertension, T2DM, inflammation, and cardiovascular disease (196).

A recent systematic review and meta-analysis from 1966 to 2016 concluded that calcium intake within tolerable upper intake limits of 2000 to 2500 mg per day is not associated with cardiovascular risk in generally healthy adults (197). The National Osteoporosis Foundation and the American Society for Preventive Cardiology concluded that calcium with or without vitamin D intake from food or supplements has no relationship to the risk for cardiovascular disease or CV mortality or for all-cause mortality in a generally healthy adult population in doses of 2000 to 2500 mg per day (198).

Summary and conclusions

The top five cardiovascular risk factors, as presently defined, are not an adequate explanation for the current limitations to prevent and to reduce CHD. Proper definition and analysis of the top five CV risk factors, evaluation of the three finite responses, and sound nutritional advice and evaluation-based the scientific studies will be required to affect an improvement in risk for CHD. Early detection of CHD coupled with aggressive prevention and treatment of all cardiovascular risk factors will diminish the progression of functional and structural cardiovascular abnormalities and clinical CHD. Utilization of targeted personalized and precision treatments with optimal nutrition coupled with exercise, ideal weight and body composition, and discontinuation of all tobacco use can prevent approximately 80% of CHD. The published nutritional studies provide evidence that CHD can be reduced with a weighted plant-based diet with 10 servings of fruits and vegetables per day, MUFA, PUFA, nuts, whole grains, cold-water fish, the DASH diets, PREDIMED-TMD diet, and reduction of refined carbohydrates and sugars, high glycemic load and index foods, sugar substitutes, high-fructose corn syrup, long-chain SFAs, and processed foods, and elimination of all TFA (**Table 1**). Eggs and dairy products are not associated with CHD with the possible exception eggs consumption affecting the risk of CHD in T2DM. Coconut oil is not recommended. Organic, grass-fed beef and wild game may reduce CHD. High intakes of potassium and magnesium are recommended in conjunction with sodium restriction. Caffeine intake should be adjusted depending on genetic ability to metabolize it via the CYP 1A2 system. Alcohol is associated with a U-shaped curve and CHD. The role of gluten, soy, and caloric restriction and CHD in humans will require more studies.

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