

Dietary and Policy Priorities for Cardiovascular Disease, Diabetes, and Obesity A Comprehensive Review

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Abstract—Suboptimal nutrition is a leading cause of poor health. Nutrition and policy science have advanced rapidly, creating confusion yet also providing powerful opportunities to reduce the adverse health and economic impacts of poor diets. This review considers the history, new evidence, controversies, and corresponding lessons for modern dietary and policy priorities for cardiovascular diseases, obesity, and diabetes mellitus. Major identified themes include the importance of evaluating the full diversity of diet-related risk pathways, not only blood lipids or obesity; focusing on foods and overall diet patterns, rather than single isolated nutrients; recognizing the complex influences of different foods on long-term weight regulation, rather than simply counting calories; and characterizing and implementing evidence-based strategies, including policy approaches, for lifestyle change. Evidence-informed dietary priorities include increased fruits, nonstarchy vegetables, nuts, legumes, fish, vegetable oils, yogurt, and minimally processed whole grains; and fewer red meats, processed (eg, sodium-preserved) meats, and foods rich in refined grains, starch, added sugars, salt, and trans fat. More investigation is needed on the cardiometabolic effects of phenolics, dairy fat, probiotics, fermentation, coffee, tea, cocoa, eggs, specific vegetable and tropical oils, vitamin D, individual fatty acids, and diet-microbiome interactions. Little evidence to date supports the cardiometabolic relevance of other popular priorities: eg, local, organic, grass-fed, farmed/wild, or non-genetically modified. Evidence-based personalized nutrition appears to depend more on nongenetic characteristics (eg, physical activity, abdominal adiposity, gender, socioeconomic status, culture) than genetic factors. Food choices must be strongly supported by clinical behavior change efforts, health systems reforms, novel technologies, and robust policy strategies targeting economic incentives, schools and workplaces, neighborhood environments, and the food system. Scientific advances provide crucial new insights on optimal targets and best practices to reduce the burdens of diet-related cardiometabolic diseases. (*Circulation*. 2016;133:187-225. DOI: 10.1161/CIRCULATIONAHA.115.018585.)

Key Words: cardiovascular diseases ■ delivery of health care ■ diet ■ diabetes mellitus ■ nutrition ■ obesity ■ policy ■ prevention and control ■ review

Suboptimal diet is the leading risk factor for death and disability in the United States and worldwide.^{1,2} Among disadvantaged populations in all nations, hunger and malnutrition cause enormous suffering. Simultaneously, diet-related cardiometabolic diseases such as coronary heart disease (CHD), stroke, type 2 diabetes mellitus, and obesity produce even larger global health burdens. Other vascular conditions including peripheral arterial disease, chronic kidney disease, cognitive decline, heart failure, and atrial fibrillation are also influenced by diet-related risk factors. Worldwide, chronic diseases will cause \$17.3 trillion of cumulative economic loss between 2011 and 2030 from healthcare expenditures, reduced productivity, and lost capital.³ Considering these health and economic burdens, diet-related illnesses are among the leading priorities of our time.

In recent years, global dietary patterns have shifted in nearly every nation in the world.⁴ At the same time, nutrition

science has advanced remarkably. In comparison with historical dietary recommendations which were based largely on cross-national studies, short-term experiments, and animal models, nutrition science has been transformed in the past 2 decades by more rigorous evidence from well-designed metabolic studies, prospective cohorts, and randomized clinical trials.

Several key lessons have emerged (Table 1). First, it is now evident that dietary habits influence diverse cardiometabolic risk factors, including not only obesity and low-density lipoprotein (LDL) cholesterol, but also blood pressure (BP), glucose-insulin homeostasis, lipoprotein concentrations and function, oxidative stress, inflammation, endothelial health, hepatic function, adipocyte metabolism, cardiac function, metabolic expenditure, pathways of weight regulation, visceral adiposity, and the microbiome (Figure 1). Whereas decades of dietary recommendations focused on dietary fat and blood

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DOI: 10.1161/CIRCULATIONAHA.115.018585

cholesterol and current dietary discussions are often preoccupied with total calories and obesity, the full health impact of diet extends far beyond these pathways. Cardiometabolic consequences of any nutrient, food, or overall diet should not be extrapolated from any single surrogate outcome,⁵ but assessed based on the totality of evidence including interventional trials evaluating multiple risk pathways, prospective cohort studies of clinical events, and, where available, randomized trials of clinical events.^{6,7}

A second key lesson is the importance of specific foods and overall diet patterns, rather than single isolated nutrients, for cardiometabolic risk.^{8,9} Indeed, focusing on isolated nutrients often leads to paradoxical dietary choices and industry formulations. A food-based approach also better facilitates public guidance and minimizes industry manipulation.

Third, the science of obesity has progressed dramatically. Similar to lessons for CHD risk, the primary prevention of obesity – avoidance of long-term weight gain – may prove more effective and enduring than secondary prevention – obesity treatment after it has occurred. The diverse, complex physiological mechanisms of long-term weight homeostasis are also being elucidated. These lines of evidence indicate that an energy-imbalance concept of obesity is oversimplified. Whereas short-term weight loss can be achieved by any type of calorie-reduced diet, in the long term, counting calories may not be biologically nor behaviorally relevant. Rather, the quality and types of foods consumed influence diverse pathways related to weight homeostasis, such as satiety, hunger, brain reward, glucose-insulin responses, hepatic de novo lipogenesis, adipocyte function, metabolic expenditure, and the microbiome. Thus, all calories are not equal for long-term adiposity: certain foods impair pathways of weight homeostasis, others have relatively neutral effects, and others promote the integrity of weight regulation.

Finally, major strides have been made in the science of individual, sociocultural, and environmental determinants of dietary choices. Influences are complex, including individual-level, sociocultural, community, agricultural, industry, governmental, and global contributors.¹⁰ Several individual, health

system, and policy-level strategies now have strong evidence for efficacy.¹¹ Elucidation of methods for better translation of these approaches is needed.

This article summarizes the modern evidence for health effects of diet on cardiometabolic diseases, including key evidence-based priorities, relevant mechanisms, and major unanswered questions, and the evidence on barriers and opportunities for behavior change in the clinic, health system, and population, including novel policy and technology strategies.

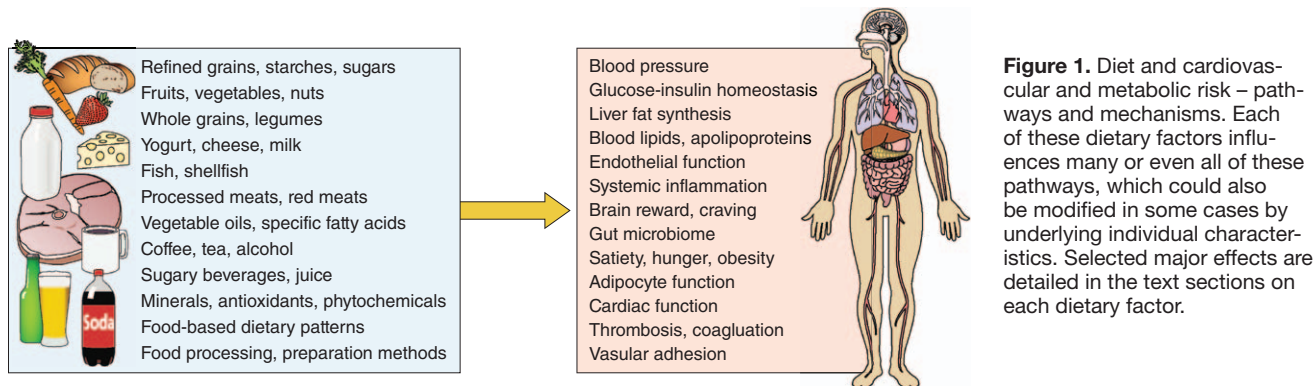
Nutrients, Foods, and Diet Patterns – a Historical Evolution

In 1747, Captain James Lind performed one of the earliest recorded clinical trials. Based on earlier observations, he assigned British sailors who had scurvy to several different treatments.^{9,12} Only 1 group – those receiving citrus fruits – improved, providing new evidence that a specific dietary factor could cure disease. By the turn of the century, the British fleet routinely added lemon or lime juice to rations, a practice making them famous as “limeys”.

Yet, it was not until 1932 that the first vitamin was isolated – vitamin C – and was verified as the active protective constituent against scurvy. This confirmed, for the first time, that specific dietary nutrients could prevent disease. Over the next 2 decades, an explosion of nutrition science confirmed other single-nutrient diseases such as beriberi (thiamine), pellagra (niacin), anemia (iron), goiter (iodine), night blindness (vitamin A), and rickets (vitamin D). Coincident to these scientific advances, geopolitical events – the Great Depression, World War II – greatly magnified attention on food shortages and nutrient inadequacy. Indeed, the first Recommended Dietary Allowances originated in 1941 by order of President Franklin Roosevelt, when he convened the National Nutrition Conference on Defense to ensure a population fit for war by minimizing nutrient deficiency diseases.^{13,14} That same year, the American Medical Association declared that, “research in nutrition be encouraged” with primary aims of

Table 1. Key New Lessons from Modern Nutritional Science

Diverse physiological effects of diet	Dietary habits influence a myriad of cardiometabolic risk factors, including blood pressure, glucose-insulin homeostasis, lipoprotein concentrations and function, inflammation, endothelial health, hepatic function, adipocyte metabolism, cardiac function, metabolic expenditure, and pathways of weight regulation, visceral adiposity, and the microbiome. Focus on single surrogate outcomes can be misleading. Based on these diverse effects, diet quality is more relevant than quantity, and the primary emphasis should be cardiovascular and metabolic health, not simply body weight or obesity.
Importance of foods and diet patterns	Specific foods and overall diet patterns, rather than single isolated nutrients, are most relevant for cardiometabolic health. The historical focus on isolated nutrients contributes to confusion about what constitutes a healthy diet, distracts from more effective strategies, and drives industry, policy makers, and the public toward diets which meet selected nutrient cut points but provide little health benefit.
Complexity of obesity and weight regulation	Diet quality influences diverse pathways related to weight homeostasis, including satiety, hunger, brain reward, glucose-insulin responses, hepatic de novo lipogenesis, adipocyte function, metabolic expenditure, and the microbiome. For long-term weight control, all calories are not created equal because of the divergent long-term effects of different foods on these pathways of weight homeostasis.
Individual, health systems, and policy approaches for behavior change	Multiple evidence-based strategies for improving dietary behaviors have now been identified, including at the individual (patient) level, in health systems, and in populations. Integrated, multicomponent approaches that include upstream policy measures, midstream educational efforts, and downstream community and environmental approaches may be especially effective.



“estimating the amounts of essential nutrients in foods,” “detection of nutritional deficiency states,” and more precise determination of “optimum and minimum requirements” for each nutrient.¹⁵ Consequently, all of the first Recommended Dietary Allowances focused on nutrient deficiency, including for calories, protein, iron, calcium, thiamin, riboflavin, niacin, and vitamins A, C, and D. Based on this chance convergence of scientific and geopolitical events, US dietary guidelines over most of the 20th century emphasized prevention of single-nutrient deficiencies.¹⁴

With the modernization of agriculture, food processing, and food formulations, nutrient deficiencies rapidly receded in the United States and other high-income nations. In their place, a growing epidemic of chronic diseases was recognized. Beginning in 1980, for the first time, US dietary guidelines began to focus on chronic disease.¹⁴ The main available evidence derived from less robust study designs: eg, crude cross-national comparisons, short-term experiments of surrogate outcomes in healthy volunteers. Furthermore, after decades of emphasis on deficiency diseases, the single-nutrient paradigm continued to dominate research approaches and interpretations. Together, these factors caused oversimplified inferences on how diet influences cardiovascular disease (CVD), diabetes mellitus, and obesity. Scientists and policy makers intuitively followed earlier methods that had been so successful in reducing deficiencies: identify the relevant nutrient, establish its target intake, and translate this to recommendations. To many, saturated fat and cholesterol became *the* causes of CHD, and total fat became *the* cause of obesity. Thus, the 1980 Dietary Guidelines remained heavily nutrient-focused: “avoid too much fat, saturated fat, and cholesterol; eat foods with adequate starch and fiber; avoid too much sugar; avoid too much sodium.”

Modern evidence now demonstrates the limitations of this single-nutrient component focus. The framework of Recommended Dietary Allowances was quickly recognized as methodologically and conceptually inappropriate for chronic diseases, leading to the creation of new nutrient-based metrics (eg, Adequate Intakes; Acceptable Macronutrient Distribution Ranges) which were themselves limited by imprecise definitions and inconsistent usage.¹⁶ Furthermore, although scientific investigation of macro- and micronutrients remains essential to elucidate biological mechanisms, the complex matrix of foods, food processing,

and food preparation strongly modifies the final health effects.^{8,9,17,18} Translation of nutrient-based targets to the public also proved difficult: few people understand or can accurately estimate without guidance their daily consumption of nutrients such as calories, fats, cholesterol, fiber, salt, or single vitamins. Most importantly, methodologic advances in nutrition science now demonstrate that nutrient-focused metrics are inadequate to explain most effects of diet on chronic diseases. Rather, cardiometabolic diseases are largely influenced not by single nutrients, but by specific foods and overall diet patterns.^{19–21}

These historical events elucidate the current state of nutrition. Modern dietary science is surprisingly young – only 83 years have elapsed since the first vitamin was isolated – and much of its existence was focused on single-nutrient diseases. The major impact of diet on chronic diseases was not widely appreciated until even more recently, 35 to 40 years ago. And, not until the last 15 to 20 years has the scientific methodology become sufficiently advanced to provide strong, consistent inference on diet, chronic diseases, and relevant metabolic pathways. Thus, the present period is one of exciting, rapid transition away from single-nutrient theories and simple surrogate outcomes and toward foods, dietary patterns, and evaluation of clinical end points. This transition forms the basis for our modern understanding of diet and cardiometabolic health.

Dietary Patterns

Dietary patterns represent the overall combination of foods habitually consumed, which together produce synergistic health effects. Evidence-informed beneficial diet patterns share several key characteristics (Table 2).^{19,21–23} These include more minimally processed foods such as fruits, nuts/seeds, vegetables (excluding russet or white potatoes), legumes, whole grains, seafood, yogurt, and vegetable oils; and fewer red meats, processed (sodium-preserved) meats, and foods rich in refined grains, starches, and added sugars. Such diets are higher in fiber, vitamins, antioxidants, minerals, phenolics, and unsaturated fats, and lower in glycemic index, glycemic load, salt, and trans fat.

The scientific concordance, controversy, and related evidence for these and other key dietary targets are variable (Table 3). As described above, this reflects the youthful nature of the science of nutrition and chronic disease, together with

Table 2. Dietary Priorities for Cardiometabolic Health*

		Goal*	One Serving Equals...	Examples
Consume more	Fruits	3 servings/d	1 medium-sized fruit; ½ cup of fresh, frozen, or unsweetened canned fruit; ½ cup of dried fruit; ½ cup of 100% juice	Blueberries, strawberries, apple, orange, banana, grapes, grapefruit, avocado, mango. Whole fruits are preferable to 100% juice, which should be limited to no more than 1 serving/d.
	Nuts, seeds	4 servings/wk	1 ounce	Almonds, walnuts, peanuts, hazelnuts, cashews, pecans, Brazil nuts, sunflower seeds, sesame seeds.
	Vegetables, including legumes (excluding russet or white potatoes)	3 servings/d	1 cup of raw leafy vegetables; ½ cup of cut-up raw vegetables, cooked vegetables, or 100% vegetable juice	Spinach, kale, and other green leafy plants; broccoli, carrots, onions, peppers; peas, beans, lentils. Minimize starchy vegetables, especially russet or white potatoes.
	Whole grain†	3 servings/d, in place of refined grains	1 slice of whole-grain bread; 1 cup of high-fiber, whole-grain cereal; ½ cup of cooked whole-grain rice, pasta, or cereal	Oats, bulgur, whole-wheat couscous, barley, whole-grain breads and cereals, brown rice.
	Fish, shellfish	≥2 servings/wk	3.5 ounces (100 g)	The best choices are oily fish such as salmon, tuna, mackerel, trout, herring, and sardines.
	Dairy products, especially yogurt and cheese ‡	2–3 servings/d	1 cup of milk or yogurt; 1 ounce of cheese	Whole-fat or low-fat yogurt, cheese, milk.
	Vegetable oils	2–6 servings/d	1 teaspoon oil, 1 tablespoon vegetable spread	The best evidence supports phenolic- and unsaturated fat-rich oils such as soybean, canola, and extra virgin olive oil; also consider safflower oil, peanut oil, and soft margarine spreads made with these oils.
Consume less	Refined grains, starches, added sugars†	No more than 1–2 servings/d	1 slice of bread, ½ cup of rice or cereal, 1 sweet or dessert	White bread, white rice, most breakfast cereals, crackers, granola bars, sweets, bakery desserts, added sugars.
	Processed meats	No more than 1 serving/wk	1.75 ounces (50 g)	Preserved (sodium, nitrates) meats such as bacon, sausage, hot dogs, pepperoni, salami, low-fat deli meats (eg, chicken, turkey, ham, beef).
	Unprocessed red meats	No more than 1–2 servings/wk	3.5 ounces (100 g)	Fresh/frozen beef, pork, lamb.
	Industrial trans fat §	Don't eat	Any food containing or made with partially hydrogenated vegetable oil	Certain stick margarines, commercially prepared baked foods (cookies, pies, donuts, etc), snack foods, deep-fried foods.
	Sugar-sweetened beverages	Don't drink	8 ounces of beverage; 1 small sweet, pastry, or dessert	Sugar-sweetened soda, fruit drinks, sports drinks, energy drinks, iced teas.
	Sodium	No more than 2000 mg/d	n/a	Sodium is commonly high in foods as a preservative or to mask unpleasant flavors when previously cooked. Common sources include bread, chicken (often injected to increase succulence), cheese, processed meats, soups, canned foods.

*Based on a 2000 kcal/d diet. Servings should be adjusted accordingly for higher or lower energy consumption.

†As a practical rule-of-thumb for selecting healthful whole grains and avoiding carbohydrate-rich products high in starches and added sugars, the ratio of total carbohydrate to dietary fiber (g/serving of each) appears useful.^{168,169} Foods with ratios <10:1 are preferable; ie, food containing at least 1 g of fiber for every 10 g of total carbohydrate. In addition, minimally processed whole grains (eg, steel-cut oats, stone-ground bread) are generally preferable to finely milled whole grains (eg, many commercial whole-grain breads and breakfast cereals) because of the larger glycemic responses of the latter.

‡Current evidence does not permit clear differentiation of whether low-fat or whole-fat products are superior for cardiometabolic health. Other characteristics, such as probiotic content or fermentation, may be far more relevant than fat content.

§The US Food and Drug Administration recently ruled that the use of partially hydrogenated vegetable oils is no longer “generally regarded as safe,”³⁸⁴ which should effectively eliminate the majority of industrial trans fats from the US food supply. Several countries including Denmark, Argentina, Austria, Iceland, and Switzerland have effectively eliminated the use of partially hydrogenated vegetable oils through direct legislation on the amounts of allowable trans fats in foods. Small amounts of certain trans fatty acids may be formed through other industrial processes, including oil deodorization and high-temperature cooking; the health effects of these trace industrial trans fats require careful investigation.

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the remarkable advances in research and knowledge over just the past 1–2 decades.

The most well-studied dietary patterns are traditional Mediterranean and DASH diets (see <http://circ.ahajournals.org/content/123/24/2870/T3.expansion.html>). In comparison with the conventional low-fat, high-carbohydrate DASH diet, a modified DASH diet higher in vegetable fats and lower in carbohydrates – ie, more similar to a Mediterranean

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diet – produces larger cardiometabolic benefits.^{24–26} Both Mediterranean and DASH diet patterns improve a range of risk factors, reduce long-term weight gain, and are consistently associated with lower risk of clinical events.^{19,21,27–29} Pathways of benefit appear diverse, including effects on BP, glucose-insulin homeostasis, blood lipids and lipoproteins, inflammation, endothelial function, arrhythmic risk, and possibly coagulation/thrombosis, paraoxonase 1 activity, and the gut microbiome.^{20,21,30} Based on sociocultural and feasibility considerations, not every population in the world can consume a traditional Mediterranean diet. Other examples of Mediterranean-style dietary patterns, with adaption to various regions of the world, have been proposed.³¹

Randomized clinical trials in both primary and secondary prevention populations confirm the benefits of healthful, food-based diet patterns that were identified in prospective cohort studies and short-term interventional trials: such diets significantly reduce both cardiovascular events and diabetes mellitus.^{32–35} In comparison, both observational cohorts and randomized trials confirm little clinical benefit of diets focused on isolated nutrient targets, such as low-fat, low-saturated fat diets, which produce no significant benefits on cardiovascular disease, diabetes mellitus, or insulin resistance.^{36–39} This contrast in effectiveness of healthful, food-based versus nutrient-focused dietary targets is exemplified by comparing the results of 2 of the largest, longest-duration dietary trials ever performed (Figure 2).

Based on this evidence, the 2015 Dietary Guidelines Advisory Committee concluded that low-fat diets have no effect on CVD and emphasized the importance of healthful, food-based diet patterns.²¹ Notably, because additives such as sodium and industrial trans fats can be added to or removed

from otherwise similar commercially prepared foods, a specific emphasis on their reduction is also warranted.²¹

Focusing on overall diet patterns, rather than individual nutrients or foods, can also facilitate individual behavioral counseling and population dietary recommendations, because such patterns permit greater flexibility and personal preferences in diet choices.²¹ In addition, such patterns can lead to health benefits by means of smaller changes across several dietary factors, rather than major changes in a few factors, potentially increasing effectiveness and compliance.

People who follow vegetarian diets are often health conscious and tend toward healthful food patterns. However, vegetarianism per se is neither necessary nor sufficient for a good diet: indeed, french fries and soda are vegetarian, as are other harmful factors such as refined grains, starches, added sugars, sweets, trans fats, and sodium. Thus, a vegetarian diet is not a guarantee of health, whereas a nonvegetarian diet can be rich in healthful foods. A cardioprotective diet pattern must be characterized by the healthful foods that are included, not simply specific items to be avoided (Table 2).

Other increasingly popular dietary patterns include low-carbohydrate diets (minimizing all carbohydrates) and paleo diets (attempting to conform to food types consumed over millennia during human evolution). A main benefit of both low-carbohydrate and paleo diets is reduced refined grains, starches, and added sugars, which represent the majority of total carbohydrates and ultraprocessed foods in modern diets (see Carbohydrate-Rich Foods, below). Paleo diets also emphasize fruits, nonstarchy vegetables, nuts, and fish, each of which has health benefits. However, focus on low carbohydrate could paradoxically reduce intakes

Table 3. Selected Areas of Concordance and Controversy Related to Diet and Cardiometabolic Health*

	Broad Concordance and Less Controversy or Uncertainty†	General Concordance but Some Remaining Controversy and Uncertainty	Substantial Controversy and Uncertainty	Insufficient Evidence for Meaningful Conclusions
Benefits of:	Fruits, nonstarchy vegetables, nuts/seeds, legumes, yogurt Dietary fiber, potassium Moderate alcohol use Mediterranean-style or higher fat DASH-style diet patterns	Seafood, whole grains Certain vegetable oils (eg, soybean, canola, extra virgin olive) n-3 and n-6 polyunsaturated fats, plant-derived monounsaturated fats Phenolic compounds	Cheese, low-fat milk Certain vegetable oils (eg, corn, sunflower, safflower) Total or animal-derived monounsaturated fats Coffee, tea, cocoa Vitamin D, magnesium, fish oil	Whole-fat milk Starchy vegetables other than potatoes Coconut oil
Harms of:	Partially hydrogenated vegetable oils, processed meats High sodium Sugar-sweetened beverages, foods rich in refined grains, starches, added sugars Greater than moderate alcohol use	Moderate sodium White/russet potatoes High glycemic index/load	Saturated fats, dietary cholesterol Unprocessed red meats, eggs Butter	Whole-fat milk Palm oil
Little effect of:	Total fat	Total carbohydrate Isolated antioxidant vitamins, calcium	Poultry 100% fruit juice Total protein, specific amino acids Noncaloric sweeteners	Concepts of local, organic, farmed/wild, grass fed, genetic modification

DASH indicates Dietary Approaches to Stop Hypertension.

*See article text for details on these topics and on other foods and nutrients.

†Some amount of controversy can be identified for almost any topic in science.

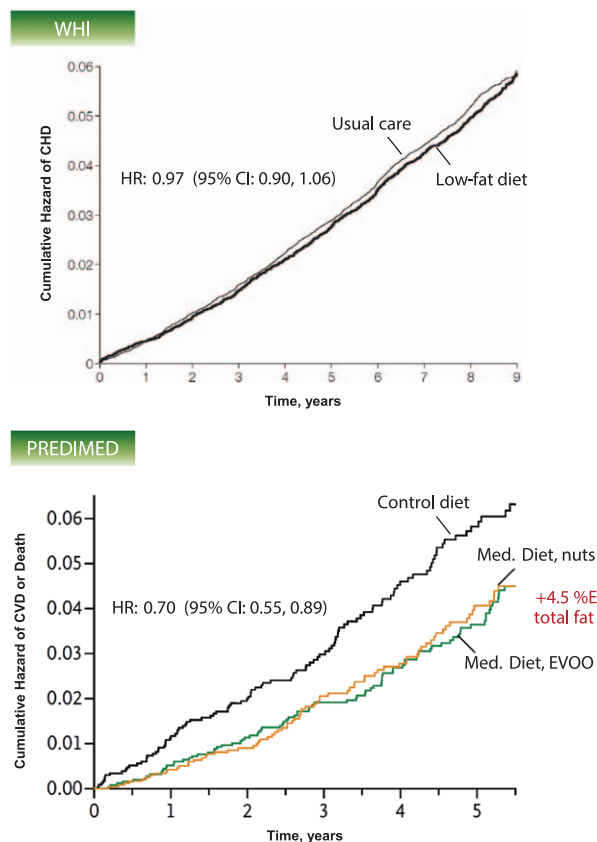


Figure 2. Contrasting results of randomized controlled dietary trials focusing on isolated nutrients (**Top**) versus food-based diet patterns (**Bottom**). The Women’s Health Initiative (WHI, **Top**) focused on nutrient targets and reducing total fat and achieved large long-term changes in these targets, yet had no significant effect on cardiovascular disease or diabetes mellitus. The Prevención con Dieta Mediterránea (PREDIMED) trial (**Bottom**) focused on food-based diet patterns and increasing specific healthful foods, especially nuts and extra virgin olive oil (EVOO), with smaller dietary changes than in WHI, yet demonstrating significant reduction in cardiovascular disease and diabetes mellitus. Both trials successfully altered long-term diets, although with more modest dietary changes in PREDIMED. However, only the food-based intervention resulted in clinical benefit. CHD indicates coronary heart disease; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction. Adapted from Howard et al³⁶ with permission of the publisher. Copyright © 2006, *JAMA*; and Estruch et al³⁴ with permission of the publisher. Copyright © 2013, *The New England Journal of Medicine*. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

of other, healthful carbohydrate-containing foods such as fruits, legumes, and minimally processed whole grains; while paleo guidelines often recommend liberal intakes of red meats, lard, and salt and the avoidance of legumes and dairy. A maximally beneficial diet pattern should concurrently emphasize reductions in refined (not all) carbohydrates, processed meats, and foods high in sodium and trans fat; moderation in unprocessed red meats, poultry, eggs, and milk; and high intakes of fruits, nuts, fish, vegetables (excluding russet/white potatoes), vegetable oils, minimally processed whole grains, legumes, and yogurt (Figure 3).

Diet Quality, Energy Balance, Obesity, and Weight Gain

Just as the science of cardiovascular risk is moving away from theories based on single-nutrient components and single-surrogate outcomes toward empirical evidence on foods and dietary patterns and clinical events, the science of obesity is moving away from simplistic ideas of energy balance, will power, and calorie counting toward the elucidation of effects of foods and diet patterns on the complex physiological determinants of long-term weight regulation. Of course, total calories matter in the short term, which is why people can initially lose weight on nearly any type of diet²¹ – and explaining why so many fad diets initially seem to work. In the short term, the best predictor of success is mindfulness with one’s chosen diet. However, for long-term weight maintenance and for cardiometabolic health independent of adiposity, healthful food-based patterns are most relevant (Table 2).²¹

Because obesity is so challenging to treat after it has developed, the primary prevention of weight gain is a promising strategy for individual patients and for populations. An average American adult gains only ≈ 1 lb (0.45 kg) per year,²⁸ consistent with habitual excess energy intakes as small as ≈ 50 kcal/d explaining the gradual weight gain seen in many people.⁴⁰ This finding accentuates just how well our body’s homeostatic mechanisms actually function to maintain long-term weight stability. Yet, when sustained over many years, this minor annual weight gain drives population obesity, eg, leading to 10 lbs weight gain over 10 years, 20 lbs over 20 years, and so on.

In many countries, the current obesity epidemic is a striking change from decades of prior relative stability; in the United States, for instance, obesity began steeply rising only about 30 years ago.⁴¹ Abdominal adiposity, which produces the largest metabolic harms, has also increased to a greater extent than overall weight in many nations, especially in younger women and certain middle-income countries.⁴² This modern rise in overweight and obesity is also occurring in children across most nations.⁴³ The full long-term health consequences of adiposity in these youthful generations remain to be seen, in whom rates of type 2 diabetes mellitus, nonalcoholic fatty liver disease, dyslipidemia, and hypertension exceed anything observed at these ages in previous human history.⁴⁴ The escalation of adiposity at youngest ages, including those <5 years of age, is also informative for considering potential causes. At such ages, population-wide declines in willpower, ability to count calories, or physical activity are difficult to invoke, reinforcing the likely role of environmental determinants of weight dysregulation.

Elucidating the specific dietary and nondietary determinants of long-term weight homeostasis is critical to understand and reverse the environmental changes contributing to this population imbalance. Growing evidence suggests that energy imbalance is a consequence of multiple complex, upstream effects, in particular poor diet quality (Figure 4). In other words, poor diet quality is a driver of excess diet quantity. Furthermore, independently of energy balance, diet quality influences metabolic risk and propensity toward abdominal adiposity. Mechanisms appear to include calorie-independent effects of different types of foods on satiety, glucose-insulin

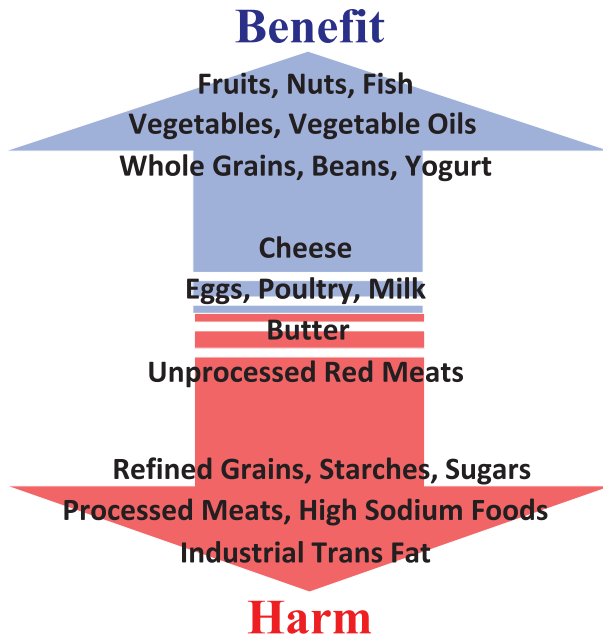


Figure 3. Evidence-based dietary priorities for cardiometabolic health. The placement of each food/factor is based on its net effects on cardiometabolic health, across all risk pathways and clinical end points, and the strength of the evidence, as well. For dietary factors not listed (eg, coffee, tea, cocoa), the current evidence remains insufficient to identify these as dietary priorities for either increased or decreased consumption (see Table 3).

responses,⁴⁵ liver fat synthesis,⁴⁶ adipocyte function,⁴⁷ visceral adiposity,⁴⁸ brain craving and reward,⁴⁹ and even metabolic expenditure.⁵⁰ The gut microbiome also appears increasingly important; eg, probiotics in yogurt appear to interact with microbiota to reduce weight gain.^{28,29,51–54} In addition, independent of calories and body weight, one's dietary pattern strongly influences metabolic dysfunction including the risk of diabetes mellitus.^{19,21} This is analogous to the weight-independent metabolic benefits of physical activity; diet quality has similar robust metabolic benefits (or harms).

Based on these influences, when consumed over years, certain foods may interfere with long-term weight homeostasis, others have relatively neutral effects, and others promote healthy weight regulation (Figure 5).^{19,21} For long-term weight gain, food rich in refined grains, starches, and sugar appear to be major culprits.^{28,29} Such rapidly digested, low-fiber carbohydrates drive many obesogenic pathways.^{45,46,48–50} Key foods in this group include potatoes, white bread, white rice, refined breakfast cereals, crackers, sweets, soda, and other ultraprocessed foods high in starches or sugars. In contrast, intakes of other foods, such as low-fat milk and whole-fat milk, appear relatively neutral, suggesting they do not perturb the normal homeostatic mechanisms for long-term weight control.^{29,51} For meats, cheese, and eggs, influences on long-term weight gain appear to vary depending on whether they are consumed together with refined carbohydrates (in which case more weight gain is evident) or in place of refined carbohydrates (in which less weight gain or even relative weight loss is seen).²⁹

Conversely, increased fruits, nonstarchy vegetables, nuts, yogurt, fish, and whole grains each appear to protect against

chronic weight gain: the more these foods are consumed, the less the average weight gain.^{28,29,51,55} The mechanistic pathways underlying these observed benefits are still being elucidated, but may partly reflect opposing, protective effects in comparison with those of rapidly digested, refined carbohydrates.

Based on these complexities, choosing foods based on calorie content can lead to paradoxical dietary choices, industry formulations, and policy recommendations. For example, the US National School Lunch Programs recently banned whole milk, but allows sugar-sweetened chocolate skim milk.⁵⁶ This untested intervention in 31 000 000 American children is based on hypothesized effects of total calories, total fat, and saturated fat in milk,⁵⁶ rather than empirical evidence on the health effects of whole versus skim milk. Longitudinal studies suggest no harms of whole-fat milk for obesity, diabetes mellitus, or cardiovascular disease in adults^{28,29,51,57,58}; that dairy fat may have potential benefits for diabetes mellitus^{59–61}; that people switching to low-fat dairy products compensate elsewhere in their diet by increasing consumption of carbohydrates²⁹; and that children who habitually drink low-fat milk gain more weight, and those who drink whole-fat milk gain less weight, over time.^{62–66} Many other ironies result from a calorie focus: eg, recommendations to consume fat-free salad dressing, in which healthful vegetable oils have been removed and replaced with starch, sugar, and salt; to minimize nuts because of their fat content and energy density; and to consume low-fat deli meats that are loaded with sodium.

In sum, modern evidence indicates that different foods have very different obesogenic potential depending on their influence on complex, multifactorial pathways of weight regulation. To prevent long-term weight gain, calories and portion sizes from certain types of foods should be minimized; from others, not emphasized; and from others, actually increased. Other conventional metrics – eg, total fat, energy density, even added sugar – may not reliably identify how specific foods influence weight gain.^{28,29,51} Consistent with this modern science, the 2015 Dietary Guidelines Advisory Committee Report emphasizes food-based, healthful diet patterns as a primary recommendation to address obesity.²¹

Several other lifestyle factors appear to interact with diet to influence adiposity. These include TV watching, sleep duration, circadian alignment, and possibly maternal-fetal (eg, placental) influences.^{28,41,67–70} For example, lower sleep duration and altered circadian rhythms are linked to greater weight gain and obesity, alter hunger and food preferences, and may influence leptin, ghrelin, insulin, and gut-peptide concentrations.^{28,67} Greater hours spent TV watching also independently increase obesity and weight gain^{28,68}; 2 randomized trials in children suggest this is primarily mediated by changes in diet (rather than changes in, physical activity) owing to increased eating in front of the TV and altered food choices attributable to viewed marketing.^{71,72} Increasing physical activity, of course, has complementary benefits on weight maintenance and metabolic health. Other societal and environmental influences likely have additional effects, including education, income, race/ethnicity, social norms and networks, industry marketing, and local food availability.^{10,11,73}

In sum, these complex and often insidious influences make unintended weight gain very easy. Conversely, based on

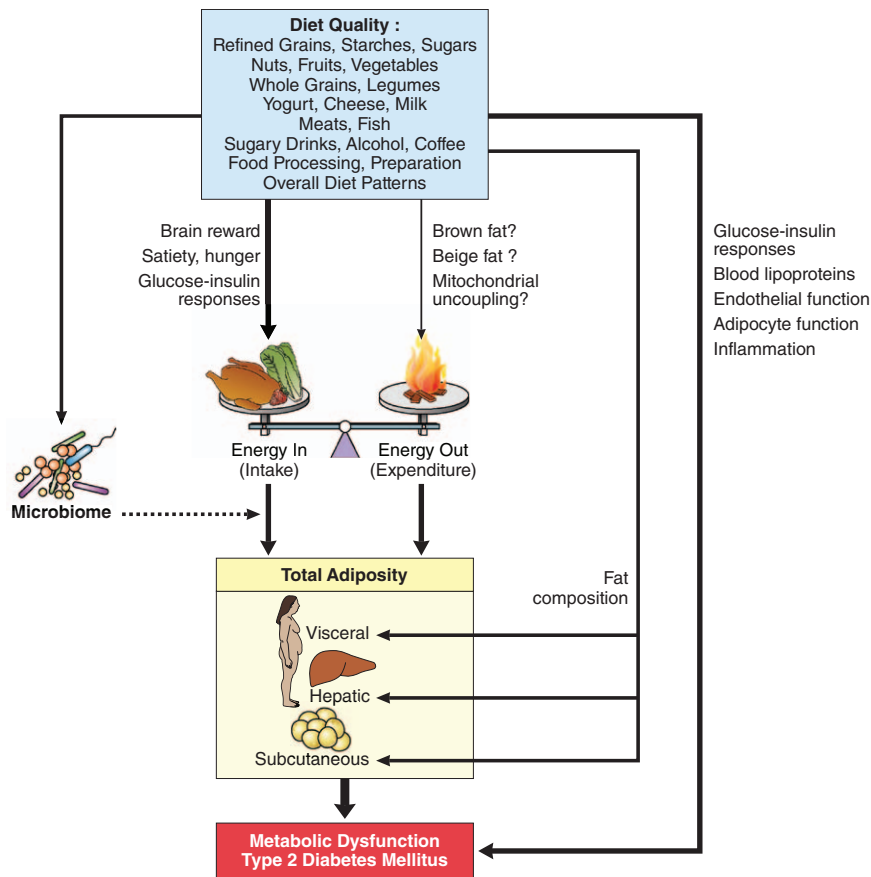


Figure 4. Diet quality, obesity, and metabolic risk – a modern paradigm. Diet quality influences risk of adiposity through multiple pathways, including altering energy intake, energy expenditure, microbiome-host interactions, body fat composition, and metabolic function.

these effects, modest behavioral and environmental improvements can attenuate or reverse chronic energy gaps, weight gain, and adiposity. Based on current available evidence, key diet-related priorities to reduce adiposity are reduction in refined grains, starches, sugars, and meats; limiting industry marketing especially from TV; increasing intakes of fruits, vegetables, nuts, yogurt, fish, vegetable oils, and whole grains; sleeping at least 7 to 8 hours nightly; and further elucidating maternal-fetal, microbiome, and sleep/circadian influences.

Individual Susceptibility – Genetics and Personalized Nutrition

Interest is growing in quantifying and understanding the determinants of interindividual variation in responses to diet. One aim is personalized nutrition – the ability to provide customized dietary advice specialized to each person’s unique profile of genes and other underlying characteristics.

Although candidate gene approaches have identified several potential gene-diet interactions for traits including blood cholesterol levels, a major challenge has been lack of replication.^{74–77} Even for better documented gene-diet interactions – eg, for the APOE locus, dietary saturated fat, and LDL-cholesterol; or for the CETP locus, alcohol, and high-density lipoprotein (HDL) cholesterol – evidence for clinical relevance of these differences remains weak.⁷⁴ Large investigations pooling multiple cohorts have observed main (population) effects of either dietary influences or genes on major cardiometabolic risk factors, but evidence for interactions

between diet and these genes is uncommon and, more relevantly, magnitudes of such potential interactions are often small.^{78–83} One of the more promising gene-diet interactions, notable in Hispanic populations, involves PNPLA3 and sugar consumption in relation to obesity and liver fat accumulation^{84–86}; additional interaction with dietary polyunsaturated fats could also be present.⁸⁷ Potential influences of diet on epigenetic changes (eg, DNA methylation) and subsequent cardiometabolic risk pathways are also of considerable interest,⁸⁸ but relevant between-individual variation in these diet-epigenetic responses has yet to be identified. At present, compelling evidence is lacking to design personalized nutritional recommendations for cardiometabolic health based on genetic variation.

Other underlying individual characteristics may be better determinants of personalized guidance. For instance, carbohydrate-induced glycemic responses appear especially detrimental in women,⁸⁹ suggesting the particular need for women to avoid rapidly digested carbohydrates. Other studies suggest that people with greater insulin resistance experience greater short-term weight loss with low-carbohydrate than with low-fat diets.⁹⁰ Similarly, patients with diabetes mellitus, impaired glucose tolerance, or atherogenic dyslipidemia may also benefit most from reducing refined carbohydrates and increasing proteins and vegetable fats.^{91–93} In addition, personalized cognitive-behavioral and culturally and socio-economically sensitive strategies increase effectiveness of clinical approaches to behavior change.^{94,95}

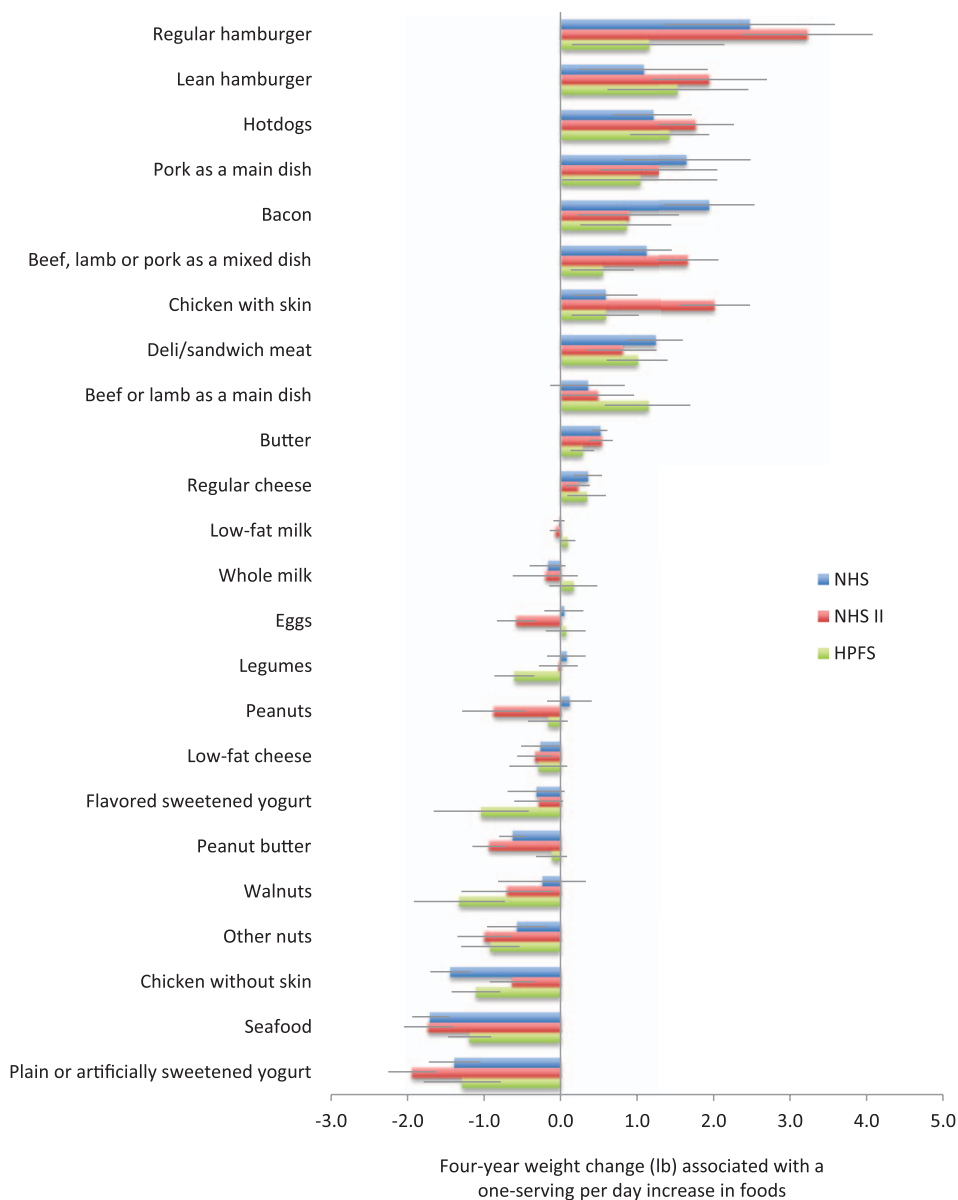


Figure 5. Protein-rich foods and long-term weight gain in 3 separate US prospective cohort studies, based on 16 to 24 years of follow-up. Weight changes every 4 years are shown for each 1-serving/d increase in consumption; decreased consumption would be associated with the inverse weight changes. To convert pounds to kilograms to pounds, divide by 2.2. All weight changes were adjusted for age, baseline body mass index, sleep duration, and concurrent changes in smoking status, physical activity, television watching, alcohol use, and consumption of fruits, vegetables, glycemic load, and all of the dietary factors in the figure simultaneously. NHS indicates Nurses' Health Study; and HPFS, Health Professionals Follow-up Study. Reproduced from Smith et al²⁹ with permission of the publisher. Copyright © 2015, *The American Journal of Clinical Nutrition*.

Overall, although a promise of precision medicine has been promoted,⁹⁶ the massive, rapid shifts in cardiometabolic disease occurring across nations and within populations over time⁹⁷ demonstrate the dominant influence of environmental risk factors—and therefore the crucial importance of population approaches to address these environmental risks, including improved nutrition. In addition, population strategies to address diet, such as economic incentives, can reduce socioeconomic-related disparities in health, whereas individual-based approaches may exacerbate inequities.^{98,99} Evidence-based personalized approaches, especially related to underlying non-genetic characteristics, should be considered a complement to such population efforts.

Food Processing

Potential health effects of food processing are receiving increasing attention.^{100–102} Nearly all foods must undergo some processing to be consumed—eg, cooking, smoking, drying, salting, fermenting, preserving, heating, milling, refining. Benefits of processing include improved palatability, variety, nutrient bioavailability, shelf life, and convenience, and reduced risk of food-borne pathogens. Potential harms include loss of nutrients such as fiber, phenolics, minerals, fatty acids, vitamins, and other bioactives; increased doses and rapidity of digestion of starch and sugar; and introduction of harmful factors such as sodium, other preservatives, trans fats, heterocyclic amines, advanced glycation end products, and other compounds.

Many healthful foods are minimally processed (eg, fruits, nuts, seafood), whereas several classes of processed foods are harmful (eg, refined grains and cereals, preserved meats and other high-sodium foods, food made with partially hydrogenated oils). This can lead to an impression to always select “natural” and always avoid processed or ultraprocessed foods. Because many minimally processed foods are healthful, and many more highly processed foods are not, this can serve as a useful general rule. However, it is not absolute. For example, some more natural foods such as eggs, butter, and unprocessed red meats are not linked to improved cardiometabolic outcomes (see Foods, below), whereas other packaged or processed foods (eg, nut- and fruit-rich snacks, phenolic- and polyunsaturated-rich vegetable oils and margarines) improve cardiometabolic health.

Consequently, both the type of food and its processing are relevant. Rather than focusing only on natural versus processed, the clinician, consumer, policy maker, and food producer should emphasize foods that are both innately healthful and less processed; and reject foods rich in refined grains, starch, and added sugars and harmful additives such as sodium and trans fat (Table 2). In addition, as the global food system moves toward more processed foods,¹⁰³ further rigorous investigation is needed to define and disseminate methods for optimal processing, rather than an impractical focus on complete absence of processing.

Dietary Supplements, Functional Foods

Use of dietary supplements, often at high or pharmacological doses, is commonplace, despite the absence of convincing evidence for health benefits. Many supplements have been evaluated in observational studies and controlled trials as potential therapies to prevent CVD or other conditions (Table 4).^{104–110} Evaluated doses in such trials have often exceeded usual or even recommended dietary intakes, often under the assumptions that higher levels would produce greater benefits, and

that there was little risk of harm. Evidence has accrued that most of these supplements have little CVD benefit, and that certain supplements including β -carotene, calcium, and vitamin E may even be harmful.^{105–108,111–113} Presently, fish oil may be considered as a supplement for CVD prevention, especially among patients with prevalent CHD, based on reduction of cardiac death¹⁰⁹ (see Fish, above). Overall, the current evidence does not support use of other dietary supplements to duplicate or complement the cardioprotective benefits of consumption of healthful foods.

Similar to dietary supplements, functional foods attempt to improve health by incorporating bioactive compounds that may alter lipid, vascular, and other metabolic pathways, microbiome composition and function, and digestive and inflammatory systems.^{114–121} Such putative compounds include specific peptides, fatty acids, phenolics, vitamins, dietary fibers, prebiotics/probiotics, and plant sterols/stanols. Many of these bioactive compounds have demonstrated effects on cardiovascular risk pathways in animal and human studies; effects on blood lipids have been most often studied. To date, the potential impact of these and other promising functional foods on clinical end points is generally not established and requires investigation.

Based on cholesterol-lowering effects, some organizations suggest that functional foods with plant sterols/stanols can be considered for people with higher cholesterol levels who do not qualify for or have insufficient response to pharmacotherapy¹¹⁶; although others have concluded that plant sterols/stanols could have unacceptable toxicities.^{122,123} In the *Prevención con Dieta Mediterránea* (PREDIMED) trial, supplementation with extra virgin olive oil or mixed nuts, combined with advice to consume a Mediterranean-type diet, led to significant reductions in cardiovascular events,³⁴ suggesting that these more natural foods could be considered as evidence-informed functional foods to reduce CVD events.

Table 4. Selected Dietary Supplements and Cardiovascular Health – Summary of the Evidence

β -Carotene	Some cohort studies have linked low serum levels or low dietary intake of β -carotene with higher CVD risk. Trials of β -carotene supplements document no benefit in the general population and increased risk of lung cancer in patients who were at high risk of lung cancer.
Calcium	Meta-analysis of trials suggests that calcium supplementation could increase the risk of myocardial infarction. No evidence for cardiometabolic benefits.
Vitamin D	Evidence from observational studies indicates that low serum vitamin D levels, which are largely determined by sun exposure, are associated with higher risk of CVD. Trials of vitamin D supplementation have not shown reductions in risk of CVD. Additional trials using higher doses of vitamin D supplementation are ongoing.
Vitamin E	Several prospective cohort studies have linked vitamin E consumption or supplementation with lower risk of CHD. Trials have failed to show reductions in CVD events with supplemental vitamin E, and 2 meta-analyses suggest that high-dose vitamin E supplements may increase total mortality.
Folic acid, Vitamins B ₆ , B ₁₂	Observational studies have associated low folate intake, low serum folate levels, and high homocysteine levels with higher risk of CVD outcomes. Trials have confirmed that folic acid supplementation lowers blood homocysteine levels. Long-term trials have not documented benefits of folic acid with or without vitamin B ₆ and vitamin B ₁₂ on CVD outcomes. In some trials, supplemental folic acid was associated with increased risk of CVD.
Fish oil	Multiple cohort studies have documented an inverse relationship between fish intake and subsequent CHD, in particular, CHD death. A meta-analysis of trials, largely in higher-risk populations, demonstrated a reduction in cardiac death with fish oil supplementation, largely because of the benefits in patients with prevalent CHD.
Multivitamins	Although some cohort studies have seen lower CVD risk with multivitamin supplements, several trials, rated to be of fair to poor quality, have not documented any clear CVD benefit of multivitamin use in mixed populations.

CHD indicates coronary heart disease; and CVD, cardiovascular disease.

Table updated from Mozaffarian et al.¹⁹

Emerging Issues: Organic, Genetic Modification

Public and media attention have increasingly considered whether foods are organic (ie, produced without artificial chemicals or pesticides) or genetically modified. Compared with conventionally grown foods, organically grown foods can contain higher concentrations of phenolic compounds and fewer pesticide residues; yet, they also have similar nutrient profiles in many other respects.^{124–126} Evidence for the health relevance of the observed differences in certain trace compounds has generally not been identified and remains controversial.^{127–129}

Genetic modification uses biotechnology to alter crop or livestock genes to improve insect or virus resistance, herbicide tolerance, nutritional qualities, or resistance to environmental stressors. In light of challenges in population growth, global climate, soil and water availability, and changing pathogens, genetic modification holds promise to improve production, healthfulness, and sustainability. Several groups reviewing the evidence for the health hazards of genetic modification have found no evidence for harms^{130–134}; however, methods for such evaluation remain heterogeneous.^{135–139} Based on first principles, genetic modification should be considered a tool, not an end point: its potential effects on human health (positive, neutral, negative) will relate to the specific compositional changes in the food, not to the method itself.¹⁴⁰

Based on current evidence, whether a food is organic or genetically modified appears to be of relatively small health relevance in comparison with the overall types of foods and diet patterns actually consumed (Table 2). Health and environmental effects of both organic and genetically modified foods require continued evaluation as these technologies progress.

Foods and Cardiometabolic Health

Individual foods represent a complex matrix of fatty acids, proteins, carbohydrate quality, micronutrients, phytochemicals, and preparation and processing methods that together modify cardiometabolic risk.^{9,141} Inference on the health effects of different foods is optimally derived from well-designed prospective observational and interventional studies of clinical end points, together with supportive evidence from interventional studies of surrogate risk markers. Relevant mechanisms and pathways are further informed and elucidated by animal and experimental models. Cardiometabolic effects of different foods can be envisioned along a spectrum of benefit versus harm (Figure 3): when considering the health effects of any food, it is important to consider: compared with what?

Fruits, Nonstarchy Vegetables, Legumes, Nuts/Seeds

Minimally processed, plant-derived foods such as fruits, nonstarchy vegetables, beans/legumes, and nuts/seeds are consistently linked to better cardiometabolic outcomes (Figure 6).^{142–145} These observed long-term benefits are supported by controlled trials of surrogate outcomes and clinical end points using dietary patterns rich in these foods.^{19–21} The effects of specific subtypes of these foods are less well established. The foods richest in phytochemicals (eg, berries, nuts) appear to be particularly potent.

Starchy Vegetables

Potatoes are a widely consumed starchy vegetable. Although potatoes contain fiber, potassium, vitamins C and B6, and other trace minerals, they predominantly contain starch (long chains of glucose) that is rapidly digested in the mouth and stomach. This high-glucose load and rapid digestion would predict cardiometabolic harms, similar to white rice and white bread (see Carbohydrate-Rich Foods, below). Relatively few long-term studies have assessed potatoes and cardiometabolic outcomes. Among those that have, higher intake of potatoes, including boiled and baked potatoes, is prospectively linked to higher incidence of diabetes mellitus, whereas potatoes, corn, and peas are linked to greater long-term weight gain, in contrast to nonstarchy vegetables that are associated with protection against weight gain and diabetes mellitus.^{28,55,146,147} Potatoes have also been cross-sectionally linked to greater diabetes mellitus, higher blood glucose, and lower HDL-cholesterol,¹⁴⁸ and, in retrospective studies, higher risk of stroke.¹⁴⁹ Based on these concerns, russet/white potatoes are generally excluded from recommendations to increase vegetable consumption.

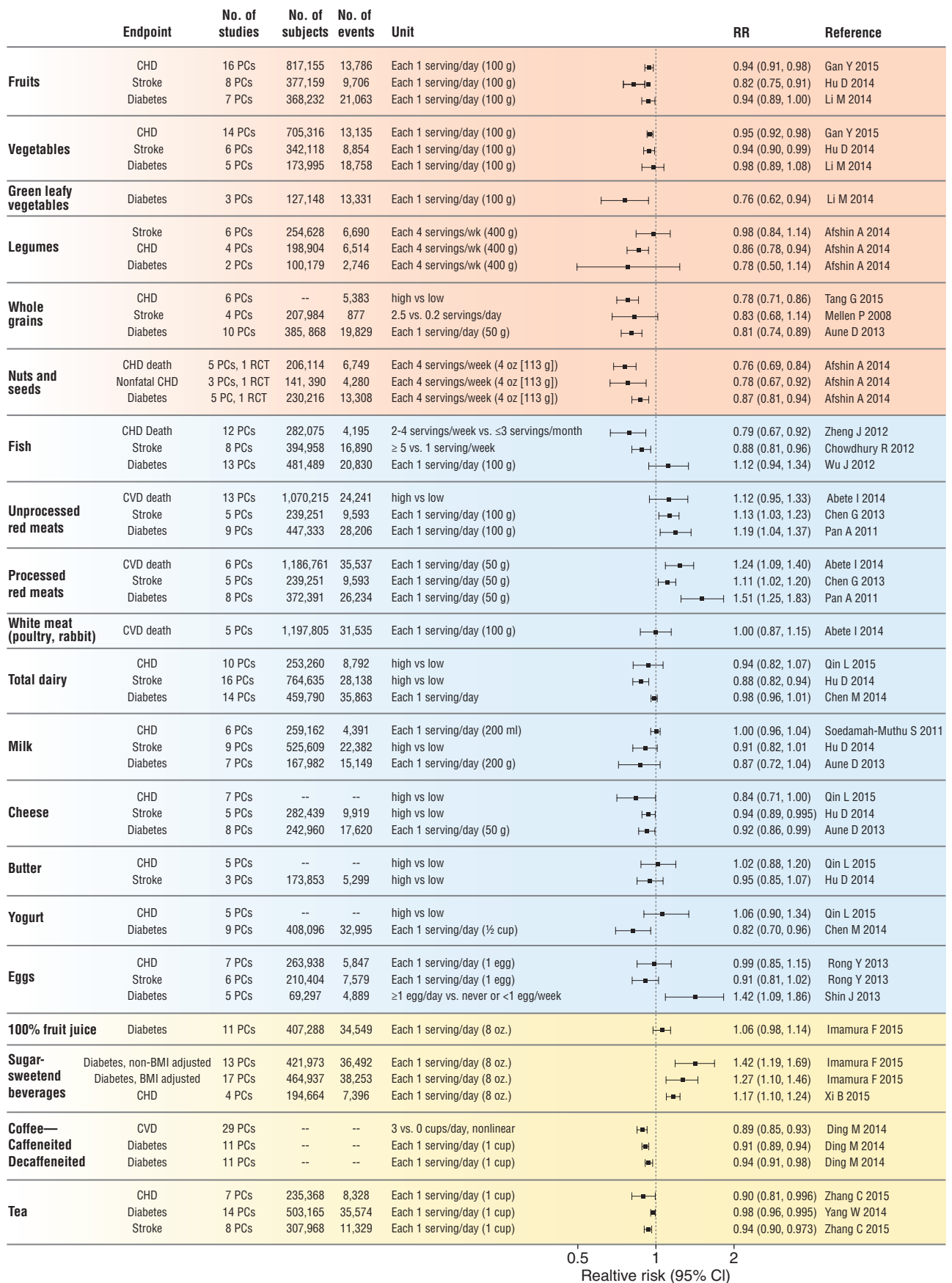
The long-term effects of other specific varieties of potatoes or other starchy vegetables are less established. Cassava is starch-rich, similar to peeled potatoes, but the long-term cardiometabolic effects remain uncertain^{150,151}; glycemic responses may be ameliorated by its consumption in mixed meals. Similarly, the long-term health effects of yams, sweet potatoes, and parsnips (which each tend to contain relatively less starch relative to fiber compared with russet or white potatoes), corn (which can be considered either a grain or vegetable), and peas (which is a legume) are not well established. In recent work, among major vegetables consumed in the United States, potatoes, corn, and peas were each associated with long-term weight gain, whereas other vegetable subtypes were each associated with weight loss.⁵⁵

Based on high-starch content, greater glycemic responses, and some adverse long-term associations with clinical end points, high intakes of potatoes are not advisable. If consumed, small portion sizes, including the (nutrient-rich) skin, and mixed meals (eg, mixed with healthful foods such as vegetable oils, fish, nonstarchy vegetables) would be prudent.

Carbohydrate-Rich Foods

Carbohydrate-rich foods comprise about half or more of all calories in most diets globally. Although total carbohydrate consumption has little relation to cardiometabolic health, the quality of carbohydrate-rich foods is linked to risk (Figures 6 and 7).^{152–160} Notably, the conventional chemistry-based classification of simple (sugar) versus complex (starch) carbohydrates has little physiological relevance, because saccharide chain length has little influence on digestion rate or metabolic effects of different carbohydrates. More meaningful characteristics include dietary fiber content, glycemic responses to digestion, processing (intact, partially milled, fully milled, liquid), and whole-grain content.¹⁹

Each of these metrics can be altered relatively independently (Figure 8). Whole grains include endosperm (starch), bran (fiber, protein, B vitamins, minerals, flavonoids, tocopherols), and germ (protein, fatty acids, antioxidants, phytochemicals). When whole grains are intact (eg, quinoa) or partially intact (eg,



0.5 1 2
Relative risk (95% CI)

Figure 6. Meta-analyses of foods and coronary heart disease, stroke, and diabetes mellitus. BMI indicates body mass index; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; PC, prospective cohort; RCT, randomized clinical trial; and RR, relative risk.

steel-cut oats, stone-ground bread), the bran protects the starchy endosperm from oral, gastric, and intestinal digestion, thereby reducing glycemic responses. In finely milled whole-grain products (eg, most whole-grain breads, breakfast cereals), the bran (fiber) and germ content remain similar, but the exposed endosperm can be rapidly digested, resulting in higher glycemic responses. When the bran and germ are removed entirely (eg, refined grains: white bread, white rice, most cereals and crackers), only starchy endosperm remains, with high glycemic response and containing little fiber, minerals, or other nutrients. Some high-starch vegetables (eg, russet or white potatoes) have similar metabolic characteristics as refined grains (see Starchy Vegetables, below). Refined grains and high-starch vegetables are digested rapidly, with blood glucose and insulin responses that can be similar to simple sugars. Finally, sugars in liquid form (eg, soda, sports drinks, sweetened ice teas) appear even less satiating and more obesogenic than equivalent sugar in solid form (see Sugar-Sweetened Beverages, Noncaloric Sweeteners; and Carbohydrates, Added Sugars, Fructose; below).

Based on these effects, refined grains (starchy endosperm without the bran or germ), other starch-rich foods (eg, white potatoes), and added sugars appear to induce relatively similar cardiometabolic harms. When starch enters the mouth without the natural shelter of a whole-grain or fiber-rich food structure, oral amylase promptly initiates its breakdown into free glucose, a process rapidly completed in the upper small intestine. Consequently, refined grains such as white bread, corn flakes, and rice; starchy foods such as russet or white potatoes; and pure table sugar all produce brisk rises in blood glucose and insulin (known as their glycemic index; or, when multiplied by portion size, as their glycemic load).¹⁶¹ This rapid digestion may induce multiple adverse effects, potentially stimulating reward/craving areas in the brain, activating hepatic de novo lipogenesis, increasing uric acid production, and promoting visceral adiposity.^{49,162–166} In addition, high glycemic load diets may even reduce total energy expenditure.⁵⁰

In addition to direct harms, low-quality carbohydrates such as refined grains, certain potatoes, sugar-sweetened beverages (SSBs), and sweets may increase cardiometabolic risk by displacing other, healthier foods in the diet, eg, fruits, vegetables, nuts, legumes, and minimally processed whole grains. Consistent with this constellation of adverse effects, poor-quality carbohydrates are associated with long-term weight gain, diabetes mellitus, and CVD.^{29,89,158,167} Harms appear to be larger in women^{89,167} and others predisposed to insulin resistance and atherogenic dyslipidemia, and smaller in men and in younger, lean individuals with high physical activity.

Based on their adverse effects and pervasiveness in modern diets, reducing refined grains, starches, and added sugars is a major dietary priority for cardiometabolic health.²¹ Although SSB intake is declining in the United States, intakes of added sugars in other foods and, even more so, of refined grains continue to represent a major part of the diet. Currently, nearly 3 in 4 Americans consume too many refined grain products.²¹ Indeed, many people seek out these products, erroneously believing they are beneficial based on their promotion as low-fat or fat-free foods. Recognizing this pervasive confusion, the 2015 Dietary Guidelines Advisory Committee specified that, “consumption of ‘low-fat’ or ‘nonfat’ products

with high amounts of refined grains and added sugars should be discouraged.”²¹ Because of the multiple independent characteristics that influence carbohydrate quality (eg, fiber, glycemic response, processing, whole-grain content), no single criterion appears perfect for distinguishing carbohydrate-rich foods. Among several recommended metrics, a ratio of total carbohydrate to dietary fiber (g/serving) of <10:1 is a helpful practical guide to identify more healthful grain choices.^{168,169}

Meats

Similar to many other foods, guidelines on meat consumption in cardiometabolic health were historically based on minimally adjusted ecological comparisons and theorized effects of isolated nutrient content (eg, saturated fat, dietary cholesterol). However, modern evidence supports relatively neutral cardiovascular effects of saturated fat and dietary cholesterol and more relevant effects of other compounds in meats, such as heme iron, sodium, and other preservatives (see Nutrients and Cardiometabolic Health, below).

Consistent with these findings, although a minority of individual studies suggest similar cardiovascular risk for unprocessed red meat versus processed meats,^{170,171} many other individual studies and meta-analyses support a much stronger effect of processed meats, including low-fat deli meats, on CVD (Figure 6).^{172–174} Based on the observed effect sizes and relationships seen with other, noncardiovascular outcomes, residual confounding could explain some or all of the observed modest associations of unprocessed red meat with CVD.¹⁷⁵ In contrast, the observed association of processed meats with CVD is quite plausible: much of it can be explained merely by the predicted effects of the high levels of sodium (~400% higher in processed meats) on BP levels and the subsequent effects of this elevated BP on clinical endpoints.¹⁷⁶ Diet-microbiome interactions may also play a role,¹⁷⁷ although such interactions would predict similar or stronger risk for unprocessed red meats than processed meats, when in fact the reverse is seen in many populations.

Interestingly, both red and processed meats, regardless of fat content, are linked to a higher incidence of diabetes mellitus, although with approximately double the risk, gram-for-gram, for processed meats than for unprocessed red meats.^{172,178} Mechanisms require further study, but this observed risk for diabetes mellitus may be linked to iron content^{179,180} and possibly lipid and amino acid metabolites, advanced glycation end products, trimethylamine *N*-oxide, and nitrates/nitrites.^{181,182}

In sum, these findings provide little support for conventional guidelines to choose meats based on fat content, ie to focus on selecting lower-fat or lean meats. Rather, it would be prudent to consume small amounts of unprocessed red meats (eg, 1–2 servings/wk) to obtain readily bioavailable iron and zinc, while minimizing or entirely avoiding processed meats such as bacon, sausage, salami, and low-fat processed deli meats (chicken, turkey, pork, roast beef).¹⁸³

Differences in bovine feeding systems can influence nutrient contents of meats. For example, in comparison with grain, grass feeding results in less intramuscular fat and therefore, when visible (extramuscular) fat is trimmed away, higher contents of omega-3 polyunsaturated fats, conjugated linoleic acid, and vitamins A and E, and lower contents of saturated,

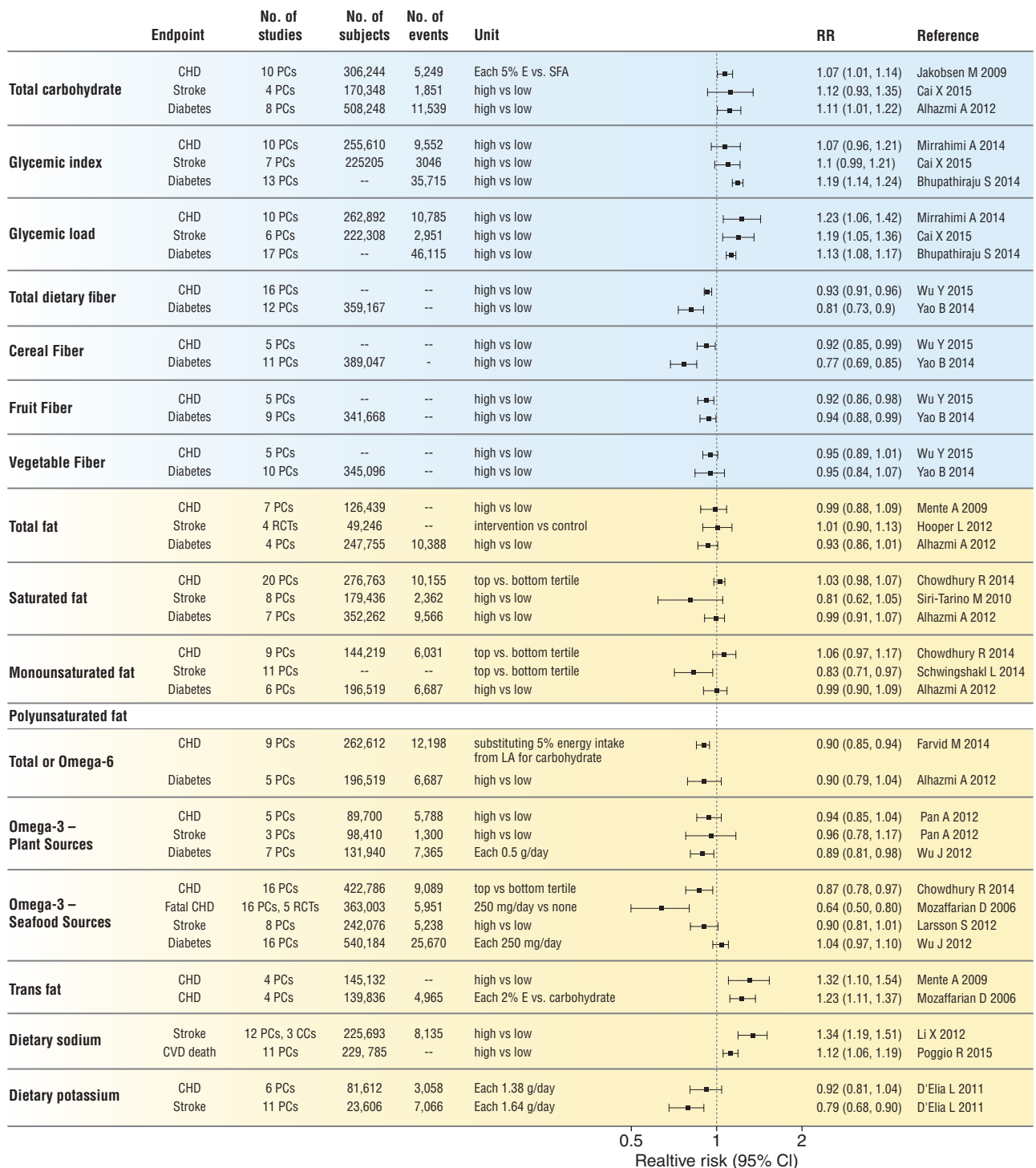


Figure 7. Meta-analyses of nutrients and coronary heart disease, stroke, and diabetes mellitus. CHD indicates coronary heart disease; CI, confidence interval; LA, linoleic acid; PC, prospective cohort; RCT, randomized clinical trial; RR, relative risk; and SFA, saturated fatty acid.

monounsaturated, and trans-18:1 fats.^{184,185} However, although grass feeding consistently increases the relative proportions (as a percent age of total fatty acids) of omega-3 fats, the absolute content (g per 100 g beef) can be the same, higher, or even lower because of decreased total fat content of the meat.^{184,185} Thus, the health implications of grass feeding and these modest nutrient differences require further study.

Poultry, Eggs

Relatively few studies have focused on poultry as a risk factor for CVD or diabetes mellitus, with few systematic reviews or meta-analyses (Figure 6).¹⁷⁴ In several large studies, poultry is not significantly associated with CVD events;^{174,186–189} and in other cohorts, with modestly lower risk of CVD, with smaller observed benefits than seen for fish, nuts, or legumes.^{52,53} Large

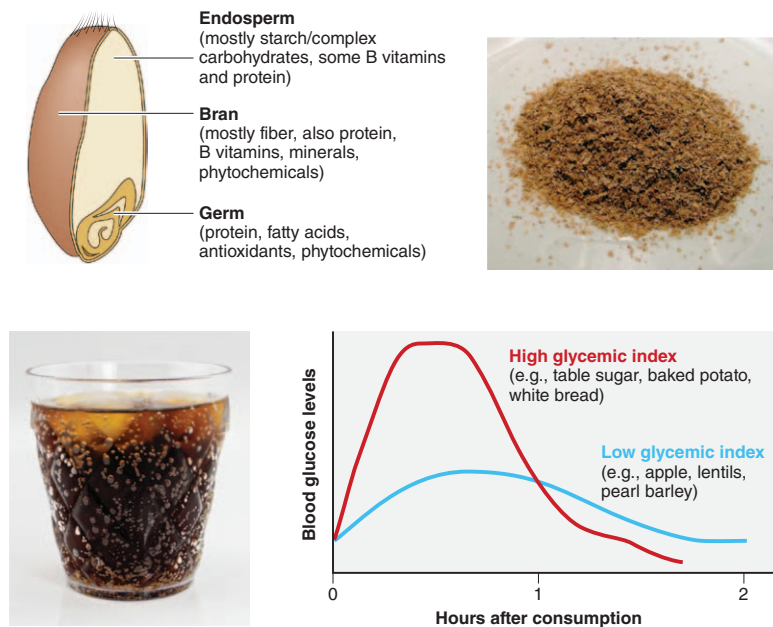


Figure 8. For defining carbohydrate quality, several characteristics appear to independently alter the cardiometabolic health effects of carbohydrate-rich foods. These include whole-grain content (**top left panel**), ie, based on the content of milled, semiprocessed, or intact whole grain including the bran and germ; fiber content (**top right panel**), influenced largely by the content of bran; food structure (**bottom left panel**), in particular, whether the food is solid or liquid (such as sugar-sweetened beverages); and glycemic response (**bottom right panel**), determined by the amount and accessibility of starch and sugar. GI indicates glycemic index.

studies evaluating poultry and incident diabetes mellitus have shown mixed results including higher risk, no risk, and lower risk.^{178,190–195} These conflicting findings do not permit a strong inference on the cardiometabolic effects of poultry.

Egg consumption has no significant association with incident CVD in general populations (Figure 6).^{196,197} Conversely, eggs may influence and interact with diabetes mellitus.¹⁹⁷ Frequent consumers (7+ eggs/wk) have higher new-onset diabetes mellitus; and among patients with prevalent diabetes mellitus, frequent consumers experience more clinical CVD events. On the other hand, higher egg consumption is associated with lower risk of hemorrhagic stroke,¹⁹⁶ potentially related to the protective effects of dietary cholesterol on vascular fragility.^{198,199} As with poultry, the relevance of these conflicting findings remains uncertain. Overall evidence suggests small cardiometabolic effects of occasional consumption (eg, up to 2–3 eggs/wk); and possible harm with frequent consumption, especially among diabetics patients. Of note, the 2015 Dietary Guidelines Advisory Committee concluded that dietary cholesterol is not a “nutrient of concern for overconsumption,”²²¹ based on low mean population cholesterol intake and no appreciable relationships between dietary cholesterol and serum cholesterol or clinical cardiovascular events in general populations.^{21a}

In sum, occasional consumption of poultry and eggs appears relatively neutral for cardiometabolic health, without strong evidence for either risks or benefits. Until more evidence is generated, it may be prudent to consider these foods as healthful alternatives to harmful foods (eg, processed meats, refined grains, sugars) and yet as relatively unhealthy alternatives in comparison with beneficial foods (eg, fish, nuts, legumes, fruits).

Fish

The cardiovascular effects of fish and omega-3 consumption have been studied for decades. In comparison with little or no consumption, moderate consumption of fish ($\approx 2+$ servings/wk) and long-chain omega-3 (≈ 250 mg/d) associates with

lower risk of fatal CHD (Figures 6 and 7).^{200–202} In contrast, higher intakes do not appear to appreciably reduce risk further. In comparison with fatal cardiac events, fish consumption has weaker associations with nonfatal cardiac events and with stroke.^{201,203,204} The specificity for fatal CHD, rather than all CVD events, suggests that this association may not be fully explained by residual confounding. This finding is also consistent with meta-analyses of randomized fish oil trials that demonstrate risk reductions for cardiac death, but not total CVD, CHD, or stroke.¹⁰⁹ However, these latter pooled results obscure the differences in results of individual randomized trials over time: 4 of 5 earlier trials, yet none of several newer trials, demonstrate benefits.²⁰⁵ These discrepant results could be attributable to more aggressive lipid- and BP-lowering drug treatment in recent trials. Alternatively, because the dose-response effect of omega-3’s for fatal CHD appears nonlinear,^{200,201} higher background intakes of fish among subjects enrolled in more recent trials may have diminished the ability to detect any benefits of adding fish oil.²⁰⁵ Additional clinical trials of fish oil supplements are ongoing,²⁰⁶ but may not be adequately powered to evaluate fatal (rather than total) CHD or subgroups with low fish intake, for whom the benefits appear most plausible.

Notably, in meta-analyses of multiple controlled interventions, fish and omega-3 consumption improve major physiological risk factors for CVD including BP, heart rate, endothelial function, triglycerides, and adiponectin.^{201,205} Omega-3s also reduce inflammatory biomarkers, reduce myocardial oxygen use, and enhance cardiac function.^{201,205} Overall, although the null results of recent fish oil trials are concerning, the cumulative evidence from observational studies, clinical trials, and controlled interventional studies continues to favor plausible cardiovascular benefits of modest dietary fish consumption, in particular for the endpoint of CHD death. Based on conflicting findings from recent trials, fish oil supplementation has uncertain benefits but an excellent safety profile and may be

considered as an adjunct to fish intake or for high-risk patients who do not eat fish.

The effects of fish consumption on other vascular conditions including stroke, heart failure, atrial fibrillation, and cognitive decline remain unclear, with conflicting findings.^{201,203,207,208} Fish and omega-3 intake also have little association with the risk for diabetes mellitus, although protective associations are seen in Asian populations^{209–211} and fish oil supplementation modestly raises adiponectin.²¹² Types of fish consumed and preparation methods may influence cardiometabolic effects, with greatest benefits perhaps obtained from nonfried, dark-meat (oily) fish that contain up to 10-fold higher omega-3 fatty acids than white-meat fish.²⁰¹

Growing evidence suggests that the presence of persistent organic pollutants (eg, dioxins, polychlorinated biphenyls) may partly reduce cardiometabolic benefits of fish consumption^{213–215}; less evidence suggests a potential for net harm, due to the countervailing benefits of omega-3s. Methylmercury consumed from fish has no detectable influence on incident cardiovascular events, hypertension, or diabetes mellitus.^{216–218} To optimize neurodevelopment in their children attributable to the benefits of fish consumption, women who are or may become pregnant or nursing should follow US Food and Drug Administration guidance to eat 2 to 3 servings/wk of a variety of fish lower in mercury, while avoiding only selected specific species (Gulf of Mexico tilefish, shark, swordfish, king mackerel; albacore tuna up to 6 oz/wk).²¹⁹

While patients often ask about health effects of farmed (aquaculture) versus wild-caught species, few species are commonly available as both: most are either predominantly farmed (eg, tilapia, catfish, carp, shrimp, oysters) or wild-caught (eg, tuna, pollock, crab, cod).²²⁰ One exception is salmon, of which about one-third are wild-caught (principally from Alaska) and two-thirds are farmed (eg, from Norway, Chile). Because farmed salmon are fed, while wild salmon hunt for their food, farmed salmon have similar or higher levels of omega-3 fatty acids²⁰¹ and likely similar net health benefits.²⁰⁰

Milk, Cheese, Yogurt

The cardiometabolic effects of different dairy foods represent a major unanswered question of modern nutrition science. Most dietary guidelines simply group different types together (eg, grouping milk, cheese, and yogurt as “dairy”), categorize these by fat content, and then recommend selection of low-fat products.²¹ Such recommendations largely derive from theoretical considerations about selected single nutrients (calcium, vitamin D, calories, saturated fat), rather than empirical evidence on health effects of the actual foods.

In longitudinal studies evaluating habitual intakes of dairy foods, relationships with CVD and diabetes mellitus do not consistently differ by fat content but appear more specific to food type: eg, cheese, yogurt, milk, butter (Figure 6).^{57,221–226} For example, the intake of yogurt, but not milk, is consistently associated with lower incidence of diabetes mellitus, whereas the intake of cheese, which has high calorie, fat, and saturated fat content, is also associated with lower diabetes risk in several although not all studies.^{57,179–184,224,226–228} Although total milk intake is generally unassociated with diabetes mellitus, fermented milk is linked to lower risk,^{57,227,229} suggesting a potential influence of fermentation, particularly in light of

the separate findings for cheese. Bacterial cultures used for fermentation can synthesize vitamin K2 (menaquinones), which may improve insulin sensitivity.^{230,231} These findings suggest that the health effects of dairy may depend on multiple complex characteristics, eg, probiotics in yogurt, fermentation of cheese. The metabolic effects of specific dairy foods and fermented products represent promising areas for further investigation.

In short-term randomized trials, adding milk or dairy to energy-restricted diets increases lean mass and reduces body fat, whereas no significant body compositional effects are seen when adding dairy to ad libitum diets.^{232,233} Long-term effects may vary by the type of dairy. For instance, children who drink more low-fat milk gain more weight, whereas those who drink more whole-fat milk gain less weight, over time.^{62–66} In longitudinal studies among adults, neither low-fat nor whole-fat milk are appreciably related to chronic weight gain.^{28,29,51} This lack of difference may relate to caloric compensation: when adults consume more low-fat dairy, they compensate in the long term by increasing their consumption of carbohydrates.²⁹

The STRIP trial randomly assigned 1062 Finnish infants to dietary intervention versus control, with follow-up for up to 20 years. For the first 3 years, the intervention focused on lowering total fat and saturated fat, while also increasing unsaturated fats from canola oil, other vegetable oils, and fish. At 3 years, no differences were seen in body weight, even among children most compliant with the low-fat diet.²³⁴ Subsequently, the intervention group received comprehensive dietary counseling, including to replace saturated fat with unsaturated fat, reduce salt intake, replace refined grains/cereals with whole grains, increase dietary fiber, increase fruits and vegetables, avoid smoking, and be physically active.²³⁵ The control group received only basic health education. Unsurprisingly, this comprehensive lifestyle advice, in comparison with no intervention, improved metabolic health.²³⁵ These results provide little inference on the specific effects of lowering saturated fat or dairy fat among children.

The impact of cheese consumption on long-term weight may vary depending on how it is consumed: more weight gain is seen when cheese is accompanied by refined carbohydrates, and less weight gain or even relative weight loss when cheese replaces refined carbohydrates.²⁹ Yogurt appears protective against long-term weight gain,^{28,29,51} although when sugar-sweetened, approximately half the benefit appears lost.²⁹ Animal-experimental studies and trials in humans suggest that probiotics and probiotic-microbiome interactions play a key role in the protective effects of yogurt, both for obesity and related conditions such as gestational diabetes.^{52–54,236–241}

Interestingly, dairy fat itself may promote cardiometabolic health. In cohorts using objective blood biomarkers, greater dairy fat consumption is associated with a lower incidence of diabetes mellitus^{59–61,242,243} and CHD,^{39,244,245} and with mixed findings for stroke.²⁴⁶ It remains unclear whether such findings relate to health benefits of specific dairy fatty acids (eg, branched-chain fatty acids, medium-chain saturated fats, specific ruminant trans fats), other lipid-soluble factors in dairy fat, other factors in high-fat dairy foods (eg, production of vitamin K2 from fermentation of cheese), or unknown endogenous (nondietary) determinants of these blood biomarkers.²⁴⁷

Whatever the explanation, little evidence supports the opposing hypothesis, ie, the superiority of low-fat dairy products for health, including for risk of obesity.

In sum, dairy products represent a diverse class of foods, with complex effects that vary by specific product type and with emerging mechanistic pathways that appear to include influences of fermentation and probiotics. No long-term studies support harms, and emerging evidence suggests some potential benefits, of dairy fat or high-fat dairy foods such as cheese. Together these findings provide little support for the prevailing recommendations for dairy intake that are based largely on calcium and vitamin D contents, rather than complete cardiometabolic effects; that emphasize low-fat dairy based on theorized influences on obesity and CHD, rather than empirical evidence; or that consider dairy as a single category, rather than separately evaluating different dairy foods. The current science supports consuming more yogurt and possibly cheese; with the choice between low-fat versus whole-fat being personal preference, pending further investigation. This new evidence also calls for substantial further investment in research on cardiometabolic effects of dairy foods, including relevant components and molecular mechanisms.

Butter

In a large pooling project of European cohorts, individuals consuming any butter, in comparison with none, experienced a lower risk of diabetes mellitus.²⁴⁸ However, among butter consumers, no further dose-response was seen, suggesting potential for reverse causation (bias) among nonconsumers. In either case, these findings would suggest that butter is, at worst, neutral for diabetes mellitus. Butter consumption is also not significantly associated with incident CHD,²²³ stroke,²²² or total mortality⁵⁸ (Figure 6). Remarkably few studies have reported on these relationships, suggesting potential for publication bias. Because such bias would skew toward the reporting of large associations, the absence of significant associations in published reports makes it implausible that multiple other studies have identified but not reported harmful relationships. Increases in butter consumption are associated with modestly greater long-term weight gain.²⁹ In sum, butter appears relatively neutral for cardiometabolic health, consistent with findings for total saturated fat (see Saturated Fat, below); and slightly adverse for long-term weight regulation.

Vegetable Oils

The cardiometabolic effects of vegetable oils have conventionally been considered in light of their fatty acid composition, ie, of monounsaturated, polyunsaturated, and saturated fats (see sections on each of these fats, below). Emerging evidence suggests that health effects may also relate to other constituents, in particular, flavonoid (phenolic) compounds (see Phenolic Compounds, below).^{30,249–252} For instance, extra virgin olive oil contains oleocanthal, a phenolic that binds cyclooxygenase (COX) 1 and 2 receptors (causing a characteristic burning throat sensation, similar to that induced by chewing non-coated aspirin) and exhibits anti-inflammatory properties.^{30,251,252} In the PREDIMED randomized trial, participants receiving extra virgin olive oil and dietary advice to consume a Mediterranean diet experienced 30% lower risk of stroke, MI, or death, in comparison with control.³⁴ In the intervention group, ≈60% of the extra virgin olive oil simply

replaced regular olive oil, commonly used in Spain. These findings, together with mixed evidence for cardiovascular benefits of monounsaturated fats²¹ (see below), which represent most of the fats in olive oil, suggest that fatty acid profiles may not be the only relevant determinant of health effects of oils.

Little investigation has been done on the long-term health effects of tropical oils, such as palm or coconut. These oils contain saturated fat, but also other compounds, eg, medium-chain fatty acids in coconut oil that could have health benefits.²⁵³ Modern nutritional science has demonstrated the limitations of drawing conclusions about health effects of any food product based on theories about its nutrient contents.⁹ Thus, long-term investigations are urgently needed to make evidence-informed decisions about avoiding or increasing the use of tropical oils. Industrially interesterified oils are increasingly common, but similarly without long-term evidence on their health effects or safety.²⁵⁴

Based on overall evidence for cardiometabolic effects, the current evidence supports generally increased consumption of vegetable oils in place of refined grains, starches, sugars, meats, butter, and lard. Among different oils, the benefits of soybean, extra virgin olive, and canola oil may be best established. Virgin oils (eg, extra virgin olive oil, virgin soybean oil) may be preferable because of their low-temperature refining that may better preserve trace phenolic compounds; further study of how processing methods of vegetable oils influence phytochemicals and health effects is needed. In the future, certain vegetable oil blends may offer particular cardiometabolic benefits, eg, combining flax and safflower oils, or canola oil and omega-3 fatty acids.²⁵⁵ Sufficient evidence to support strong promotion or avoidance of tropical oils is lacking. Additional metabolic and long-term studies of different specific vegetable oils, including refined and unrefined versions, are urgently needed.

SSBs, Noncaloric Sweeteners

Both long-term prospective cohorts and clinical trials demonstrate that SSBs increase adiposity.²⁵⁶ Per serving, SSBs associate with greater long-term weight gain than nearly any other dietary factor.²⁸ These effects are likely attributable to their high glycemic and insulin responses and low satiation (see Carbohydrate-Rich Foods, above). SSBs are also associated with increased incidence of diabetes mellitus and CHD (Figure 6).^{257,258} These effects appear partly but not entirely mediated by adiposity, consistent with independent adverse effects of SSBs on other pathways such as hepatic de novo lipogenesis, visceral fat accumulation, and uric acid production (see Carbohydrate, Added Sugars, Fructose, below). Globally, SSB consumption is highest at younger ages,²⁵⁹ boding poorly for long-term global health if such high intake continues as these populations age. Worldwide, 184 000 cardiometabolic deaths per year are estimated to be attributable to SSB consumption.²⁶⁰

With growing policy attention on sugar-sweetened beverages and added sugars, the food industry is increasingly seeking low-calorie and noncaloric alternatives.²⁶¹ These include artificial sweeteners (eg, saccharin, sucralose, aspartame) and natural low-calorie (also termed high-intensity or nonnutritive) sweeteners (eg, stevia). Based on long-term observational studies and intermediate-duration (eg, 2 years) clinical

trials,^{28,256} these appear to be better alternatives than sugar for people who consume large quantities of SSBs. However, based on animal experiments and limited human data, these artificial and nonnutritive sweeteners may not be benign, with potential for impact on cognitive processes (eg, reward, taste perception), oral-gastrointestinal taste receptors, glucose-insulin and energy homeostasis, metabolic hormones, and the gut microbiome.^{262–265} Cognitive effects, for example, may be especially relevant in children: if tastes become accustomed to such intense sweetness, will palates and attraction be reduced for naturally sweet, healthful foods such as apples or carrots? In sum, based on limited available evidence, artificial and non-nutritive sweeteners appear to be a useful intermediate step to reduce harms of SSBs (eg, to switch from regular to diet soda) but should subsequently also be reduced (eg, to switch from diet soda to seltzer water) to prevent potential long-term harms. Other uses of such sweeteners should not yet be considered innocuous for cardiometabolic health.

100% Fruit Juice

Although SSB and 100% fruit juice have similar sugar content, the latter is linked to relatively smaller long-term weight gain.²⁸ Furthermore, the intake of sugar-sweetened fruit juice, but not 100% fruit juice, is associated with incident diabetes mellitus in longitudinal studies (Figure 6).^{257,266} These findings suggest that 100% fruit juice may have other beneficial components, eg, dietary fiber, vitamins, and phytochemicals, that at least partly offset any harms. In short-term trials, fruit juice has no appreciable effects on blood pressure, cholesterol levels, or glucose-insulin homeostasis.^{267,268} In sum, moderate intake of 100% juice (eg, up to one serving/d) appears reasonable, especially given the low intakes of whole fruit in most populations; higher intake of 100% juice may not be prudent because of links to long-term weight gain.

Coffee, Tea

While coffee is commonly thought of in relation to its caffeine content, it represents a liquid extract of legumes (coffee beans) that contains many active compounds. Both caffeinated and decaffeinated coffee are associated with lower onset of diabetes mellitus in a dose-dependent fashion (Figure 6).²⁶⁹ Coffee intake also is associated with lower risk of CHD and stroke but in a nonlinear fashion: in comparison with no intake, the lowest risk is seen at 3 to 4 cups/d, with increasing risk at higher intakes.²⁷⁰ Several small controlled trials have evaluated the potential effects of habitual coffee consumption on cardiometabolic risk factors, with mixed and inconsistent findings to date.^{271–273} A Mendelian randomization study, evaluating genetic variants linked to coffee intake, did not find associations with any cardiovascular or metabolic risk factors.²⁷⁴

Similar to coffee consumption, tea consumption is associated with a lower risk of diabetes mellitus and CVD, especially comparing very frequent consumption (3–4 cups/d) with none (Figure 6).^{275,276} Yet, controlled trials of tea have not identified robust benefits on markers of glucose-insulin homeostasis.^{277,278} In comparison, in meta-analyses of trials, green tea, black tea, and herbal roselite tea each modestly lower BP,^{279–281} whereas green and black tea, but not herbal roselite tea, also lower LDL-cholesterol.^{282–284}

Overall, observational studies support potential cardio-metabolic benefits of both coffee and tea. Plausible biological mechanisms that could explain the size of these associations have not been confirmed, with the exception perhaps for tea and cardiovascular risk. Based on current data, tea and coffee do not increase cardiometabolic risk and can be safely consumed, and green and black tea may reduce cardiovascular risk. Further research on these potential benefits is needed before actively encouraging consumption as a means to reduce risk.

Alcohol

Habitual heavy alcohol use causes up to one-third of nonischemic dilated cardiomyopathy in many nations.²⁸⁵ Ventricular dysfunction is often irreversible, even when alcohol use is stopped; while continued drinking is associated with high mortality. Habitual alcohol and acute binges are associated with higher risk of atrial fibrillation.²⁸⁶ Like other liquid calories (with the exception of milk), alcohol intake also is associated with higher long-term weight gain.²⁸⁷ Conversely, in comparison with nondrinkers, regular moderate alcohol consumption – up to ≈ 2 drinks per day for men, ≈ 1 to 1.5 drink per day for women – is associated with lower incidence of CHD and diabetes mellitus, although not stroke.^{288,289} Such observational analyses could partly overestimate benefits, because never drinkers could include those who have avoided alcohol because of unmeasured factors that relate to later poor health.²⁹⁰ Yet, magnitudes and consistency of observed lower risks of CHD and diabetes across diverse populations, together with favorable effects on HDL-cholesterol, insulin resistance, and fibrinogen in controlled trials,²⁹¹ provide strong evidence for at least some cardiometabolic benefit of moderate alcohol use. Although a common perception is that the effects are specific to red wine, cardiometabolic benefits have also been seen for white wine, beer, and spirits.²⁹² This could relate to the physiological effects of alcohol itself,²⁹¹ or the phenolics in wine and beer, as well.²⁹²

Alcohol use exhibits a “J-shape” with all-cause mortality, with lowest risk observed between 1 drink/wk and 1 drink/d, and higher risk thereafter.²⁸⁹ In addition, the pattern of drinking is important: benefits are seen with moderate use across multiple days per week, not with high levels on a few days.²⁹³ Across the population, alcohol produces net harms because of the increased risk of cancers, liver disease, cardiomyopathy, accidents, violence, homicides, and suicides.^{1,294} Thus, alcohol intake should not be recommended as a means to reduce CVD risk. Adults who already drink alcohol should be advised to limit their use to moderate levels.

Nutrients and Cardiometabolic Health

Phenolic Compounds

Bioactive polyphenols include flavonols (eg, in onions, broccoli, tea, various fruits), flavones (in parsley, celery, chamomile tea), flavanones (in citrus fruits), flavanols (flavan-3-ols) such as catechins and procyanidins (in cocoa, apples, grapes, red wine, tea), anthocyanidins (in colored berries), and iso-flavones (in soy). In laboratory studies and randomized trials, flavonoid-rich cocoa has small but measurable benefits on BP, endothelial function, insulin resistance, and blood lipids.^{295–297}

BP-lowering occurs with as little as 6.3 g/d (30 kcal/d) of commercial dark chocolate and correlates with increased endothelial nitric oxide production.²⁹⁸ The latter mechanism also suggests potential cardiovascular benefits beyond lower BP per se. A few short-term trials of other dietary sources (eg, tea, red wine, grapes) or specific flavonoid extracts have not consistently improved BP, lipid levels, or endothelial function.^{295–297} Some observational studies evaluating total or selected dietary flavonoids observe lower risk of cardiometabolic events^{299,300}; no long-term clinical trials have been performed. The remarkable heterogeneity of different flavonoids and their dietary sources limits inference for class effects, and clinical benefits and dose-responses are not well-established. Yet, many foods with growing evidence for cardiometabolic benefits – eg, berries,³⁰¹ nuts,¹⁴⁵ extra virgin olive oil³⁴ – are rich in phenolics, and the documented physiological effects are promising and provide clear impetus for further study.

Sodium

In North America and Europe, most sodium ($\approx 75\%$) comes from packaged foods and restaurants, and a minority from home cooking or table salt; whereas in Asian countries, most sodium comes from soy sauce and salt added during cooking or at the table.³⁰² Nearly every country in the world exceeds the recommended mean national intake of 2000 mg/d.³⁰³

Sodium raises BP in a dose-dependent fashion, with stronger effects among older individuals, people who have hypertension, and blacks.³⁰⁴ In meta-analyses of longitudinal studies, high sodium intakes are associated with incident total stroke, stroke mortality, and CHD mortality (Figure 7).^{305–307} This is supported by the strength of BP as a surrogate outcome³⁰⁸ and by ecological and experimental studies of sodium and CVD.³⁰⁴ Indeed, the latter studies suggest that chronically high sodium induces additional, BP-independent damage to renal, myocardial, and vascular tissues.^{309,310}

Nearly all observational studies demonstrate a positive association between very high sodium intakes (eg, 4000+ mg/d) and CVD events, in particular stroke.^{305–307} Some studies have also observed a potential J-shaped relationship, with increased CVD risk at modest intakes (eg, <3000 g/d).^{311–313} These findings have generated recent controversy about the optimal lowest levels of sodium consumption.³¹⁴

The assessment of sodium in observational studies, whether by urine spot, 24-hour collection, or diet questionnaire, has unique potential biases.³¹⁵ These include potential for incomplete 24-hour urine collections (leading to underestimation of sodium intake, especially in less compliant, sicker individuals); reverse causation (ie, due to at-risk subjects, such as those with higher BP or diabetes mellitus, actively lowering their sodium intake); confounding by physical activity (which increases total energy consumption, that then increases total sodium intake³¹⁶); and confounding by frailty and other reasons for low total energy consumption (given the very strong correlation between sodium and total energy consumption). These limitations together could explain the J-shapes seen in certain observational studies.

In comparison, during extended surveillance in a large sodium study that excluded sick individuals at baseline and collected multiple 24-hour urine samples per subject, minimizing the potential influence of these biases, participants

with lowest intakes (<2300 mg/d) experienced 32% lower CVD risk than those consuming high intakes, with evidence for linearly decreasing risk.³¹⁷ In ecological studies, the lowest mean intake level associated with both lower systolic BP and a lower rise in BP with aging is 614 mg/d.³¹⁸ In randomized controlled feeding trials, BP reductions have been documented down to intakes of 1500 mg/d.³¹⁹ In meta-analyses of prospective observational studies, the lowest mean intakes associated with lower risk of CVD events ranged from 1787 to 2391 mg/d.³⁰⁵ Together, these findings support the recommended target intakes in current national and international dietary guidelines, which range from 1200 to 2400 mg/d.^{110,313,320–323}

Although large reductions in sodium can increase renin-aldosterone and serum triglyceride levels,³²⁴ the effects of more moderate, gradual reductions on these pathways are not established. It also remains unclear whether such physiological effects could offset, let alone reverse, the BP-lowering benefits of sodium reduction in order to explain the J-shaped relations with CVD risk seen in some observational studies. Overall, although adverse effects of rapid sodium reduction cannot be excluded, and true optimal lower limits remain uncertain, the sum of evidence suggests that optimal levels of sodium intake are ≈ 2000 mg/d^{193,200–204} (or lower).³⁰⁴ Based on a target consumption level of 2000 mg/d, 1.65 million annual global cardiovascular deaths are estimated to be attributable to excess sodium intake.³⁰⁴

Potassium, Calcium, Magnesium

Vegetables, fruits, whole grains, legumes, nuts, and dairy are major sources of minerals. In randomized trials, potassium lowers BP, with stronger effects among individuals who have hypertension and when dietary sodium intake is high.³²⁵ This BP lowering has been correlated with both increased urinary potassium excretion and a lower urine sodium-to-potassium ratio. Consistent with these benefits, potassium-rich diets are associated with lower risk of CVD, especially stroke (Figure 7).³²⁶ Diets rich in potassium also attenuate, whereas diets low in potassium exacerbate, the BP-raising effects of sodium. For instance, a Mediterranean or DASH-type diet (eg, richer in fruits, vegetables, nuts) reduces, whereas a typical Western diet increases, the BP-raising effects of sodium.^{326,327} In sum, the evidence strongly supports the importance of potassium-rich foods for reducing BP and CVD.

In short-term trials, calcium and magnesium supplements also modestly lower BP, although with substantial heterogeneity among studies. However, calcium supplements with or without vitamin D may significantly increase risk of MI in long-term randomized trials.^{328,329} In observational analyses, dietary and blood magnesium levels are inversely associated with CVD, especially fatal CHD³³⁰; long-term trials have not been performed. Calcium and magnesium supplements cannot yet be recommended for general CVD prevention.

Antioxidant Vitamins

Several vitamins and nutrients are associated with lower CVD risk in observational studies, but trials of supplements, including folate, B vitamins, β -carotene, vitamin C, vitamin E, and selenium, have shown no significant effects on atherosclerosis progression or CVD events.^{19,331,332} Most of these trials, for reasons of power, evaluated up to a few years of treatment in patients

with established CVD or at high risk. In contrast, most observational studies evaluated long-term or habitual intake among generally healthy populations. Thus, discrepancies in findings could relate in part to different time periods of biological sensitivity — eg, some vitamins and nutrients could be important only early in the disease course. Such explanations require confirmation in prospective studies and trials. Discrepancies between observational studies and supplement trials may also relate to residual bias in observational studies, eg from other lifestyle behaviors (ie, observed benefits are not attributable to diet) or from other nutritional factors in vitamin-rich foods (ie, observed benefits are caused by diet but not by the specific measured vitamins or nutrients). For example, diets higher in antioxidant vitamins tend to be rich in fruits, vegetables, nuts, and whole grains, foods that contain multiple other beneficial factors including other vitamins, minerals, phytochemicals, and fiber, and being foods that can provide benefit by replacing unhealthful foods, as well. Thus, isolating one or even several components of these foods in a supplement may not produce similar effects as would occur from consuming the whole food.^{8,9}

Vitamin D

Observational studies demonstrate links between higher plasma vitamin D, which is largely driven by sun exposure, and CVD risk; however, large trials of vitamin D supplements have shown no benefits.¹⁰⁴ If higher plasma vitamin D proves to lower CVD risk, brief sun exposure can efficiently provide such levels in comparison with dietary intake. Ongoing trials are now testing whether higher doses of vitamin D supplements influence CVD; for now, such supplementation is not warranted as a means to improve cardiometabolic health.

Carbohydrates, Added Sugars, Fructose

For decades, carbohydrates were considered a foundation of a healthful diet, as evidenced by the placement of grain products at the base of the 1992 Food Guide Pyramid. Since that time, it has become clear that, although total carbohydrate has little influence on cardiometabolic health, the types and quality of carbohydrate have a major impact (Figures 6 and 7; see Carbohydrate-Rich Foods, above). Certain carbohydrate-containing foods (eg, fruits, legumes, vegetables, minimally processed whole grains) are protective, whereas foods rich in refined grains (eg, white bread, white rice, crackers, cereals, bakery desserts), starches (eg, russet or white potatoes), and added sugars (eg, SSBs, candy) are harmful. Because of this diversity, the cardiometabolic effects of total carbohydrate are modified by the quality of carbohydrate. For people who consume mostly low-fiber, rapidly digested, refined grains, starches, and added sugars, a lowering of total carbohydrate will produce substantial metabolic benefits. Yet, recommending a low-carbohydrate diet per se is not ideal: the focus should be on reducing less healthful carbohydrates, not all carbohydrates.

The US Food and Drug Administration has recently proposed revising the Nutrition Facts Panel to include added sugars.³³³ Although added sugars are not healthful, targeting added sugars alone, rather than overall carbohydrate quality, could push consumers toward foods low in added sugars but rich in equally harmful refined complex carbohydrates (eg, many breakfast cereals, breads, crackers); and away from

otherwise healthful foods containing modest amounts of added sugar (eg, nuts or minimally processed whole grain-rich cereals sweetened with honey). Appropriately, the 2015 Dietary Guidelines Advisory Committee explicitly advises restriction of both refined grains and added sugars.²¹

Much public attention has focused on the potential harms of high-fructose corn syrup. Because glucose, the main sugar in regular corn syrup (which is mostly starch), tastes less sweet than fructose, high-fructose corn syrup has been modified to increase the fructose-to-glucose ratio to about 1:1, ie, a similar ratio as in natural sugar (sucrose) found in cane sugar, beet sugar, or honey. Consequently, there are few expected or observed physiological or health differences between high-fructose corn syrup versus sucrose.^{165,166,334} In contrast, there are important metabolic differences between glucose and fructose — each equally present in both high-fructose corn syrup and natural sugar (sucrose). In particular, high doses of rapidly digested glucose induce postprandial hyperglycemia, hyperinsulinemia, and related metabolic disturbances. When glycogen stores are replete, excess glucose is further converted to fat via hepatic de novo lipogenesis. In comparison, high doses of rapidly digested fructose have little influence on blood glucose or insulin levels, but more directly stimulate hepatic de novo lipogenesis, hepatic and visceral adiposity, and uric acid production.^{164–166} Thus, high doses of rapidly digested glucose and fructose are each harmful, with such effects occurring via both separate and partly overlapping pathways. In contrast, low doses of slowly digested glucose or fructose (eg, as found in fruit) would each have minimal cardiometabolic harms. Ultimately, the health differences between high-fructose corn syrup versus natural added sugar are small in comparison with their overall dose, rapidity of digestion, and accompanying nutrients in the foods in which they are consumed.

Total Fat

In 1980, the US Dietary Guidelines recommended limiting dietary fat to <30% of calories. Based on evidence for harms of very low-fat diets, and little evidence to support a 30% restriction, the Guidelines were moderated in 2005 to a new range of 20% to 35% of calories.³³⁵ A primary motivation for restricting total fat was to lower saturated fat and dietary cholesterol because of concern that these increased cardiovascular risk. Thus, total fat was targeted as a means to lower saturated fat. In addition, based on the calorie density of fat and some limited interventional studies, it was theorized that low-fat diets might help prevent obesity.³³⁵ Unfortunately, the focus on restricting total fat did not account for the health benefits of high intakes of plant-derived fats (see Nuts, Vegetable Oils, above) nor the harms of processed carbohydrates (see Carbohydrate-Rich Foods, above), the most common replacement when dietary fat is reduced.

In recent years, the lack of cardiometabolic benefit of low-fat diets has been convincingly demonstrated. In trials of short-term weight loss, high-fat diets are at least as effective as low-fat diets (see Dietary Quality, Energy Balance).²¹ For long-term weight maintenance, the fat content of foods is a poor metric for differentiating protective versus harmful effects.^{28,29,51} Both prospective cohorts and large randomized trials confirm that low-fat diets have no benefits for major

chronic diseases (Figure 7).^{157,331} The large WHI randomized trial substantially lowered total dietary fat among nearly 50 000 US women followed for nearly a decade, and did not show benefits for any major end point including heart disease (Figure 2, top), stroke, cancers, diabetes mellitus, or insulin resistance.^{36–39} In contrast, randomized trials have confirmed the many prior observational cohort findings that diets higher in healthful fats, including in excess of the current 35% limit, reduce the risk of cardiovascular disease (Figure 2, bottom) and diabetes mellitus.^{24,25,34,35} These latter trials confirm decades-old ecological evidence that some of the healthiest traditional diets in the world are rich in fats from vegetable oils, nuts, and seafood.¹⁹ Based on this evidence, the 2015 Dietary Guidelines Advisory Committee stated, for the first time, that dietary guidelines should not focus on lowering total fat.²¹

The current restriction on total fat shapes numerous government feeding programs and policies;³³⁶ drives industry marketing of fat-reduced desserts, snacks, salad dressings, processed meats, and low-fat other products of poor nutritional value; and leads most Americans to actively avoid dietary fat³³⁷ and instead consume far too many refined carbohydrates.²¹ Avoidance of total fat also undermines attempts to limit refined starch and added sugar, while discouraging the food industry from providing products higher in healthful fats. Based on the accumulated evidence, a comprehensive restructuring of nutritional policy away from fat reduction is warranted.³³⁶

Saturated Fat

Saturated fat represents a highly heterogeneous category of fatty acids, with chain lengths ranging from 6 to 24 carbons, deriving from diverse foods, and possessing dissimilar biology. For instance, palmitic acid (16:0) exhibits *in vitro* adverse effects; whereas medium-chain (6:0–12:0), odd-chain (15:0, 17:0), and very long-chain (20:0–24:0) saturated fats may have metabolic benefits.^{61,338,339} This biological and metabolic diversity does not support the grouping together of all saturated fatty acids based on only one chemistry characteristic: the absence of double bonds.³⁴⁰

Even for any single saturated fatty acid, the physiological effects are complex. For instance, in comparison with carbohydrate, 16:0 raises blood LDL-cholesterol, yet simultaneously raises HDL-cholesterol, reduces triglyceride-rich lipoproteins and remnants, and has no appreciable effect on ApoB,³⁴¹ the most salient LDL-related characteristic. Effects of 16:0 on ApoCIII, an apolipoprotein modifier of LDL- and HDL-related risk, are unknown; the triglyceride-lowering effects of 16:0³⁴¹ would suggest potential benefit on lowering ApoCIII. Saturated fats also lower lipoprotein(a), an independent and casual cardiovascular risk factor,³⁴² in comparison with monounsaturated fat or carbohydrate.³⁴³

Dietary saturated fats are also obtained from very different foods – eg, cheese, grain-based desserts, dairy desserts, chicken, processed meats, unprocessed red meat, milk, yogurt, butter, vegetable oils, and nuts. Each of these possesses, in addition to saturated fat, numerous other ingredients and characteristics that modify their health effects. Judging the long-term health impact of foods or diets based on isolated macronutrient composition

is unsound, often creating paradoxical food choices and product formulations.^{336,340} Furthermore, tissue levels of even-chain saturated fatty acids (eg, 14:0, 16:0), that appear most harmful *in vitro*, commonly result from endogenous hepatic synthesis of fat in response to dietary intake of carbohydrate⁴⁶; 14:0 and 16:0 blood levels correlate more with intakes of dietary starches and added sugars than meats or dairy.⁶¹

These complexities clarify why total saturated fat consumption has little relation to health. Judging a food or a person's diet as harmful because it contains more saturated fat, or as beneficial because it contains less, is unsound. This is consistent with the many longitudinal cohort studies demonstrating largely neutral effects of overall saturated fat intake (Figure 7).^{39,157,344} Consistent with this, meats higher in processing and sodium, rather than saturated fat, are most strongly linked to CHD (see Meats, above). Cheese, a leading source of saturated fat, is also linked to neutral or even beneficial effects on CHD and diabetes mellitus (see Milk, Cheese, Yogurt, above). In sum, these lines of evidence – complex lipid effects including little influence on ApoB, no relation of overall intake with CHD, and no observed cardiovascular harm for most major food sources – provide powerful and consistent evidence for absence of appreciable harms of total saturated fat.

Yet, while certain saturated fat-containing foods such as dairy, nuts, and vegetable oils promote health,²⁰ these findings do not support the benefits of other saturated fat-rich foods. Although unprocessed red meats and butter may be relatively neutral for CHD, no studies demonstrate appreciable benefits, all meats appear to increase diabetes mellitus, and processed meats are strongly linked to CHD (see Meats, above).^{20,29,173,178} This is the mistake of recent media reports: conflating complexities of health effects and benefits of some saturated fat-containing foods (and possibly some specific saturated fatty acids) with unsupported recommendations to eat more butter and bacon as routes to health.³⁴⁵

Yet, even among scientists, the cardiovascular health effects of saturated fat remain a controversial topic. Continued prioritization of saturated fat reduction appears to rely on selected evidence: eg, effects on LDL-cholesterol alone (discounting the other, complex lipid and lipoprotein effects); historical ecological trends in certain countries (eg, Finland) but not in others; and expedient comparisons with polyunsaturated fat, the most healthful macronutrient. For example, although falling blood cholesterol concentrations in some Western countries correlate with decreases in national saturated fat intake, trends in intakes of dietary fats cannot explain most of the blood cholesterol changes across or within most nations. For instance, total blood cholesterol fell similarly in the United States and France between 1980 and 2000, but national changes in dietary fats may explain only ~20% of the decline in the United States, and virtually none of the decline in France.³⁴⁶

In certain Western nations, statin use may account for a large proportion of declining blood cholesterol after 2000^{347,348}; however, because of the relatively low use for primary prevention before this period, statins cannot explain the observed similar declines in blood cholesterol over the preceding 20 to 30 years. Reasons for the large and steady declines in blood cholesterol and blood pressure over the past 4 decades in

nearly all Western nations are not fully elucidated, particularly when viewed against the backdrop of increasing obesity. The extent to which these pervasive declines reflect trends in medication use, dietary fats, other dietary changes, physical activity, or other unknown influences (eg, related to fetal nutrition, the microbiome, or other unknown pathways) remains unclear.

Based on the similar cardiovascular effects of consuming total carbohydrate versus saturated fat, and the comparative benefit of polyunsaturated fats, guidelines to lower saturated fat are increasingly highlighting the importance of consuming polyunsaturated fats as the specific replacement.²¹ Yet, the resulting benefit appears specific to increased intake of polyunsaturated fat, rather than reduced saturated fat. For instance, total saturated fat, carbohydrate, and protein each appear relatively neutral for CHD, whereas the effects of total monounsaturated fat remain uncertain (see below).^{21,349} The relatively neutral effects of each of these macronutrients likely reflect substantial heterogeneity in nutrient subtypes and food sources within each of these categories. In comparison with any of these broad categories, polyunsaturated fat appears to be similarly beneficial.³⁵⁰ Consequently, it makes little sense to focus on saturated fat, which represents a smaller proportion of calories than these other macronutrients, especially carbohydrate. Indeed, in comparison with refined carbohydrates, saturated fat appears slightly beneficial.^{155,351} These lines of evidence support guidelines to increase healthful vegetable oils rich in polyunsaturated fats and phenolics, optimally in place of refined grains, starches, and added sugars.

Monounsaturated Fat

Although monounsaturated fat (predominantly oleic acid, 18:1) has conventionally been considered a cardioprotective fat, the evidence supporting this notion is mixed (Figure 7).^{21,39,157,352} Monounsaturated fat improves BP and cholesterol³⁵³ and, when consumed in place of saturated fat, lowers glucose among those predisposed to insulin resistance.³⁵⁴ Yet, total monounsaturated fat intake is not associated with lower incidence of diabetes mellitus³⁵⁵; it is associated with trends toward greater CVD in some cohort studies¹⁵⁵; and it increases atherosclerosis in primate experiments, potentially because of the enrichment of LDL cholesteryl oleate and increased LDL proteoglycan binding.³⁵⁶ Taken together, the current evidence for cardiometabolic benefits of total monounsaturated fat (largely oleic acid) is not strong.²¹

The food source may modify these health effects. For instance, cohort studies suggest that the consumption of olive oil, but not mixed animal and plant sources of monounsaturated fat, is linked to lower risk,³⁵² whereas vegetable oil sources of monounsaturated fat increase LDL cholesteryl oleate but reduce LDL proteoglycan binding.³⁵⁷ These results suggest that other compounds in these fats/oils may modify the overall health effects (see Phenolic Compounds, below). Thus, focusing on specific types of foods and oils, rather than monounsaturated fat content per se, may be most prudent. Extra virgin olive oil and mixed nuts, and perhaps high-oleic canola oil, appear to be good dietary choices to improve cardiometabolic health.^{24,25,34,35,145,255}

Polyunsaturated Fat

Polyunsaturated fats include n-6 and n-3 fatty acids, with this distinction based on the carbon location of the first double bond. The most common are n-6 linoleic acid (LA, 18:2n-6) and n-3 α -linoleic acid (ALA, 18:3n-3), derived principally from vegetables and their oils (eg, soybean, canola, flaxseed, walnuts). Seafood is the major source of long-chain n-3 polyunsaturated fats, principally EPA and DHA.²⁰¹ Although the liver readily synthesizes saturated and monounsaturated fats from carbohydrate (by means of hepatic de novo lipogenesis), humans cannot synthesize or interconvert LA or ALA, making them essential fatty acids that must be consumed in the diet. Humans also synthesize relatively little EPA and DHA,³⁴⁴ for which diet remains the major source. Evidence for cardiometabolic effects of seafood-derived n-3 fats are reviewed above (see Fish).

LA consumption lowers LDL-cholesterol and triglyceride-rich lipoproteins and raises HDL-cholesterol.³⁴⁹ Although potential proinflammatory effects of LA have been theorized³⁵⁸ and popularized, such inference is based largely on rodent experiments, with little supportive evidence in humans.^{359–362} Indeed, in people, LA appears to have anti-inflammatory and insulin-sensitizing effects.^{363–365} In controlled trials, in comparison with saturated fat, LA reduces hepatic steatosis and systemic inflammation and increases lean muscle mass.^{366,367} Arachidonic acid, the prototypical metabolite of LA, is also commonly considered proinflammatory, but is also the natural precursor to specialized proresolving mediators of inflammation.^{368,369} In prospective studies, higher biomarker levels of arachidonic acid are linked to significantly lower risk of CHD.³⁹ LA is also associated with significantly lower risk of CHD (Figure 7), whether in comparison with carbohydrate or saturated fat³⁵⁰; and, in meta-analysis of controlled clinical trials, consumption of n-6–rich vegetable oils, in place of animal fats, reduces CHD events (Figure 7).³⁴⁹ Notably, in these latter trials, the average intake of n-6 polyunsaturated fat was \approx 15% energy,³⁴⁹ higher than current dietary guidelines that recommend no more than 10% to 11% energy from polyunsaturated fat.³⁷⁰

In comparison with seafood sources, ALA is a relatively available and inexpensive plant source of n-3 polyunsaturated fat. Ecological studies suggest health benefits of increasing ALA intakes in populations with low overall n-3 polyunsaturated fat intake.³⁵⁶ Yet, the findings of trials of ALA and risk markers, such as platelet function, inflammation, endothelial function, and arterial compliance, and observational studies of ALA's association with CVD and diabetes mellitus endpoints, have been mixed and inconclusive.^{371,372} Few long-term trials of ALA and clinical events have been conducted; in 1 Dutch trial, 40 months of an ALA-containing margarine led to a small, nonsignificant reduction in major cardiovascular events (hazard ratio, 0.91; 95% confidence interval, 0.78–1.05).³⁷³ Further investigation of ALA's role in cardiometabolic health is warranted (Figure 7).^{211,372}

LA has similar CHD benefits whether replacing carbohydrate or saturated fat (see Saturated Fat, above).^{349,350} Thus, increased consumption of polyunsaturated fat-rich vegetable oils is an evidence-based strategy to lower CHD risk, whether in place of saturated fat or carbohydrate. Optimally, polyunsaturated fat-rich vegetable oils should perhaps replace refined starches and added sugars, given the independent harms of

these refined carbohydrates. Because the controlled trials demonstrating CHD benefits of PUFA used soybean oil,³⁴⁹ which contains both n-6 (LA) and n-3 (ALA) polyunsaturated fats, the selection of vegetable oils containing both n-6 and n-3 fatty acids (eg, soybean, canola) may be most prudent. Because both n-3 and n-6 polyunsaturated fats are beneficial, little interaction between them is evident, and the n-3:n-6 ratio is not a practical metric to evaluate health effects.^{364,374}

Trans Fatty Acids

Trans fatty acids (TFAs) are mono- or polyunsaturated fats with one or more double bonds in a *trans* position, rather than the mammalian synthesized *cis* position. Although small amounts of natural TFA are found in meats and milk of ruminants (eg, cow, sheep, goat; formed by gut microorganisms), these contribute minimally to diet (<0.5%E) and do not associate with CVD risk³⁷⁵; indeed, *trans*-16:1n-7, a trace TFA biomarker of dairy fat, is linked to a lower risk of diabetes mellitus and sudden cardiac death.²⁴⁷ Conversely, high levels of industrially produced TFA can be consumed from partially hydrogenated vegetable oils, which typically contain 30% to 60% TFA. These fats have industrial advantages for commercial deep frying, baked goods, packaged snacks, and shortening. Higher TFA intake from partially hydrogenated oils is consistently associated with the risk of CHD and sudden death (Figure 7).^{331,376} In trials, TFAs have unique adverse effects on blood lipids and lipoproteins, including raising LDL-cholesterol, ApoB, triglycerides, and lipoprotein(a), and lowering HDL-cholesterol and ApoA1; these effects are generally consistent whether the TFA replaces saturated, monounsaturated, or polyunsaturated fat.³⁷⁷ TFAs also appear to have nonlipid adverse effects, promoting inflammation, endothelial dysfunction, insulin resistance, visceral adiposity, and arrhythmia, although the strength of evidence for these different nonlipid effects varies.^{378,379} In sum, the implicated pathways suggest that TFA-containing partially hydrogenated oils influence pathways related to adipocyte dysfunction and insulin resistance. Emerging evidence suggests that 18:2 TFA isomers may be the most adverse; these can be formed through not only partial hydrogenation, but also other industrial processes such as oil deodorization and high-temperature cooking.^{380,381} Because partially hydrogenated oils are food additives with clear adverse effects, their elimination is a public health priority.^{247,382–384}

Protein

The cardiometabolic effects of dietary protein are not well established. In meta-analysis of randomized trials, increased protein consumption has little effect on cardiometabolic risk factors including adiposity, lipids, blood pressure, inflammation, or glucose.³⁸⁵ Few longitudinal studies have reported on total protein intake and CHD events, with generally null results.^{189,386} This is not surprising: similar to total fat or total carbohydrate, total protein represents the sum of very different foods (red meats, processed meats, milk, cheese, yogurt, fish, nuts, legumes, etc) with widely divergent health effects. Thus, a focus on dietary protein per se appears much less relevant for CVD than a focus on specific types of foods consumed. A few cohorts have seen protective associations of animal protein intake with the risk of hemorrhagic stroke; causality and mechanisms remain unclear, but have been hypothesized to

relate to the potentially protective effects of animal protein or dietary cholesterol on vascular fragility.^{198,199}

Behavior Change

Barriers and Opportunities for Healthy Eating

Many current approaches to improving nutrition – eg, clinical counseling, food labels, menu labeling, dietary guidelines – arise from an implicit assumption that dietary habits are primarily a function of individual choice. In reality, multiple complex factors influence dietary choices (Figure 9). Even at the individual level, dietary habits are determined not simply by personal preference but also by familial norms, education, income, nutritional and cooking knowledge and skills, and health status.³⁸⁷ Additional relevant factors include attitudes toward food and health, incentives, motivation, and values.³⁸⁸ Other lifestyle behaviors such as television watching and sleep also influence patterns of food consumption.^{28,71,72,389} Outside the individual, sociocultural determinants include cultural norms, social pressures, and social networks.³⁹⁰ Additional environmental influences include neighborhood accessibility (eg, food availability, cost, convenience). Each of these individual, environmental, and sociocultural determinants is shaped by, and in turn shapes, much broader drivers of food choice such as agricultural policy and production practices, food industry formulations and marketing, national and international trade agreements, other market forces, climate, and agricultural policies.³⁹¹ These complex determinants each represent a potential barrier, but also a promising lever and opportunity, for encouraging healthful diets.

Some have argued that humans are biologically wired to prefer specific unhealthful foods, eg, rich in fat, sugar, and salt. This perspective is overly simplistic and inconsistent with several lines of empirical evidence. For instance, most dietary fats are healthful, making a food's fat content a poor marker of its intrinsic harm or benefit (see Total Fat). In addition, taste preferences are highly complex, influenced by considerations of aroma, appearance, color, shape, and texture. The observed diversity of diets within and across individuals, generations, cultures, and populations further belies a particular biological preference for food.^{4,346,392–394} Even the brain's unconscious reward/craving (addiction) centers are plastic and can be trained over months to respond to healthful rather than unhealthful foods.³⁹⁵ Furthermore, for the food industry, the success or failure of specific products has often depended not on differences in contents of fat, sugar, or salt, but on the prowess and power of their convenience, packaging, marketing, and promotion.³⁹⁶ Undoubtedly, taste plays a role in consumer choice, but so do availability, price, packaging, marketing, convenience, and culturally driven perceptions of norms, status, and prestige. Each of these levers are powerful and can be used to influence the selection of healthier foods.

Clinical (Individual-Based) Strategies

Numerous randomized controlled trials have identified effective approaches for successful individual behavior change (Table 5).^{94,95} These strategies have demonstrated efficacy and should be incorporated by providers into their practice to target specific dietary behaviors and other lifestyle habits, such as tobacco use, physical inactivity, and medication

noncompliance. Providers should recognize that, although patient compliance with both lifestyle and medications is similarly imperfect, such strategies, even imperfectly implemented, improve clinical outcomes.³⁹⁷

Health Systems Strategies

For many clinicians, a variety of barriers within the health system can limit their ability to fully implement effective behavior change strategies. Such barriers might include, for example, limited patient visit time to focus on behavior change, insufficient financial or other provider incentives for health promotion, sub-optimal knowledge or experience on the most effective behavior change strategies and relevant behavioral targets, and inadequate tools for assessing and monitoring behaviors over time. Specific changes in the healthcare system can strongly support and facilitate behavior change efforts by providers (Table 6).^{10,95,398,399} Such healthcare systems approaches are being introduced for tobacco and obesity control efforts. Many electronic medical records systems have fields for tobacco use and body weight, although their accuracy and consistency of use remain variable. The expansion of these healthcare system approaches to target diet quality is crucial, especially in light of new incentives in the Affordable Care Act for creating new electronic health record systems and for focusing on prevention in Accountable Care Organizations.

Novel Technology Strategies

Recent years have witnessed an explosion of novel personal technologies that aim to improve health, including mobile device applications (mHealth), Internet-based programs, and personal tracking devices (eg, FitBits). These technologies are

promising because of the potential for low cost, scalability, use in multiple settings (including middle- and low-income nations), and opportunities for continuous, personalized modifications and improvements. Many incorporate established behavior-change strategies (Table 5) such as setting proximal, targeted goals; self-monitoring; feedback; and peer support.

A systematic review identified numerous randomized trials and quasi-experimental studies evaluating these approaches for dietary change and/or weight loss (Afshin A, Mozaffarian D; unpublished data; 2015). Most were Internet based or combined Internet and mobile approaches. The great majority had durations between 6 weeks and 6 months; very few extended beyond 1 year. Approximately two-thirds of these studies identified improved dietary behaviors or greater weight loss with the use of these novel technologies, in comparison with usual care. Although promising, little is known on their long-term effectiveness and sustainability, and longer-term studies are required.

Policy Strategies

Given the key roles of social and environmental factors in shaping dietary habits, policy (population-based) approaches are crucial to achieve broad success. Effective strategies can be designed and implemented at local levels (eg, schools, work-sites, communities), and at city, state, national, and international levels. Several specific approaches have strong evidence for efficacy (Table 7).^{10,11} These experiences generally demonstrate that education or information alone, without additional economic or environmental changes, has a limited influence on behavior.^{11,400,401} Integrated, multicomponent approaches

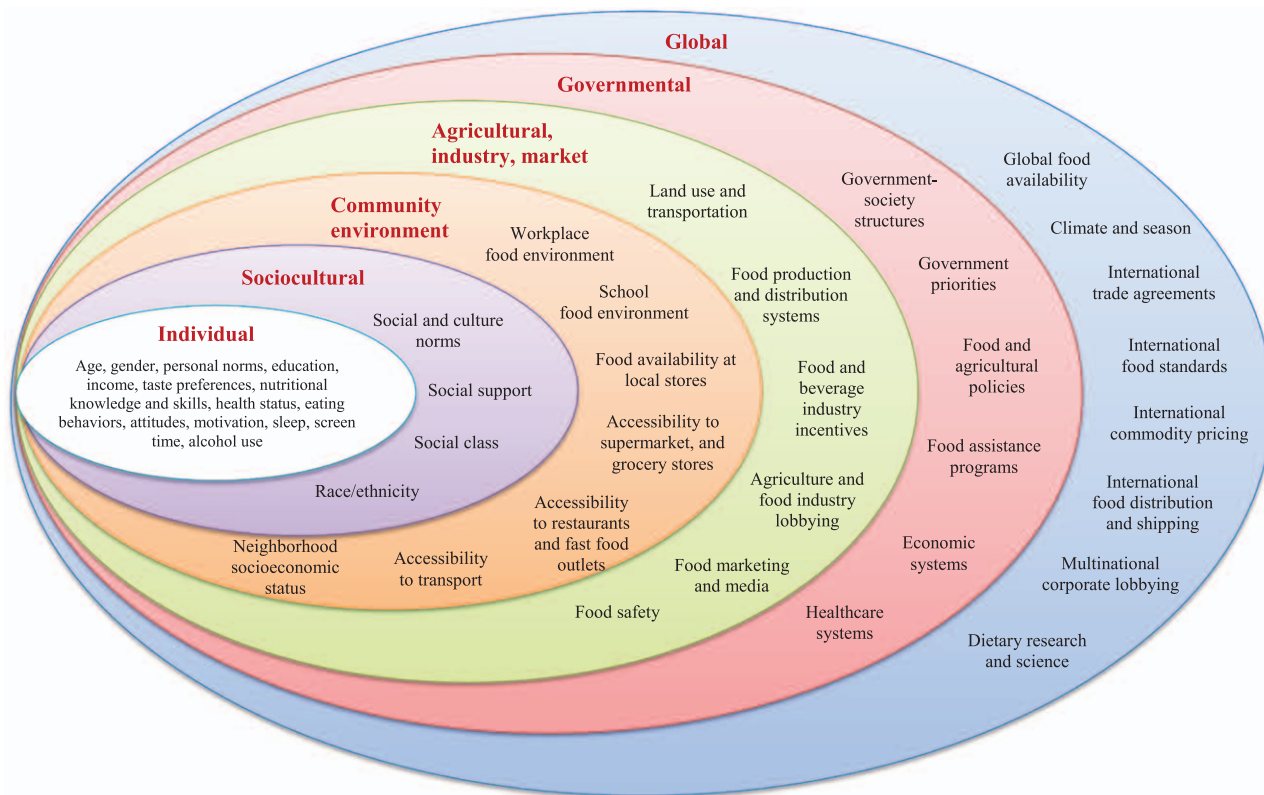


Figure 9. Barriers and opportunities for healthy eating. Reproduced from Afshin et al¹⁰ with permission of the publisher. Copyright © 2014, John Wiley & Sons, Ltd.

that include upstream policy measures, midstream educational efforts, and downstream community and environmental approaches may be especially effective. Policy strategies can complement health systems efforts while also reducing social and racial disparities caused by the clustering of suboptimal diet habits, local environments, and disease risk factors.

Several factors have limited the translation of this knowledge to action, including evolving messages and confusion about specific dietary priorities, uncertainty regarding effective methods for behavior change, and inadequate tools to monitor diets efficiently. Fortunately, other public health successes for complex behavioral challenges—eg, tobacco use, motor vehicle safety—encourage optimism for the success of concerted multicomponent strategies that include strong quality standards and policy actions to improve diet. At the population level, even modest shifts in risk factors can substantially and rapidly alter population health.^{97,402}

Role of Multiple Stakeholders

Successful, sustainable improvements in population dietary behaviors will require close collaboration among multiple stakeholders, including academics, clinicians, health systems, insurers, community organizations, schools, workplaces, advocacy groups, policy makers, farmers, retailers, restaurants, and food manufacturers.^{10,391,403} For instance, academic institutions should prioritize research on optimal dietary targets and cost-effective policies; engage with communities,

advocacy groups, and policy makers; and inform and evaluate industry efforts. Clinicians should implement behavior change strategies; advocate for broad health system changes to support these efforts; and engage with local communities. Communities, schools, and workplaces should demand and support comprehensive programs for dietary change. Advocacy groups should partner with scientists to disseminate best practices while holding government and industry accountable for meaningful action.

Local and national governments should prioritize nutrition and facilitate participation of other stakeholders in policy development, implementation, and evaluation. Based on its impact on health, the environment, and the economy, nutrition is among the leading global issues of our time. Policy makers at all levels must recognize and focus on these topics. Surveillance, monitoring, and evaluation of dietary habits and diet-related policies are necessary to develop solutions, assess whether implemented programs have intended effects, identify and address disparities, and detect unintended consequences. Organized global public health efforts must complement these activities, assist smaller governments with effective food policies, and provide a countervailing force to multinational industry lobbying. Key global economic and political institutions that must play more assertive roles include the United Nations, the World Health Organization, the World Trade Organization, and the World Bank.

The food industry, from agricultural producers to food manufacturers, retailers, and restaurants, must also commit to healthier foods. Although big food has shared many tactics with big tobacco—eg, lobbying, deception, denial, resistance to regulation⁴⁰⁴—these 2 industries are not fully analogous. The food industry is far more heterogeneous, from types of products to strengths of commitment to healthfulness. The food industry has also demonstrated some responsiveness to dietary guidelines and public preferences over the past 40 years: eg, generating low-fat products, margarines, noncaloric sweeteners, low-carbohydrate products, gluten-free and organic foods, and many others. Our food systems have also made tremendous progress in reducing food-borne illness, increasing volume and production, improving convenience and stability, and reducing cost—all important

Table 5. Evidence-Based Approaches for Individual Behavior Change in the Clinic Setting

- **Specific, proximal, shared goals.** Set specific, proximal goals in collaboration with the patient, including a personalized plan to achieve the goals (eg, increase fruits by 1 serving/d over the next 3 mo).
- **Self-monitoring.** Establish a strategy for self-monitoring, such as a dietary or physical activity diary or web-based or mobile phone application.
- **Scheduled follow-up.** Schedule regular follow-up (in-person, telephone, written, or electronic), with clear frequency and duration of contacts, to assess success, reinforce progress, and set new goals as necessary.
- **Regular feedback.** Provide feedback on progress toward goals, including using in person, telephone, or electronic feedback.
- **Self-efficacy.*** Increase the patient's perception that they can successfully change their behavior.
- **Motivational interviewing.†** Use motivational interviewing when patients are resistant or ambivalent about behavior change.
- **Family and peer support.** Arrange long-term support from family, friends, or peers for behavior change, such as in workplace, school, or community programs.
- **Multicomponent approaches.** Combine 2 or more of the above strategies into the behavior change effort.

*Examples of strategies to increase self-efficacy include mastery experiences (set a reasonable, proximal goal that the person can successfully achieve); vicarious experiences (have the person see someone with similar capabilities performing the behavior, such as walking on a treadmill or preparing a healthy meal); physiological feedback (explain to the patient when a change in their symptoms is related to worse or improved behaviors); and verbal persuasion (persuade the person that you believe in their capability to perform the behavior).

†Motivational interviewing represents the use of individual counseling to explore and resolve ambivalence toward changing behavior. Major principles include fostering the person's own awareness and resolution of their ambivalence, and their own self-motivation to change, in a partnership with the counselor or provider.

Table 6. Evidence-Based Health Systems Approaches to Support and Facilitate Behavior Change

- Ongoing training for providers on evidence-based behavior change strategies as well as relevant dietary targets, including relevant ethnic and cultural issues.
- Integrated systems to facilitate coordinated care by multidisciplinary teams, including physicians, nurse practitioners, dietitians, physical activity specialists, and social workers.
- Practical electronic systems to help assess, track, and report on specific dietary behaviors, including during, before, and after provider visits.
- Electronic systems for scheduling and tracking regular follow-up visits for behavior change.
- Electronic systems to facilitate provision of feedback to patients and providers on progress during behavior change efforts.
- Reimbursement guidelines and incentives that reward behavior change efforts.
- Restructuring of practice goals and quality benchmarks to incorporate key dietary interventions and targets.

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priorities of the last century. Healthfulness for chronic diseases, in particular, cardiometabolic diseases, has been the great failure – one that must now be addressed with modern nutrition and policy science. Perhaps most importantly, with tobacco, the ultimate aim is total elimination. In contrast, we need major agribusiness, food manufacturers, and retailers to successfully feed the 7+ billion people on the planet. These businesses must support and be informed by modern evidence, advance their technical expertise to formulate and sell healthier products, and use consumer education, marketing, and product pricing to promote dietary health. Agriculture and food industry should form transparent, sincere partnerships with advocacy groups, governments, and other stakeholders to replace less healthy foods with more healthful options. Their ultimate success must be linked to selling of healthful, optimally processed foods in a sustainable and profitable fashion.

Motor vehicle safety provides an informative analogy (Figure 10). The US Centers for Disease Control and Prevention named reduced fatalities from motor vehicle accidents as one of the top 5 public health successes of the 20th century.⁴⁰⁵ This remarkable success was not achieved merely by national driving guidelines, motor vehicle labeling, or other consumer-focused education – ie, many of the current emphases for dietary change – but by a comprehensive, multicomponent effort targeting the consumer (driver), product (car), environment (road), and culture (particularly drunk driving). This provides a road map for

improving population diets: address the consumer, the product (foods and beverages), the environment (retailers, cafeterias, restaurants), and the culture (unhealthy eating, marketing). For instance, just as driving under the influence of alcohol is now socially stigmatized, the acceptability of fast foods, soda, and ultraprocessed products, including industry and celebrity marketing of such foods, must be reduced. Just as the auto industry remains successful and profitable, and the public continues to use and benefit from cars, a similar multicomponent, evidence-informed approach is needed to produce a successful, profitable food system that provides safe, healthful products.

Conclusions – The Way Forward

The global challenges of diet-related obesity, diabetes mellitus, and CVD present enormous health and economic burdens⁴⁰³ and emphasize the imperative of prioritizing nutrition in clinical care, advocacy, research, and policy. Scientific advances provide a wealth of new evidence to identify several key dietary priorities for cardiometabolic health. These include food-based priorities for more fruits, nonstarchy vegetables, nuts, legumes, fish, vegetable oils, yogurt, and whole grains; and fewer processed (sodium-preserved) meats and foods higher in refined carbohydrates and salt (Figure 3). Red meats should be minimized to prevent diabetes mellitus; butter used occasionally but not emphasized; and other foods (eg, unprocessed poultry, eggs) consumed in moderation according to personal preference.

Table 7. Evidence-Based Policy Approaches to Improve Population Dietary Habits

Media and education	<ul style="list-style-type: none"> • Sustained, focused media and education campaigns, using multiple modes, for increasing consumption of specific healthful foods or reducing consumption of specific less healthful foods or beverages, either alone or as part of multicomponent strategies.* • On-site supermarket and grocery store educational programs to support the purchase of healthier foods.
Labeling and information	<ul style="list-style-type: none"> • Mandated nutrition facts panels or front-of-pack labels/icons as a means to influence industry product formulations.†
Economic incentives	<ul style="list-style-type: none"> • Subsidy strategies to lower prices of more healthful foods and beverages.‡ • Tax strategies to increase prices of less healthful foods and beverages.‡ • Long-term changes in broad agricultural policies (not subsidies alone) to create infrastructure that facilitates production, transportation, storage, and marketing of healthier foods.
Schools	<ul style="list-style-type: none"> • Multicomponent interventions focused on improving both diet and physical activity, including specialized educational curricula, trained teachers, supportive school policies, a formal physical education program, serving of healthier food and beverage options, and a parental/family component. • School garden programs including nutrition and gardening education and hands-on gardening experiences. • Fresh fruits and vegetables programs that provide free fruits and vegetables to students during the school day.
Workplaces	<ul style="list-style-type: none"> • Comprehensive worksite wellness programs including dietary, physical activity, and tobacco cessation/prevention components. • Increased availability of healthier food/beverage options and strong nutrition standards for foods and beverages served, in combination with on-site prompts, labels, or icons to select healthier choices.
Neighborhood environment	<ul style="list-style-type: none"> • Increased availability of supermarkets near homes.§
Quality standards	<ul style="list-style-type: none"> • Quality standards for marketing of foods and beverages to children, including on television, near schools and public places frequented by youths, on packages, or in other fashions. (IIa B).† • Quality standards on harmful (eg, sodium, partially hydrogenated oil) or beneficial (eg, healthful fats) ingredients in foods.

*Evidence for effectiveness of long-term campaigns (eg, > 3 y) comes mainly from multicomponent interventions, making it difficult to quantify the independent effects of the media efforts.

†Effects on industry formulations are based largely on anecdotal observations. There is not strong evidence that consumer behavior is appreciably influenced by the provision of dietary information through food product or menu nutrition labeling.^{11,400,401}

‡The magnitude of the dietary change correlates with the size of the price difference. Certain population subgroups, including youth and lower socioeconomic populations, are especially sensitive to economic incentives.

§Based largely on cross-sectional associations, few longitudinal data are available. Cross-sectional findings consistently show a beneficial association between the availability of neighborhood supermarkets and diet quality or diet-related risk factors; similar analyses for availability of grocery stores, convenience stores, and fast-food restaurants have been far less consistent.

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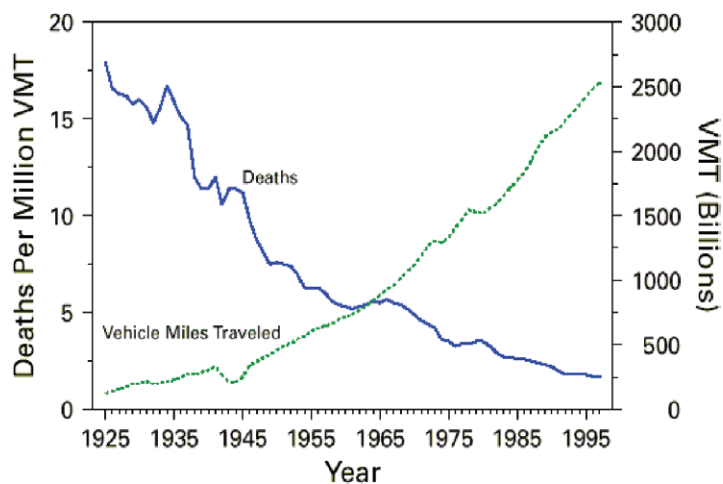


Figure 10. A roadmap for improving population dietary habits. **Top,** A great public health success of the 20th century was a 90% reduction in deaths from motor vehicle accidents, from 18 to 1.7 deaths per million vehicle miles. **Bottom,** This remarkable triumph was achieved by a comprehensive, multicomponent effort targeting the driver, car, road, and culture. This provides a road map for improving population diets: address the consumer, the product (foods and beverages), the environment (retailers, cafeterias, restaurants), and the culture (unhealthy eating). MADD indicates Mothers Against Drunk Driving. **Top** reproduced from Centers for Disease Prevention and Control⁴⁰⁵.

- **Driver: (consumer)**
 - Education
 - Licensing
 - Limits on phone use, texting
- **Car: (product)**
 - Active: seat belts, child seats, motorcycle helmets
 - Passive: padded interiors, collapsible steering columns, shatterproof glass, air bags
 - Crash safety standards
 - Safety inspections
- **Road: (environment)**
 - Road engineering, guard rails, rumble strips
 - Speed limits
 - Stop signs, stop lights, caution signs
- **Culture:**
 - Designated driver campaign
 - Drunk-driving legislation
 - Private advocacy, eg. MADD

Coffee and tea can be enjoyed, with possible (but not yet confirmed) benefits; and alcohol, if consumed, should be moderate (up to 1 drink/d for women and 2 drinks/d for men). Harmful additives, in particular sodium, trans fat, and added sugar, will generally be lower in such diets and must be further minimized through strong policy actions. There is growing evidence and consensus for such food-based dietary patterns as the best means to reduce CVD, obesity and weight gain, and diabetes mellitus,²¹ replacing outdated emphases on total fat, other isolated nutrients, and calorie counting. Clinical behavior-change efforts, health system changes, novel technologies, and robust policy strategies must complement and facilitate these individual food choices, which together will reduce cardiometabolic disease and economic burdens across the population.

Acknowledgments

I am grateful for the indispensable contributions over the years to my knowledge and perspectives on nutrition science and policy resulting from collaborations and conversations with many friends and colleagues, including David Siscovick, Rozenn Lemaitre, Walter Willett, Frank Hu, David Ludwig, Simon Capewell, Renata Micha, Jason Wu, Ashkan Afshin, and many others. I also thank Masha Shulkin and Ashley Wright for their assistance with the drafting of Figures 6 and 7; and the *Circulation* editors and peer reviewers for their critical comments during the preparation of this article.

Sources of Funding

This work was supported by the National Health, Lung, and Blood Institute (R01 HL085710, R01 HL115189), National Institutes of Health.

Disclosures

Ad hoc honoraria or consulting from Bunge, Haas Avocado Board, Amarin, Astra Zeneca, Boston Heart Diagnostics, GOED, and Life Sciences Research Organization; chapter royalties from UpToDate; and scientific advisory boards, Unilever North America (ended 2014) and Elysium Health. Harvard University holds a patent, listing Dr Mozaffarian as 1 of 3 coinventors, for use of transpalmitoleic acid to prevent and treat insulin resistance, type 2 diabetes mellitus, and related conditions.

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Comprehensive Review**
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Circulation. 2016;133:187-225; originally published online January 8, 2016;
doi: 10.1161/CIRCULATIONAHA.115.018585

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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