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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. Major identified themes include the importance of evaluating the full diversity of diet-related risk pathways, not just obesity and blood lipids; 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 (e.g., sodium-preserved) meats, and foods rich in refined grains, starch, added sugars, salt, and trans fat. More investigation is needed on 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 cardiometabolic relevance of other popular priorities: e.g., local, organic, grass-fed, farmed/wild, non-GMO. Evidence-based personalized nutrition appears to depend more on non-genetic characteristics (e.g., 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, including those 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 burdens of diet-related cardiometabolic diseases.

Keywords

diet; nutrition; cardiovascular disease; obesity; diabetes; behavior change; health systems; policy; review

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Introduction

Suboptimal diet is the leading risk factor for death and disability in the US and worldwide.[1, 2] Among disadvantaged populations globally, hunger and malnutrition cause enormous suffering. Simultaneously, diet-related cardiometabolic diseases, including coronary heart disease (CHD), stroke, type 2 diabetes, and obesity, produce even larger global health burdens. Other vascular conditions such as 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. Compared 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 two 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 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 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 physiologic 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; as well as 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 suffering from scurvy to several different treatments.[9, 12] Only one 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 he first vitamin was isolated – vitamin C – and verified as the active protective constituent against scurvy. This confirmed, for the first time, that specific dietary nutrients could prevent disease. Over the next two decades, an explosion of nutrition science confirmed other single-nutrient diseases including 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 (RDAs) 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 “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 RDAs 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 modernization of agriculture, food processing, and formulations, nutrient deficiencies rapidly receded in the US 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, e.g. 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 CVD, diabetes, 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, “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. RDAs were quickly recognized as methodologically and conceptually inappropriate for chronic diseases, leading to creation of new nutrient-based metrics (e.g., Adequate Intakes, AIs; Acceptable Macronutrient Distribution Ranges, AMDRs) which were limited by imprecise definitions and inconsistent usage.[16] Further, while scientific investigation of macro and micronutrients remains essential to elucidate biologic 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 their daily consumption of 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, 35-40 years ago. And, not until the last 15-20 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 toward foods, dietary patterns, and evaluation of clinical endpoints. 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, 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 the remarkable advances in research and knowledge over just the last decade.

The most well-studied dietary patterns are traditional Mediterranean and DASH diets (see http://circ.ahajournals.org/content/123/24/2870/T3.expansion.html). Compared to the conventional low-fat, high carbohydrate DASH diet, a modified DASH diet higher in vegetable fats and lower in carbohydrates – i.e., more similar to a Mediterranean 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 identified in prospective cohort studies and short-term interventional trials, with significant reductions in both cardiovascular events and diabetes.[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, or insulin resistance.[36-39] This contrast in effectiveness of healthful-food based vs. nutrient-focused dietary targets is exemplified by comparing the results of two 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, as 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 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; while a non-vegetarian 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-carb 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-carb and paleo diets is reduced refined grains, starches, and added sugars, which represent the majority of total carbs and ultra-processed foods in modern diets (see *Carbohydrate-rich foods,* below). Paleo diets also emphasize fruits, nonstarchy vegetables, nuts, and fish, each of which have health benefits. However, focus on “low-carb” could paradoxically reduces intakes of other, healthful carb-containing fruits, legumes, and minimally processed whole grains; while “paleo” guidelines often recommend liberal intakes of red meats, lard, and salt and avoidance of legumes and dairy. A maximally beneficial diet pattern should concurrently emphasize reductions in refined (not all) carbohydrates as well as 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 elucidation of effects of foods and diet patterns on the complex physiologic 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 diet[21] – 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 populations. An average American adult currently gains only ~1 lb (0.45 kg) per year,[28] consistent with habitual

excess energy intakes as small as ~50 kcal/day explaining the gradual weight gain occurring in most individuals.[40] This finding accentuates just how *well* our homeostatic mechanisms actually function to maintain long-term weight stability. Yet, when sustained over many years, this minor annual weight gain drives population obesity, e.g. 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 US, for instance, obesity began steeply rising only ~3 decades ago.[41] Abdominal adiposity, which produces largest metabolic harms, has also increased to a great 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, nonalcoholic fatty liver disease, dyslipidemia, and hypertension exceed anything observed at these ages in prior human history.[44] The escalation of adiposity at youngest ages, including those <age 5 years, 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 crucial 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 including poor diet quality (**Figure 4**). In other words, diet quality a driver of 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 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; e.g., 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 risk of diabetes.[19, 21] This is analogous to the weight-independent metabolic benefits of physical activity: diet quality has similar robust metabolic benefits.

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 primary culprits.[28, 29] Such rapidly digested, low-fiber carbohydrates drive many obesogenic pathways. [45, 46, 48-50] Major foods in this group include potatoes, white bread, white rice, refined breakfast cereals, crackers, sweets, soda, and other ultra-processed 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 to 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 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 health effects of whole vs. skim milk. Longitudinal studies suggest no harms of whole-fat milk for obesity, diabetes, or cardiovascular disease in adults;[28, 29, 51, 57, 58] that dairy fat may have potential benefits for diabetes;[59-61] that people switching to low-fat dairy products compensate elsewhere in their diet by increasing consumption of carbohydrates;[29] 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: e.g., 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 to due 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 – e.g., total fat, energy density, even added sugar– may also 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 the 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 (e.g., placental) influences.[28, 41, 67-70] For example, lower sleep duration and altered circadian rhythms predict greater weight gain and obesity, alter hunger and food preferences, and influence leptin, ghrelin, insulin, and gut-peptide concentrations.[28, 67] Greater hours spent TV watching also independently increase obesity and weight gain;[28, 68] two randomized trials in children suggest this is mediated by changes in diet, not physical activity, owing to increased eating in front of the TV and altered food choices due to TV marketing.[71, 72] Increasing physical activity, of course, has complementary benefits on weight maintenance and metabolic health. Other societal and environmental influences may 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 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 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 7-8 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 inter-individual 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.

While candidate genes 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 – e.g., for the APOE locus, dietary saturated fat, and LDL-cholesterol; or the CETP locus, alcohol, and 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 be present.[87] Potential influences of diet on epigenetic changes (e.g., 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 dietary priorities. For instance, glycemic responses to carbohydrate consumption appear especially detrimental in women,[89] suggesting 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-carb than with low-fat diets.[90] Similarly, patients with diabetes, 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 socioeconomically sensitive strategies increase effectiveness of clinical approaches to behavior change.[94, 95]

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 time[97] demonstrate the dominant influence of environmental risk factors and the crucial importance of population approaches to address them, 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, can complement such 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 – e.g., cooking, smoking, drying, salting, fermenting, preserving, heating, milling, refining, etc. Benefits 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 endproducts, and other compounds.

Many healthful foods are minimally processed (e.g., fruits, nuts, seafood), whereas several classes of processed foods are harmful (e.g., 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 "ultra-processed" 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), while other packaged or processed foods (e.g., 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" vs. "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.

Dietary Supplements, Functional Foods

Use of dietary supplements, often at high or pharmacologic doses, is commonplace, despite 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 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 beta-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 death[109] (see *Fish*, above). Overall, the current evidence does not support use of other dietary supplements to duplicate 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, potential impact of these and other functional foods on clinical endpoints 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 pharmacotherapy;[116] although others have concluded that plant sterols/stanols could have unacceptable toxicities.[122, 123] In the 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 foods could be considered as evidence-informed functional foods to reduce CVD events.

Emerging Issues: Organic, Genetic Modification

Public and media attention have increasingly considered whether foods are organic (i.e., 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 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 in order 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 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 endpoint: its potential effects on human health (positive, neutral, negative) will relate to the specific compositional changes in the food, not the method itself.[140]

Based on current evidence, whether a food is organic or genetically modified appears to be of relatively small health relevance compared 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 their health effects is optimally derived from well-designed prospective observational and interventional studies of clinical endpoints, 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 vs. harm (Figure 3): when considering the health effects of any food, it is important to consider: compared to 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 endpoints utilizing dietary patterns rich in these foods.[19-21] Effects of specific subtypes of these foods are less well established. Foods richest in phytochemicals (e.g., berries, nuts) appear to be particularly potent.

Starchy vegetables

Potatoes are a widely consumed starchy vegetable. While potatoes contain fiber, potassium, vitamins C and B6, and other trace minerals, they predominantly comprise starch (long chains of glucose) which 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 incidence of diabetes, while potatoes, corn, and peas are linked to greater long-term weight gain, in contrast to nonstarchy vegetables which are associated with protection against weight gain and diabetes.[28, 55, 146, 147] Potatoes have also been cross-sectionally linked to greater diabetes, higher blood glucose, and lower HDL-C;[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 different varieties of potatoes or other starchy vegetables are less established. Cassava is starch-rich, similar to peeled potatoes, but long-term cardiometabolic effects remain uncertain;[150, 151] glycemic responses may be ameliorated by its consumption in mixed meals. Similarly, long-term health effects of yams, sweet potatoes, and parsnips (which tend to contain relatively less starch vs. fiber than russet or white potatoes), corn

(which can be considered a grain or vegetable), and peas (which is a legume) are not well established. In recent work, among major vegetables consumed in the US, 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 and glycemic responses, as well some adverse long-term associations, high intakes of potatoes are not advisable. If consumed, small portion sizes, including the (nutrient-rich) skin, and mixed meals (e.g., mixed with healthful foods such as vegetable oils, fish, nonstarchy vegetables, etc.) would be prudent.

Carbohydrate-rich foods

Carbohydrate-rich foods comprise about half or more of all calories in most diets globally. While total carbohydrate consumption has little relation to cardiometabolic health, the quality of carbohydrate-rich foods is linked to risk (**Figure 6, Figure 7**).[152-160] The conventional chemistry-based classification of simple (sugar) vs. complex (starch) carbohydrates has little physiologic relevance, as saccharide chain length has little influence on digestion rate or metabolic effects. 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 comprise endosperm (starch), bran (fiber, protein, B-vitamins, minerals, flavonoids, tocopherols), and germ (protein, fatty acids, antioxidants, phytochemicals). When whole grains are intact (e.g., quinoa) or partially intact (e.g., 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 (e.g., 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 (e.g., 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 (e.g., russet or white potatoes) have similar metabolic characteristics (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 (e.g., 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 (e.g., 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, SSBs, and sweets may increase cardiometabolic risk by displacing other, healthier foods in the diet, e.g., 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, 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] While SSB intake is declining in the US, 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 specifies that, “consumption of ‘low-fat’ or ‘nonfat’ products with high amounts of refined grains and added sugars should be discouraged.”[21] Due to the multiple independent characteristics that influence carbohydrate quality (e.g., 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 on cardiometabolic health were historically based on minimally-adjusted ecologic comparisons and theorized effects of isolated nutrient contents (e.g., 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, such as heme iron, sodium, and other preservatives (see *Nutrients and Cardiometabolic Health*, below).

Consistent with this, while a minority of individual studies suggest similar cardiovascular risk for unprocessed red meat vs. processed meats,[170, 171] many other individual studies and meta-analyses support much stronger effects 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, non-cardiovascular outcomes, residual confounding could explain some or all of the observed associations of unprocessed red meat with CVD.[175] In contrast, observed harms of processed meats are consistent with high levels of sodium (~400% higher in processed meat) and predicted effects of this sodium on BP, which explain most of the observed cardiovascular risk.[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 the reverse is seen in many populations.

Interestingly, both red and processed meats, regardless of fat content, are linked to higher incidence of diabetes, although with approximately double the risk, gram-for-gram, for processed meats than for unprocessed red meats.[172, 178] Mechanisms require further study, but risk for diabetes may be linked to iron content[179, 180] as well as 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 and select lower-fat or "lean" meats. Rather, it would be prudent to consume small amounts of unprocessed red meats (e.g., 1-2 serving/week) 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 feeding systems can influence nutrient contents of meats. For example, compared with grain, grass-feeding results in less intramuscular fat and, 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, monounsaturated, and trans-18:1 fats.[184, 185] However, while grass-feeding consistently increases relative proportions (percent fatty acids) of omega-3 fats, the absolute content (g per 100 g beef) can be higher, similar, or even lower due to decreased total fat content.[184, 185] Health implications of these modest nutrient differences require further study.

Poultry, eggs

Relatively few studies have focused on poultry as a risk factor for CVD or diabetes, 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 studies evaluating poultry and incident diabetes have shown mixed results including higher risk, no risk, and lower risk.[178, 190-195] These conflicting findings do not permit strong inference on 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.[197] Frequent consumers (7+ eggs/week) have higher new-onset of diabetes; and among patients with prevalent diabetes, frequent consumers experience more clinical CVD events. On the other hand, higher egg consumption associates with lower risk of hemorrhagic stroke,[196] potentially related to protective effects of dietary cholesterol on vascular fragility.[198, 199] As with poultry, relevance of these conflicting findings remains uncertain. Overall evidence suggests small cardiometabolic effects of occasional consumption (e.g., up to 2-3 eggs per week); and possible harm with frequent consumption, especially among diabetics. Of note, the 2015 Dietary Guidelines Advisory Committee concluded that dietary cholesterol is not a

"nutrient of concern for overconsumption,"[21] based on low mean population cholesterol intake and no appreciable relationships between dietary cholesterol and serum cholesterol or clinical cardiovascular events in general populations.

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 (e.g., processed meats, refined grains, sugars) yet relatively unhealthy alternatives compared with beneficial foods (e.g., fish, nuts, legumes, fruits).

Fish

The cardiovascular effects of fish and omega-3 consumption have been studied for decades. Compared to little or no consumption, moderate consumption of fish (~2+ servings/week) and long-chain omega-3 (~250 mg/d) associates with lower risk of fatal CHD (Figures 6-7).[200-202] In contrast, higher intakes do not appear to appreciably reduce risk further. Compared with fatal cardiac events, fish consumption has weaker associations with nonfatal cardiac events and stroke.[201, 203, 204] The specificity for fatal CHD 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 which demonstrate risk reductions for cardiac death, but not total CVD, CHD, or stroke.[109] However, these pooled results from trials obscure differences over time: 4 of 5 older trials, but none of the newer trials, demonstrate benefits.[205] These discrepant results could be due to more aggressive lipid and BP drug treatment in recent trials. Alternatively, because the dose-response effect for fatal CHD appears nonlinear, [200, 201] higher background intakes of fish among subjects enrolled in more recent trials may have diminished ability to detect 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 nor subgroups with low fish intake, for whom benefits appears most plausible.

Notably, in meta-analyses of multiple controlled interventions, fish and omega-3 consumption improve major physiologic risk factors including BP, heart rate, endothelial function, triglycerides, and adiponectin.[201, 205] Omega-3's also reduce inflammatory biomarkers, reduce myocardial oxygen utilization, and enhance cardiac function.[201, 205] Overall, while 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 fish consumption, particularly for 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 diabetes risk, 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 presence of persistent organic pollutants (e.g., dioxins, polychlorinated biphenyls) may partly reduce cardiometabolic benefits of fish consumption;[213-215] less evidence suggests potential for net harm, due to the opposing benefits of omega-3's. Methylmercury consumed from fish has no detectable influence on incident cardiovascular events, hypertension, or diabetes.[216-218] To optimize neurodevelopment in their children due to benefits of fish consumption, women who are or may become pregnant or nursing should follow FDA guidance to eat 2-3 servings/week 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/week).[219]

While patients often ask about health effects of farmed (aquaculture) vs. wild-caught species, few species are commonly available as both: most are either predominantly farmed (e.g., tilapia, catfish, carp, shrimp, oysters) or wild-caught (e.g., tuna, pollock, crab, cod).[220] One exception is salmon, of which about 1/3 are wild-caught (principally from Alaska) and 2/3 are farmed (e.g., 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 acids[201] 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 products together (e.g., milk, cheese, yogurt), categorize these by fat content, and then recommend selection of low-fat products.[21] However, 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 do not consistently differ by fat content but appear more specific to food type: e.g., cheese, yogurt, milk, butter (Figure 6).[57, 221-226] For example, intake of yogurt, but not milk, is consistently associated with lower incidence of diabetes; while intake of cheese, which has high calorie, fat, and saturated fat content, also associates with lower diabetes risk in several although not all studies.[57, 179-184, 224, 226-228] While total milk intake is generally unassociated with diabetes, 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 synthesize vitamin K2 (menaquinones), which may improve insulin sensitivity.[230, 231] These findings suggest that health effects of dairy may depend on multiple complex characteristics, e.g., 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, while no significant body compositional effects are seen when adding dairy to ad libitum diets.[232, 233] Long-term effects appear to vary by the type of

dairy. For instance, children who drink more low-fat milk gain more weight, while 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 may relate to caloric compensation: when people consume more low-fat dairy, they compensate in the long-term by increasing their consumption of carbohydrates.[29]

The STRIP trial randomized 1062 Finnish infants to dietary intervention vs. 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, compared to 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 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 utilizing objective blood biomarkers, greater dairy fat consumption is associated with lower incidence of diabetes[59-61, 242, 243] and CHD,[39, 244, 245] with mixed findings for stroke.[246] It remains unclear whether such findings relate to health benefits of specific dairy fatty acids (e.g., 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 (e.g., production of vitamin K2 from fermentation of cheese), or unknown endogenous (non-dietary) determinants of these blood biomarkers.[247] Whatever the explanation, little evidence supports the opposing hypothesis, i.e., the superiority of low-fat dairy products, including for obesity.

In sum, dairy products represent a diverse class of foods, with complex effects that vary by specific product type and emerging mechanistic pathways that may include influences of fermentation and probiotics. No long-term studies support harms, and emerging evidence suggests potential benefits, of dairy fat or high-fat dairy foods such as cheese. Together these findings provide little support for prevailing recommendations that are based largely on calcium and vitamin D, 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 vs. 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 large pooling project of European cohorts, individuals consuming any butter, compared with none, experienced lower risk of diabetes.[248] However, among butter consumers, no further dose-response was seen, suggesting potential for reverse causation (bias) among nonconsumers. In either case, these findings suggest that butter is, at worst, neutral for diabetes. Butter consumption is also not significantly associated with incident CHD,[223] stroke,[222] or total mortality[58] (Figure 6). Surprisingly few studies have reported on these relationships, suggesting potential publication bias. Because such bias would skew toward 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

Cardiometabolic effects of vegetable oils have conventionally been considered in light of their fatty acid contents, i.e., 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 which 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, compared with control.[34] In the intervention group, about 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 fats[21] (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 long-term health effects of tropical oils, such as palm or coconut. These oils contain saturated fat, but also other compounds, e.g. 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 based on theories about its nutrient contents,[9] and long-term investigations are urgently needed to make evidence-informed decisions about avoiding or increasing use of tropical oils.

Industrially interesterified oils are increasingly common, but 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, benefits of soybean, extra-virgin olive, and canola oil may be best established. Virgin oils (e.g., extra-virgin olive oil, virgin soybean oil) may be preferable due to their low temperature refining that may better preserve trace phenolic compounds; further study of how processing methods influence phytochemicals and health effects is needed. In the future, certain vegetable oils blends may offer particular cardiometabolic benefits, e.g. 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.

Sugar-sweetened beverages (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 likely owe to high glycemic and insulin responses and low satiation (see *Carbohydrate-rich foods,* above). SSBs are also associated with incidence of diabetes and CHD (Figure 6).[257, 258] These effects appear partly but not entirely mediated by adiposity, consistent with independent adverse effects 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 (e.g., saccharin, sucralose, aspartame) and natural low-calorie (also termed high intensity, non-nutritive) sweeteners (e.g., stevia). Based on long-term observational studies and intermediate-duration (e.g., 2 year) 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 non-nutritive sweeteners may not be benign, with potential impact on cognitive processes (e.g., reward, taste perception), oral-gastrointestinal taste receptors and 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 (e.g., to switch from regular to diet soda) but should subsequently also be reduced (e.g., to switch from diet soda to seltzer water) to prevent potential long-term harms. Other use of such sweeteners should not yet be considered innocuous for cardiometabolic health.

100% fruit juice

Although 100% fruit juice and SSBs have similar sugar content, the former is linked to relatively less long-term weight gain.[28] Further, intake of sugar-sweetened fruit juice, but not 100% fruit juice, is associated with incident diabetes in longitudinal studies (Figure 6).[257, 266] These findings suggest that 100% fruit juice may have other beneficial components, e.g., 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 (e.g., up to one serving/day) appears reasonable; higher intake may not be prudent due to links to long-term weight gain.

Coffee, tea

Coffee is commonly considered for its caffeine content, but represents a liquid extract of legumes (coffee beans) containing many active compounds. Both caffeinated and decaffeinated coffee associate with lower onset of diabetes in a dose-dependent fashion (Figure 6).[269] Coffee intake also associates with lower risk of CHD and stroke but in a nonlinear fashion: compared with no intake, lowest risk is seen at 3-4 cups/day, with increasing risk at higher intakes.[270] Several small controlled trials have evaluated 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 lower risk of diabetes and CVD, especially comparing very frequent consumption (3-4 cups/day) with none (Figure 6).[275, 276] Yet, controlled trials of tea have not identified robust benefits on markers of glucose-insulin homeostasis.[277, 278] However, in meta-analyses of trials, green tea, black tea, and herbal roselle tea each modestly lower BP;[279-281] while green and black tea, but not herbal roselle tea, also lower LDL-cholesterol.[282-284]

Overall, observational studies support potential cardiometabolic benefits of coffee and tea. Plausible biologic mechanisms that could explain the size of these associations have not been confirmed, except 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 potential benefits is needed before actively encouraging consumption.

Alcohol

Habitual heavy alcohol consumption causes up to one-third of nonischemic dilated cardiomyopathy in many nations.[285] Ventricular dysfunction is often irreversible, even when alcohol use is stopped; continued drinking associates with high mortality. Habitual alcohol and acute binges associate with higher risk of atrial fibrillation.[286] Like other liquid calories (except milk), alcohol intake also associates with higher long-term weight gain.[287] Conversely, compared to nondrinkers, regular moderate consumption – up to ~2 drinks per day for men, ~1-1.5 drink per day for women – associates with lower incidence of CHD and

diabetes, although not stroke.[288, 289] Such observational analyses could partly overestimate benefits, as never drinkers could include those who have avoided alcohol due to unmeasured factors that relate to later poor health.[290] Yet, magnitudes and consistency of observed lower risks across diverse populations, together with favorable effects on HDL-C, insulin resistance, and fibrinogen in controlled trials,[291] provide strong evidence for at least some cardiometabolic benefit of moderate alcohol use. While a common perception is that effects are specific to red wine, cardiometabolic benefits have also been seen for white wine, beer, and spirits.[292] This could relate to physiologic effects of alcohol itself[291] as well as phenolics in wine and beer.[292]

Alcohol use exhibits a “J-shape” with all-cause mortality, with lowest risk observed between 1 drink/week and 1 drink/day, 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, due to increased risk of cancers, liver disease, cardiomyopathy, accidents, violence, homicides, and suicides.[1, 294] Thus, alcohol 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 (in onions, broccoli, tea, and various fruits), flavones (in parsley, celery, and chamomile tea), flavanones (in citrus fruits), flavanols (flavan-3-ols) such as catechins and procyanidins (in cocoa, apples, grapes, red wine, and tea), anthocyanidins (in colored berries), and isoflavones (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/day (30 kcal/day) of dark chocolate and correlates with increased endothelial nitric oxide production.[298] The latter mechanism suggests potential benefits beyond lower BP. A few short-term trials of other dietary sources (e.g., 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 – e.g., berries,[301] nuts,[145] extra-virgin olive oil[34] – are rich in phenolics, and documented physiologic are promising and provide clear impetus for further study.

Sodium

In North America and Europe, most sodium (~75%) comes from packaged foods and restaurants, and little from home cooking or table salt; while 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, hypertensives, and Blacks.[304] In meta-analyses of longitudinal studies, high sodium intakes associate with incident total stroke, stroke mortality, and CHD mortality (Figure 7).[305-307] This is supported by the strength of BP as a surrogate outcome,[308] and ecologic and experimental studies of sodium and CVD.[304] Indeed, the latter 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 (e.g., 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 low intakes (e.g., <3000 g/d).[311-313] These findings have generated recent controversy about the optimal lowest levels of sodium consumption.[314]

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, and linked to less compliant, sicker individuals); reverse causation (at-risk subjects, such as those with higher BP or diabetes, actively lowering their sodium intake); confounding by physical activity (which increases total energy consumption, that is correlated with total sodium intake[316]); and confounding by frailty and other consumption). These limitations together could explain the J-shapes seen in certain observational studies.

In comparison, during extended surveillance in a large sodium study which excluded sick individuals at baseline and collected multiple 24-hour urine 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 ecologic studies, the lowest mean intake level associated with both lower systolic BP and lower age-BP slope 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]

While 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 remains unclear whether such physiologic effects could offset, let alone reverse, BP-lowering benefits of sodium reduction and explain the J-shaped relations with CVD seen in some observational studies. Overall, while 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] and could be 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 hypertensives and when dietary sodium intake is high.[325] BP-lowering is related to both increased urinary potassium excretion and a lower urine sodium-to-potassium ratio. Consistent with these benefits, potassium-rich diets associate with lower risk of CVD, especially stroke (Figure 7).[326] Diets rich in potassium also attenuate, while diets low in potassium exacerbate, the BP effects of sodium. For instance, a Mediterranean or DASH-type diet (e.g., richer in fruits, vegetables, nuts) reduces, while 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 Mg inversely associate with CVD, especially fatal CHD;[330] 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 associate with lower CVD risk in observational studies, but trials of supplements, including folate, B-vitamins, beta-carotene, vitamin C, vitamin E, and selenium, have shown no significant effects on atherosclerosis progression or CVD events.[19, 331, 332] Most of these trial, 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 partly relate to different time periods of biologic sensitivity — e.g., 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 from other lifestyle behaviors (i.e., observed benefits are not due to diet) or due to other nutritional factors in vitamin-rich foods (i.e., observed benefits are due to diet but not to the specific identified 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, as well as being foods that can provide benefit by replacing unhealthful foods. Thus, isolating one or even several components of these foods 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 compared 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 while total carbohydrate has little influence on cardiometabolic health, the types and quality of carbohydrate have major impact (Figures 6-7; see *Carbohydrate-rich foods*, above). Certain carbohydrate-containing foods (e.g., fruits, legumes, vegetables, minimally processed whole grains) are protective, while foods rich in refined grains (e.g., white bread, white rice, crackers, cereals, bakery desserts), starches (e.g., russet or white potatoes), and added sugars (e.g., SSBs, candy) are harmful. Because of this diversity, 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] While 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 (e.g., many breakfast cereals, breads, crackers); and away from otherwise healthful foods containing modest amounts of added sugar (e.g., 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 potential harms of high-fructose corn syrup. Because glucose, the main sugar in regular corn syrup (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, i.e. the same as in natural sugar (sucrose) found in cane sugar, beet sugar, or honey. Consequently, there are few expected or observed physiologic or health differences between high-fructose corn syrup vs. 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). 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, via both distinct and partly overlapping pathways. In contrast, low doses of slowly digested glucose or fructose (e.g., as found in fruit) would each have minimal cardiometabolic harms. Ultimately, health differences between high-fructose corn syrup vs. natural added sugar are small compared 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, due to 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 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 vs. 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 endpoint including heart disease (Figure 2, top panel), stroke, cancers, diabetes, or insulin resistance.[36-39] In contrast, randomized trials confirm observational cohort findings that diets higher in healthful fats, exceeding the current 35% limit, reduce risk of cardiovascular disease (Figure 2, bottom panel) and diabetes.[24, 25, 34, 35] These trials confirm decades-old ecologic 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 states, 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 other products of poor nutritional value; and leads most Americans to actively avoid dietary fat[337] while eating far too much 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, with fatty acid 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 biologic and metabolic diversity does not support the grouping together of all saturated fatty acids based on a single chemistry characteristic: the absence of double bonds.[340]

Even for any single saturated fatty acid, physiologic effects are complex. For instance, compared 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; its triglyceride-lowering effects[341] suggest potential benefit. Saturated fat also lower lipoprotein(a), an independent and casual cardiovascular risk factor,[342] in comparison to monounsaturated fat or carbohydrate.[343]

Dietary saturated fats are also obtained from very different foods – e.g., cheese, grain-based desserts, dairy desserts, chicken, processed meats, unprocessed red meat, milk, yogurt, butter, vegetable oils, nuts. Each of these possesses, in addition to saturated fat, numerous other ingredients and characteristics that modify their health effects. Judging 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 (e.g., 14:0, 16:0), that appear most harmful, commonly result from endogenous hepatic synthesis in response to dietary carbohydrate;[46] 14:0 and 16:0 blood levels correlate more with 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 person's diet as harmful because it contains more saturated fat, or 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 (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 benefits of other saturated fat-rich foods. While unprocessed red meats and butter may be relatively neutral for CHD, no studies demonstrate appreciable benefits, all meats appear to increase diabetes, 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 relies on selected evidence: effects on LDL-cholesterol alone (discounting the other, complex lipid and lipoprotein effects); historical ecologic trends in certain countries (e.g. 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 nations correlate with decreases in saturated fat, changes in dietary fats cannot explain much of the blood cholesterol changes across or within most nations. For instance, total blood cholesterol fell similarly in the US and France between 1980 and 2000, but national changes in dietary fats may explain only about 20% of the decline in the US, 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, due to relatively low use for primary prevention prior to this period, statins cannot explain the observed similar declines in blood cholesterol over the preceding 20-30 years. Reasons for the large and steady declines in blood cholesterol and blood pressure over the past four 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 (e.g., related to fetal nutrition, the microbiome, or other unknown pathways) remains unclear.

Based on the similar cardiovascular effects of total carbohydrate vs. saturated fat, and the comparative benefit of polyunsaturated fats, guidelines to lower saturated fat are increasingly specifying the importance of consuming polyunsaturated fats as the replacement.[21] Yet, this benefit appears specific to increased polyunsaturated fat, rather than reduced saturated fat. For instance, total saturated fat, carbohydrate, and protein each appear relatively neutral for CHD; while 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. Compared to any of these broad categories, polyunsaturated fat appears to be similarly beneficial.[350] Consequently it make little sense to focus on saturated fat, which represents a smaller proportion of calories than these other macronutrients, especially carbohydrate. Indeed, when compared 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

While 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 cholesterol[353] 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;[355] associates with trends toward greater CVD in some cohort studies;[155] and increases

atherosclerosis in primate experiments, potentially due to 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 consumption of olive oil, but not mixed animal and plant sources of monounsaturated fat, is linked to lower risk;[352] while 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, 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 alpha-linoleic acid (ALA, 18:3n-3), derived principally from vegetables and their oils (e.g., soybean, canola, flaxseed, walnuts). Seafood is the major source of long-chain n-3 polyunsaturated fats, principally EPA and DHA.[201] While the liver readily synthesizes saturated and monounsaturated fats from carbohydrate (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] While pro-inflammatory effects of LA have been theorized[358] and popularized, such inference is based largely on rodent experiments; with little supportive evidence in humans.[359-362] Indeed, LA appears to have anti-inflammatory and insulin-sensitizing effects.[363-365] In controlled trials, compared 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 pro-inflammatory, but is also the natural precursor to specialized proresolving mediators (SPMs) of inflammation.[368, 369] In prospective studies, higher biomarker levels of AA are linked to significantly lower risk of CHD.[39] LA is also associated with significantly lower risk of CHD (Figure 7), whether in comparison to carbohydrate or saturated fat;[350] 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 trials, the average intake of n-6 polyunsaturated fat was ~15% energy,[349] higher than current guidelines that recommend up to 10-11% energy from polyunsaturated fat.[370]

Compared with seafood sources, ALA is a relatively available and inexpensive plant-source of n-3 polyunsaturated fat. Ecologic studies suggest benefits of increasing ALA intakes in populations with low overall n-3 polyunsaturated fat intake.[356] Yet, findings of trials of risk markers, such as platelet function, inflammation, endothelial function, and arterial

compliance, and observational studies of its association with CVD and diabetes endpoints, have been mixed and inconclusive.[371, 372] Few long-term trials of ALA and clinical events have been conducted; in one Dutch trial, 40 months of an ALA-containing margarine led to a nonsignificant reduction in major cardiovascular events RR=0.91; 95% CI: 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 their independent harms. Because the controlled trials demonstrating CHD benefits utilized soybean oil,[349] which contains both n-6 (LA) and n-3 (ALA) polyunsaturated fats, selection of vegetable oils containing both n-6 and n-3 fatty acids (e.g., soybean, canola) may be most prudent. Because both n-3 and n-6 polyunsaturated fats are beneficial, little interaction between them is evident, and their ratio is not a practical metric to evaluate health effects.[364, 374]

Trans fatty acids (TFA)

TFA are mono- or polyunsaturated fats with one or more double bonds in a *trans* position, rather than the mammalian synthesized *cis* position. While small amounts of “natural” TFA are found in meats and milk of ruminants (e.g., cow, sheep, goat; formed by gut microorganisms), these contribute minimally to diet (<0.5%E) and do not associate with CVD risk;[375] indeed, trans-16:1n-7, a trace TFA biomarker of dairy fat, is linked to lower risk of diabetes and sudden death.[247] Conversely, high levels of industrially-produced TFA can be consumed from partially hydrogenated vegetable oils, which typically contain 30-60% TFA. These fats have industrial advantages for commercial deep frying, baked goods, packaged snacks, and shortening. Higher TFA intake from partially hydrogenated oils consistently associates with risk of CHD and sudden death (Figure 7).[331, 376] In trials, TFA have unique adverse effects on blood lipid and lipoproteins, including raising LDL-cholesterol, ApoB, triglycerides, and lipoprotein(a); and lowering HDL-cholesterol and ApoA1; these effects are generally consistent whether TFA replaces saturated, monounsaturated, or polyunsaturated fat.[377] TFA also appear to have many non-lipid adverse effects, promoting inflammation, endothelial vasodilator dysfunction, insulin resistance, visceral adiposity, and arrhythmia, although strength of evidence for these non-lipid 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 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

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, and 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 dietary protein per se is far less relevant for CVD than on the specific types of foods consumed. A few cohorts have seen protective associations of animal protein intake with risk of hemorrhagic stroke; causality and mechanisms remain unclear, but have been hypothesized to relate to 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 – e.g., clinical counseling, food labels, menu labeling, dietary guidelines – arise from an implicit assumption that dietary habits are a function of individual choice. In reality, multiple complex factors influence dietary choice (**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 psychological 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] Sociocultural determinants include cultural norms, social pressures, social class, social networks, and race/ethnicity.[390] Environmental influences include neighborhood accessibility (e.g., food availability, cost, convenience) and climate. 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, 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, e.g. 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 biologic preference for food.[4, 346, 392-394] Even the brain's unconscious reward/craving (“addiction”) centers are plastic and can be trained 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 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, as well as other lifestyle habits such as tobacco use, physical inactivity, and medication noncompliance. Providers should recognize that while 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, suboptimal 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 health care system can strongly support and facilitate behavior change efforts by providers (**Table 6**).[10, 95, 398, 399] Such health care 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 remains variable. Expansion of these health care systems approaches to target diet quality is crucial.

Novel technology strategies

Recent years have witnessed an explosion of novel personal technologies for improving health, including mobile device applications (mHealth), internet-based programs, and personal tracking devices (e.g., FitBits). These technologies are promising due to potential for scalability, low-cost, use in multiple settings including middle-income 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.[400] Most were internet-based or combined internet and mobile approaches. The great majority had durations between 6 weeks to 6 months; very few extended beyond 1 year. Approximately two-thirds of these studies identified improved dietary behaviors or greater weight loss with use of these novel technologies, in comparison to usual care. While promising, little is known on 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 (e.g., schools, worksites, communities), as well as 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 limited influence on behavior.[11, 401, 402] Integrated, multicomponent approaches 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 due to clustering of suboptimal diet habits, local environments, and disease risk factors.

Several factors have limited 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 such as tobacco use and motor vehicle safety encourage optimism for success of concerted multi-component strategies that include strong quality standards and policy actions. Even modest risk factor shifts at the population level can substantially and rapidly alter population health.[97, 403]

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, 404] 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 systems 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 the leading issue of our time. Policy makers at all levels must recognize and focus on these issues. Surveillance, monitoring, and evaluation of dietary habits and dietary policies are necessary to design solutions, assess whether implemented regulations and strategies 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 multi-national 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. While “big food” has shared many tactics

with “big tobacco” – e.g., lobbying, deception, denial, resistance to regulation[405] – these two industries are not fully analogous. The food industry is far more heterogeneous, from types of products to commitments to healthfulness. The food industry has also demonstrated responsiveness to dietary guidelines and public preferences over the last 40 years: e.g., low-fat products, margarine, noncaloric sweeteners, low-carb products, gluten-free, organic, 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 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 utilize 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.[406] This remarkable success was not achieved merely by national “driving guidelines,” motor vehicle labeling, or other consumer education – i.e., many of the current emphases for dietary change – but by a comprehensive, multi-component 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 ultra-processed 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 multi-component, 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, and CVD present enormous health and economic burdens[404] and emphasize the imperative of prioritizing nutrition in clinical care, advocacy, research, and policy. Scientific advances provide a wealth of new evidence on the 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 red meats, processed (sodium-preserved) meats, and foods higher in refined carbohydrates and salt (Figure 3). Red meats should be minimized to prevent diabetes; butter used occasionally but not emphasized; and other foods (e.g., unprocessed

poultry, eggs) consumed in moderation according to personal preference. Coffee and tea can be enjoyed, with possible (but not yet confirmed) benefits; and alcohol, if consumed, should be moderate (up to 1 drink/day for women and 2 drinks/day 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,[21] replacing outdated emphases on total fat, other isolated nutrients, or 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.

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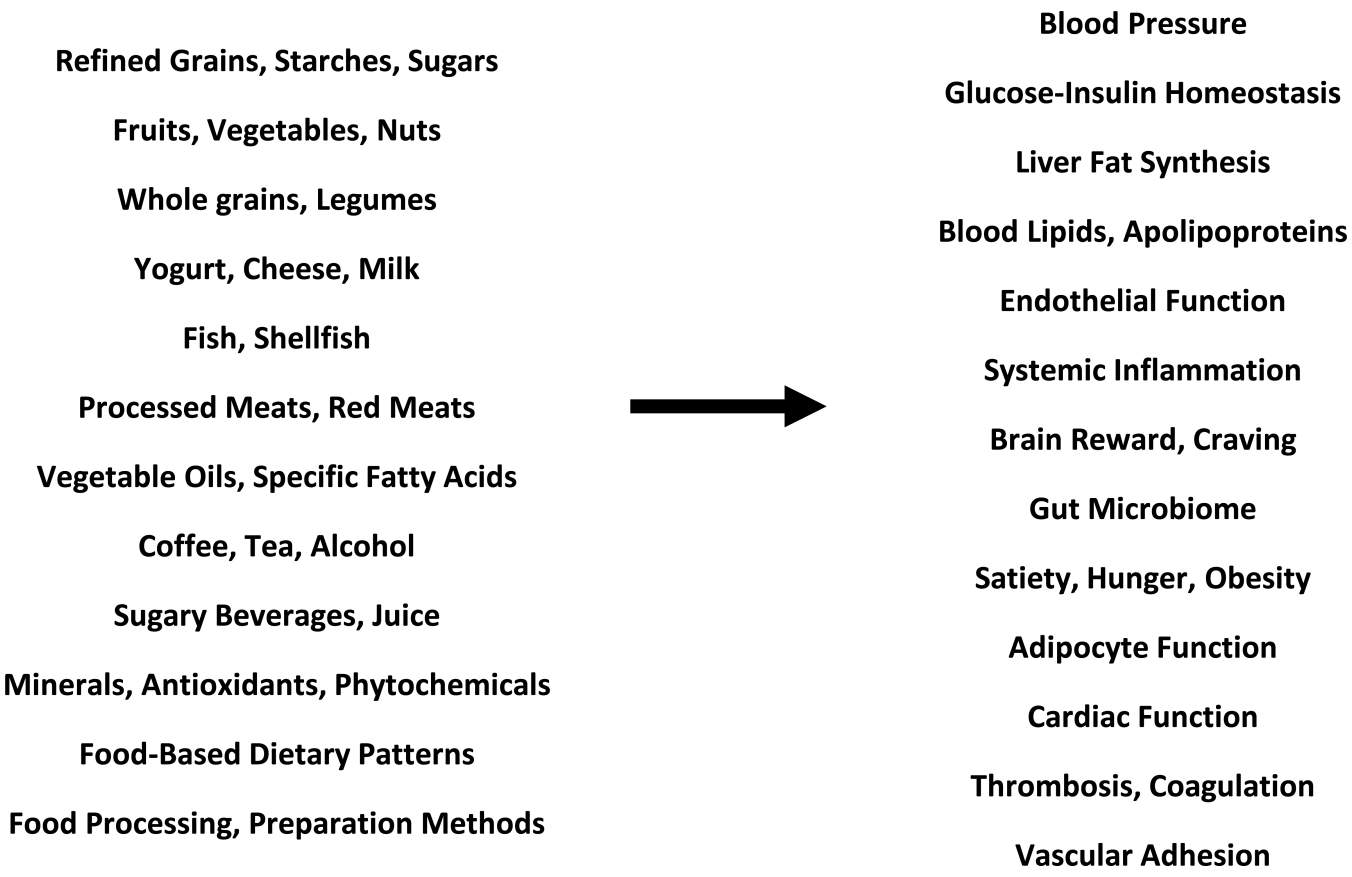


Figure 1. Diet and cardiovascular and metabolic risk – pathways and mechanisms

Each of these dietary factors influences many or even all of these pathways, which could also be modified in some cases by underlying individual characteristics. Selected major effects are detailed in the text sections on each dietary factor.

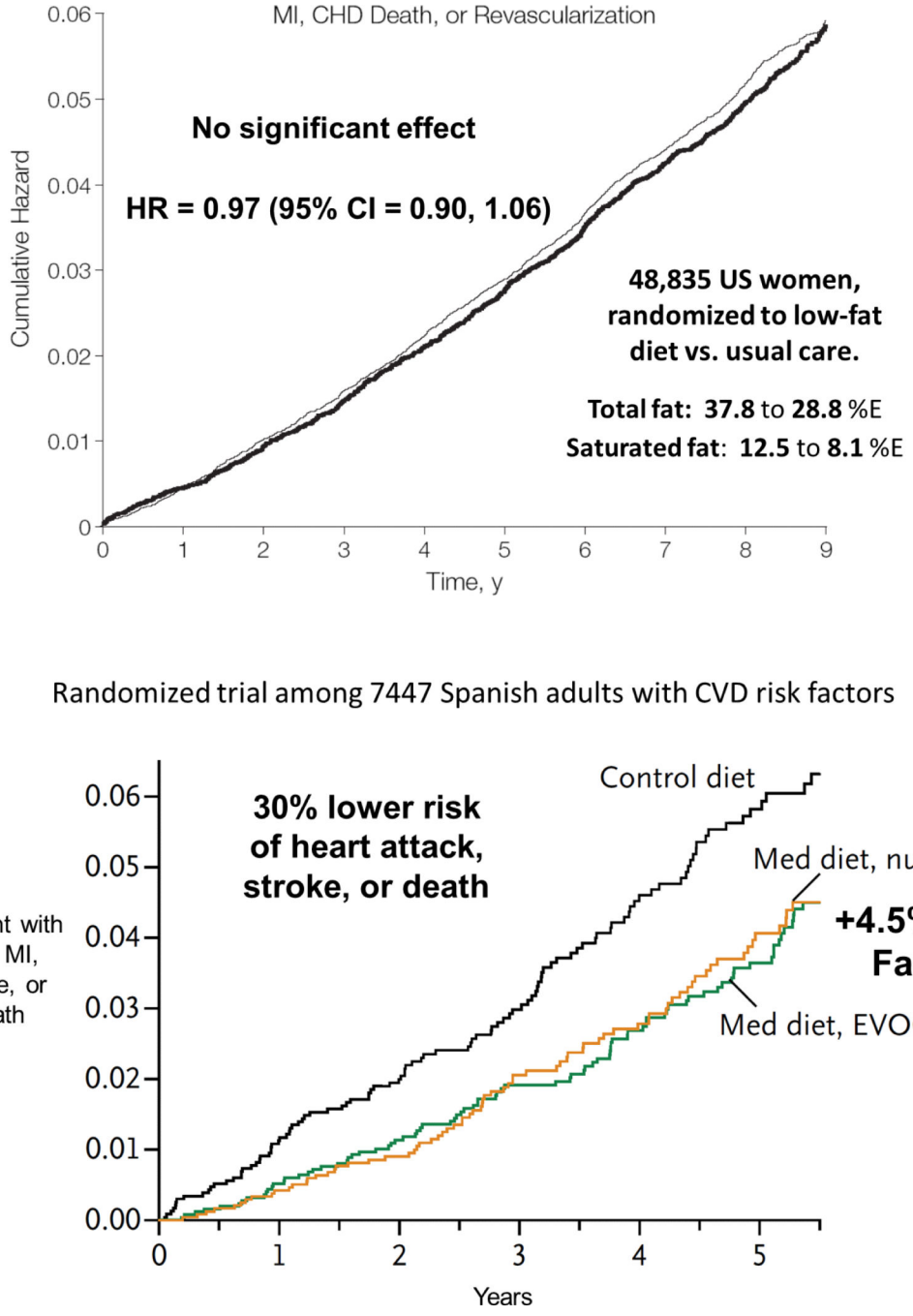


Figure 2. Contrasting results of randomized controlled dietary trials focusing on isolated nutrients (top panel) vs. food-based diet patterns (bottom panel)

The Women's Health Initiative (WHI, top panel) 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. The PREDIMED trial (bottom panel) 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. Both trials successfully altered long-term diets, although with more modest changes in PREDIMED, but only the food-

based intervention resulted in clinical benefit. Figures adapted with permission from Howard et al., JAMA 2006; and Estruch et al., NEJM 2013.

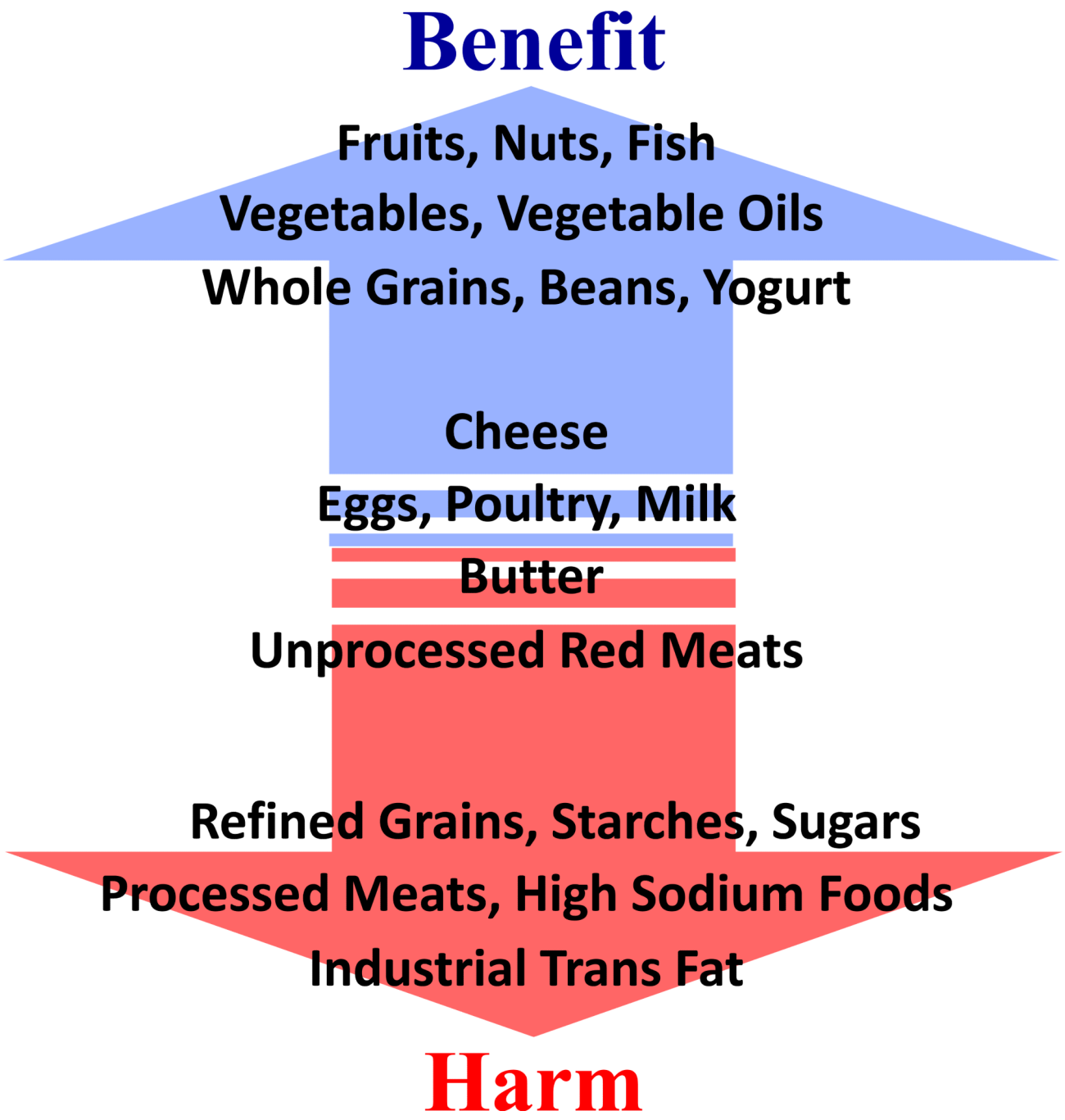


Figure 3. Evidence-based dietary priorities for cardiometabolic health

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

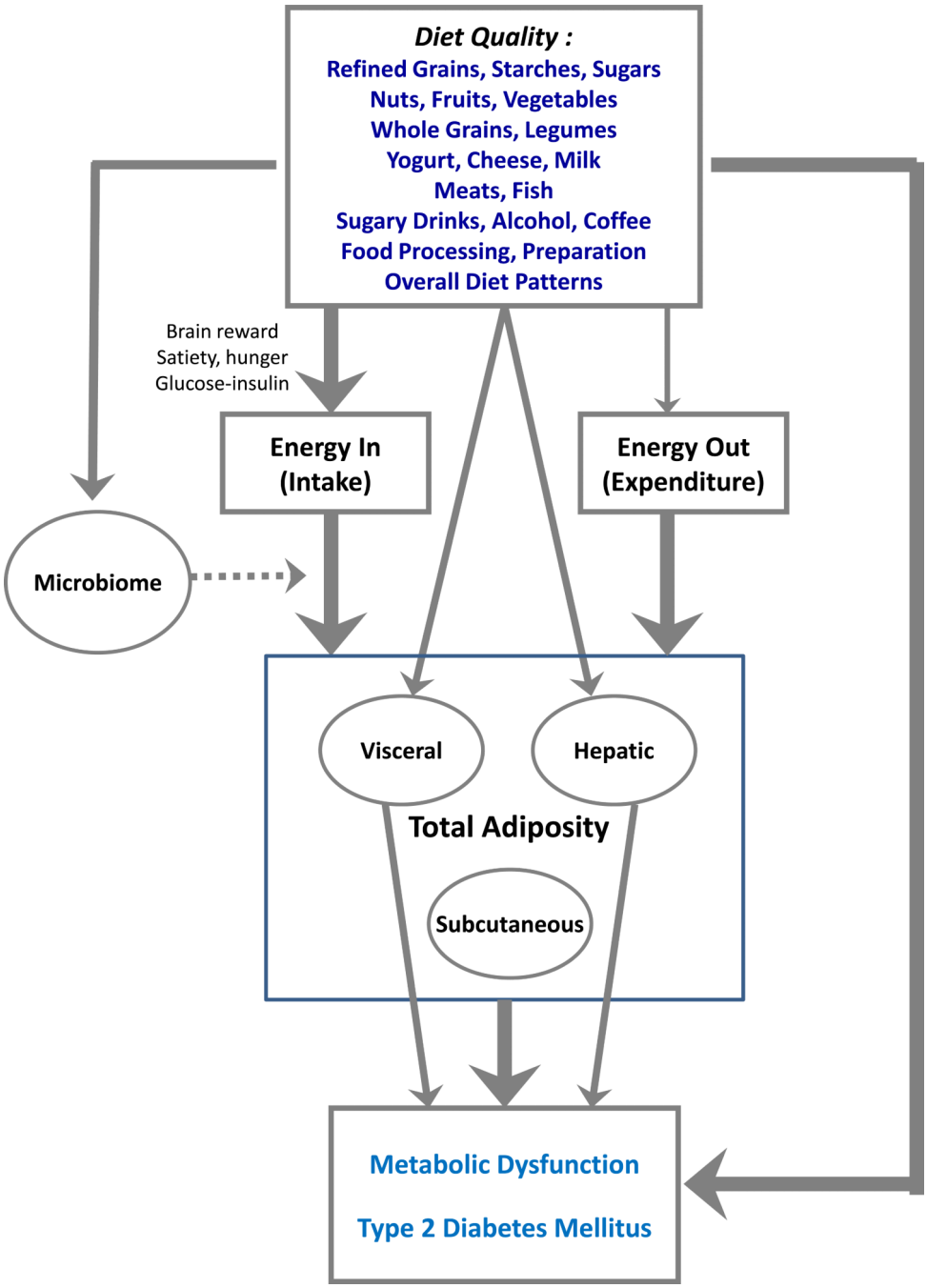


Figure 4.
Diet quality, obesity, and metabolic risk – a modern paradigm.

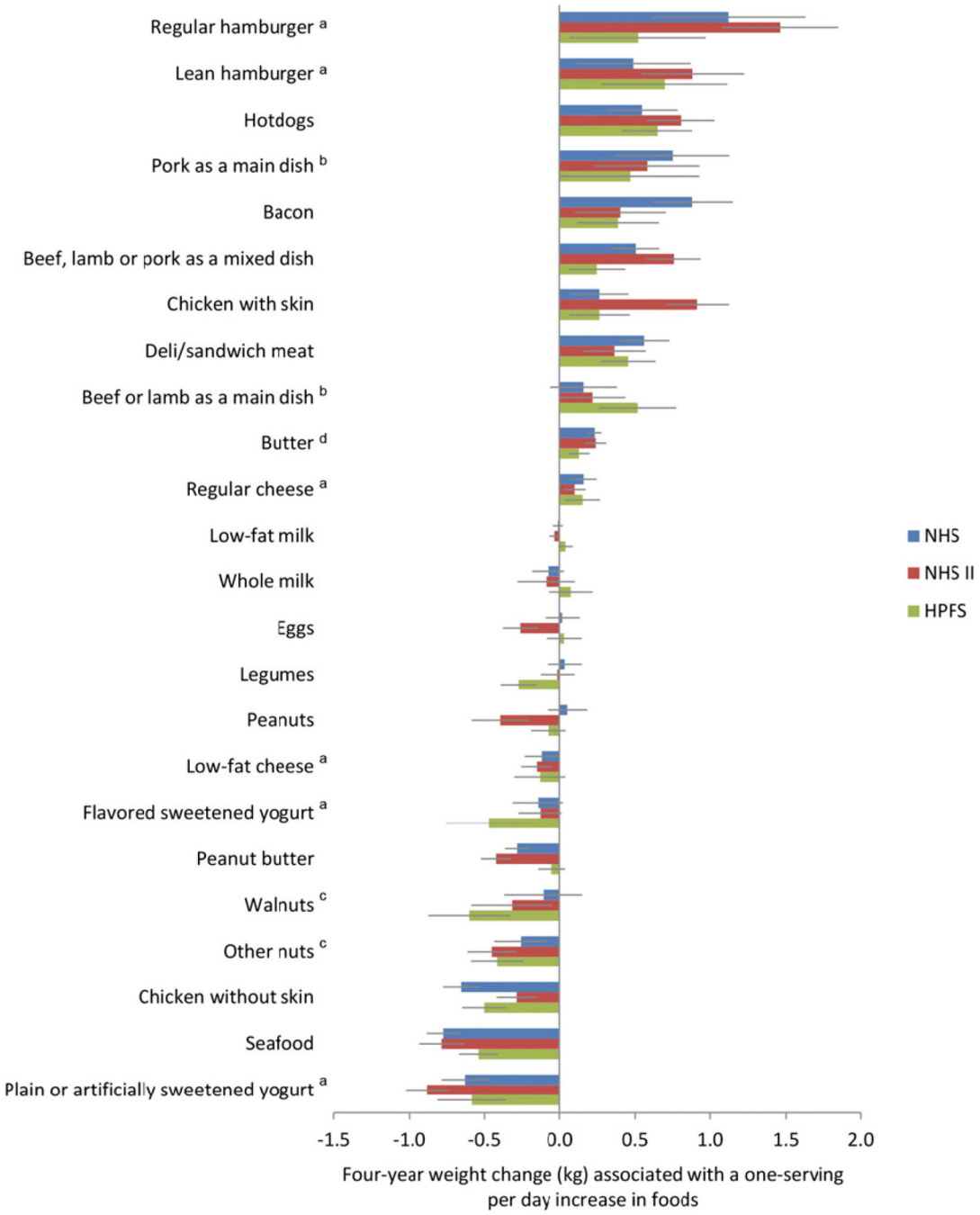
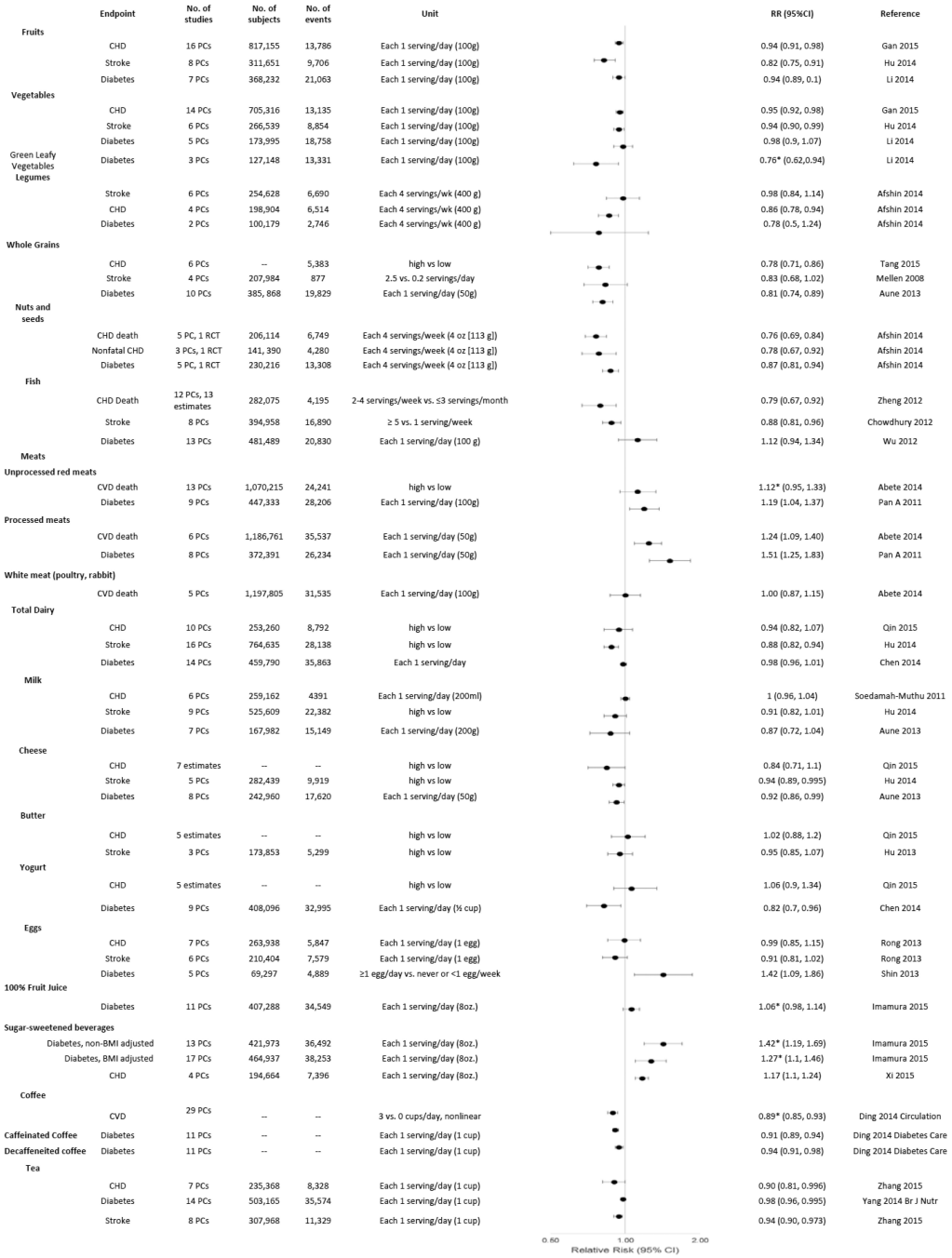


Figure 5.

Protein-rich foods and long-term weight gain in three 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/day increase in consumption; decreased consumption would be associated with the inverse weight changes. To convert kg to lbs, multiply 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.

Reproduced with permission from Smith et al., *Am J Clin Nutr*. 2015;101:1216-1224



	Endpoint	No. of studies	No. of subjects	No. of events	Unit	RR (95%CI)	Reference
Fruits							
	CHD	16 PCs	817,155	13,786	Each 1 serving/day (100g)	0.94 (0.91, 0.98)	Gan 2015
	Stroke	8 PCs	311,651	9,706	Each 1 serving/day (100g)	0.82 (0.75, 0.91)	Hu 2014
	Diabetes	7 PCs	368,232	21,063	Each 1 serving/day (100g)	0.94 (0.89, 0.1)	Li 2014
Vegetables							
	CHD	14 PCs	705,316	13,135	Each 1 serving/day (100g)	0.95 (0.92, 0.98)	Gan 2015
	Stroke	6 PCs	266,539	8,854	Each 1 serving/day (100g)	0.94 (0.90, 0.99)	Hu 2014
	Diabetes	5 PCs	173,995	18,758	Each 1 serving/day (100g)	0.98 (0.9, 1.07)	Li 2014
Green Leafy Vegetables	Diabetes	3 PCs	127,148	13,331	Each 1 serving/day (100g)	0.76* (0.62,0.94)	Li 2014
Legumes							
	Stroke	6 PCs	254,628	6,690	Each 4 servings/wk (400 g)	0.98 (0.84, 1.14)	Afshin 2014
	CHD	4 PCs	198,904	6,514	Each 4 servings/wk (400 g)	0.86 (0.78, 0.94)	Afshin 2014
	Diabetes	2 PCs	100,179	2,746	Each 4 servings/wk (400 g)	0.78 (0.5, 1.24)	Afshin 2014
Whole Grains							
	CHD	6 PCs	--	5,383	high vs low	0.78 (0.71, 0.86)	Tang 2015
	Stroke	4 PCs	207,984	877	2.5 vs. 0.2 servings/day	0.83 (0.68, 1.02)	Mellen 2008
	Diabetes	10 PCs	385, 868	19,829	Each 1 serving/day (50g)	0.81 (0.74, 0.89)	Aune 2013
Nuts and seeds							
	CHD death	5 PC, 1 RCT	206,114	6,749	Each 4 servings/week (4 oz [113 g])	0.76 (0.69, 0.84)	Afshin 2014
	Nonfatal CHD	3 PCs, 1 RCT	141, 390	4,280	Each 4 servings/week (4 oz [113 g])	0.78 (0.67, 0.92)	Afshin 2014
	Diabetes	5 PC, 1 RCT	230,216	13,308	Each 4 servings/week (4 oz [113 g])	0.87 (0.81, 0.94)	Afshin 2014
Fish							
	CHD Death	12 PCs, 13 estimates	282,075	4,195	2-4 servings/week vs. ≤3 servings/month	0.79 (0.67, 0.92)	Zheng 2012
	Stroke	8 PCs	394,958	16,890	≥ 5 vs. 1 serving/week	0.88 (0.81, 0.96)	Chowdhury 2012
	Diabetes	13 PCs	481,489	20,830	Each 1 serving/day (100 g)	1.12 (0.94, 1.34)	Wu 2012
Meats							
Unprocessed red meats							
	CVD death	13 PCs	1,070,215	24,241	high vs low	1.12* (0.95, 1.33)	Abete 2014
	Diabetes	9 PCs	447,333	28,206	Each 1 serving/day (100g)	1.19 (1.04, 1.37)	Pan A 2011
Processed meats							
	CVD death	6 PCs	1,186,761	35,537	Each 1 serving/day (50g)	1.24 (1.09, 1.40)	Abete 2014
	Diabetes	8 PCs	372,391	26,234	Each 1 serving/day (50g)	1.51 (1.25, 1.83)	Pan A 2011
White meat (poultry, rabbit)							
	CVD death	5 PCs	1,197,805	31,535	Each 1 serving/day (100g)	1.00 (0.87, 1.15)	Abete 2014
Total Dairy							
	CHD	10 PCs	253,260	8,792	high vs low	0.94 (0.82, 1.07)	Qin 2015
	Stroke	16 PCs	764,635	28,138	high vs low	0.88 (0.82, 0.94)	Hu 2014
	Diabetes	14 PCs	459,790	35,863	Each 1 serving/day	0.98 (0.96, 1.01)	Chen 2014
Milk							
	CHD	6 PCs	259,162	4391	Each 1 serving/day (200ml)	1 (0.96, 1.04)	Soedamah-Muthu 2011
	Stroke	9 PCs	525,609	22,382	high vs low	0.91 (0.82, 1.01)	Hu 2014
	Diabetes	7 PCs	167,982	15,149	Each 1 serving/day (200g)	0.87 (0.72, 1.04)	Aune 2013
Cheese							
	CHD	7 estimates	--	--	high vs low	0.84 (0.71, 1.1)	Qin 2015
	Stroke	5 PCs	282,439	9,919	high vs low	0.94 (0.89, 0.995)	Hu 2014
	Diabetes	8 PCs	242,960	17,620	Each 1 serving/day (50g)	0.92 (0.86, 0.99)	Aune 2013
Butter							
	CHD	5 estimates	--	--	high vs low	1.02 (0.88, 1.2)	Qin 2015
	Stroke	3 PCs	173,853	5,299	high vs low	0.95 (0.85, 1.07)	Hu 2013
Yogurt							
	CHD	5 estimates	--	--	high vs low	1.06 (0.9, 1.34)	Qin 2015
	Diabetes	9 PCs	408,096	32,995	Each 1 serving/day (½ cup)	0.82 (0.7, 0.96)	Chen 2014
Eggs							
	CHD	7 PCs	263,938	5,847	Each 1 serving/day (1 egg)	0.99 (0.85, 1.15)	Rong 2013
	Stroke	6 PCs	210,404	7,579	Each 1 serving/day (1 egg)	0.91 (0.81, 1.02)	Rong 2013
	Diabetes	5 PCs	69,297	4,889	≥1 egg/day vs. never or <1 egg/week	1.42 (1.09, 1.86)	Shin 2013
100% Fruit Juice							
	Diabetes	11 PCs	407,288	34,549	Each 1 serving/day (8oz.)	1.06* (0.98, 1.14)	Imamura 2015
Sugar-sweetened beverages							
	Diabetes, non-BMI adjusted	13 PCs	421,973	36,492	Each 1 serving/day (8oz.)	1.42* (1.19, 1.69)	Imamura 2015
	Diabetes, BMI adjusted	17 PCs	464,937	38,253	Each 1 serving/day (8oz.)	1.27* (1.1, 1.46)	Imamura 2015
	CHD	4 PCs	194,664	7,396	Each 1 serving/day (8oz.)	1.17 (1.1, 1.24)	Xi 2015
Coffee							
	CVD	29 PCs	--	--	3 vs. 0 cups/day, nonlinear	0.89* (0.85, 0.93)	Ding 2014 Circulation
Caffeinated Coffee	Diabetes	11 PCs	--	--	Each 1 serving/day (1 cup)	0.91 (0.89, 0.94)	Ding 2014 Diabetes Care
Decaffeneited coffee	Diabetes	11 PCs	--	--	Each 1 serving/day (1 cup)	0.94 (0.91, 0.98)	Ding 2014 Diabetes Care
Tea							
	CHD	7 PCs	235,368	8,328	Each 1 serving/day (1 cup)	0.90 (0.81, 0.996)	Zhang 2015
	Diabetes	14 PCs	503,165	35,574	Each 1 serving/day (1 cup)	0.98 (0.96, 0.995)	Yang 2014 Br J Nutr
	Stroke	8 PCs	307,968	11,329	Each 1 serving/day (1 cup)	0.94 (0.90, 0.973)	Zhang 2015

Figure 6.
Meta-analyses of foods and coronary heart disease, stroke, and diabetes.

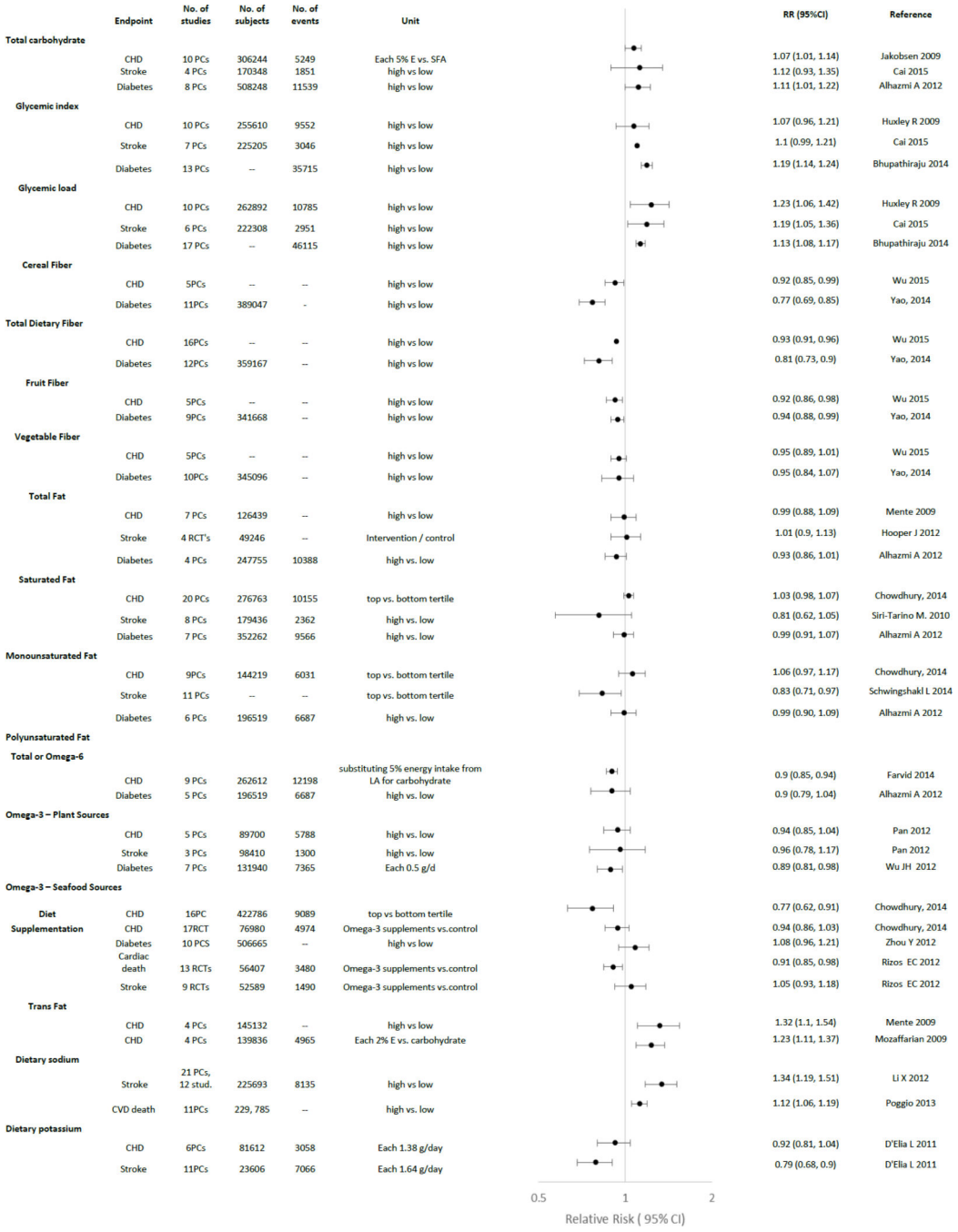


Figure 7.

Meta-analyses of nutrients and coronary heart disease, stroke, and diabetes.

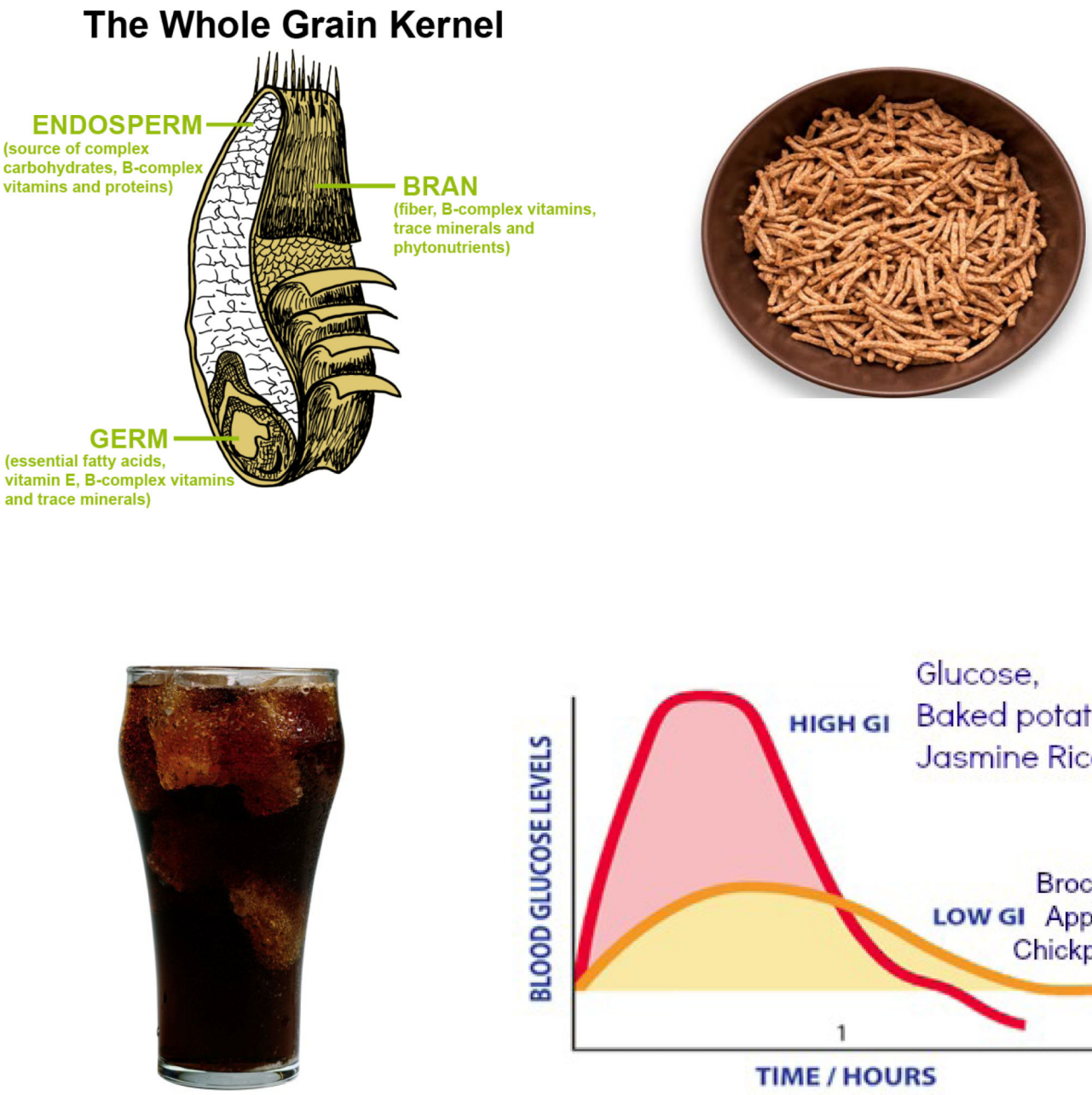


Figure 8.

For defining carbohydrate quality, several characteristics appear to independently alter the cardiometabolic health effects of carbohydrate-rich foods. These include whole grain content (panel a), i.e. based on the content of milled, semi-processed, or intact whole grain including the bran and germ; fiber content (panel b), influenced largely by the content of bran; food structure (panel c), in particular whether the food is solid or liquid (such as sugar-sweetened beverages); and glycemic response (panel c), determined by the amount and accessibility of starch and sugar.

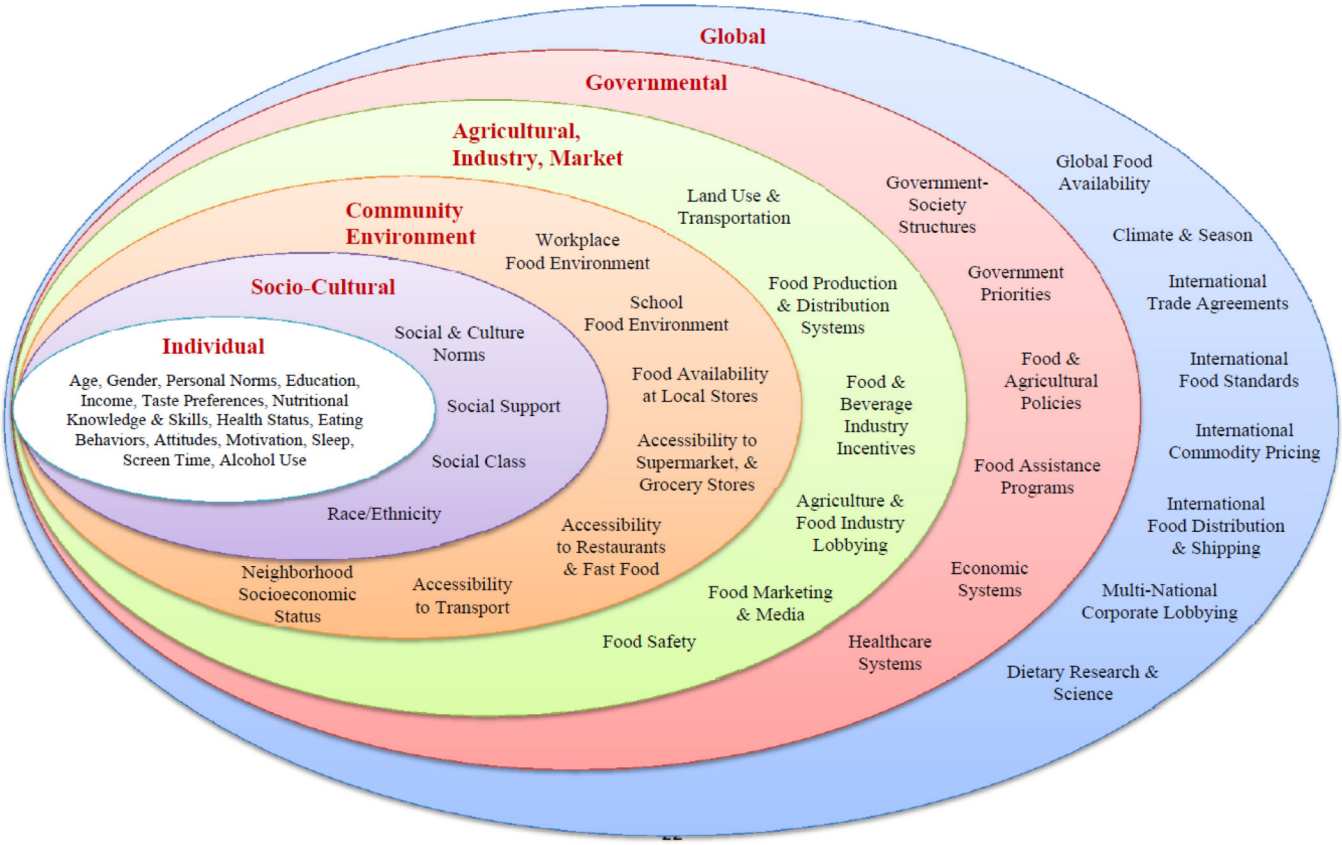


Figure 9.

Barriers and opportunities for healthy eating.

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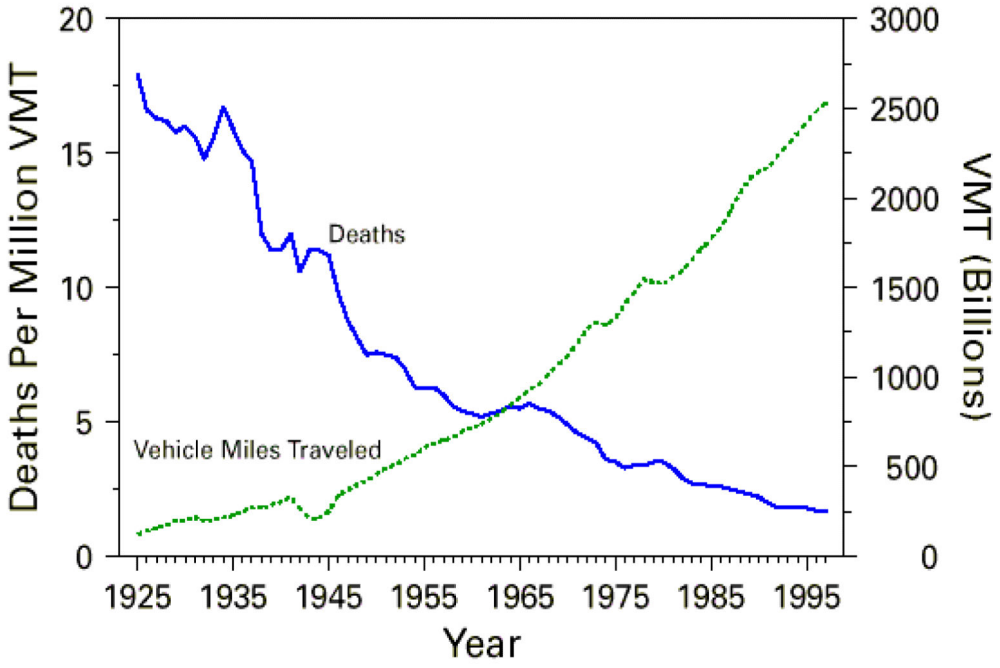
FIGURE 1. Motor-vehicle–related deaths per million vehicle miles traveled (VMT) and annual VMT, by year — United States, 1925–1997



- **Driver:**
  - Education.
  - Licensing.
  - Limits on phone use, texting.
- **Car:**
  - Active: seat belts, child seats, motorcycle helmets.
  - Passive: padded interiors, collapsible steering columns, shatterproof glass, air bags.
  - Crash safety standards.
  - Safety inspections.

Road:

- Road engineering, guard rails, rumble strips.
- Speed limits.
- Stop signs, stop lights, caution signs.

- **Culture:**
  - Designated driver campaign.
  - Drunk-driving legislation.
  - Private advocacy, e.g. MADD.

Figure 10. A roadmap for improving population dietary habits

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 100 million vehicle miles (top panel). This remarkable triumph was achieved by a comprehensive, multi-component effort targeting the driver, car, road, and culture (bottom panel). 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).

Top panel reproduced with permission from *MMWR Morb Mortal Wkly Rep*. 1999;48:369-374.

Table 1

Key New Lessons from Modern Nutritional Science.

Diverse physiologic 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-cutpoints 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 due to 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

Table 2

Dietary Priorities for Cardiometabolic Health.*

		Goal*	One Serving Equals...	Examples
Consume *More*	Fruits	3 servings per day	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/day.
	Nuts, seeds	4 servings per week	1 ounce	Almonds, walnuts, peanuts, hazelnuts, cashews, pecans, Brazil nuts, sunflower seeds, sesame seeds.
	Vegetables, including legumes (excluding russet or white potatoes)	3 servings per day	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. Minimize starchy vegetables, especially russet or white potatoes.
	Whole grains†	3 servings per day, 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 or more servings per week	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 per day	1 cup of milk or yogurt; 1 ounce of cheese	Whole-fat or low-fat yogurt, cheese, milk.
	Vegetable oils	2 to 6 servings per day	1 teaspoon oil, 1 tablespoon vegetable spread	Best evidence for 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 per day	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 servings per week	1.75 ounces (50 g)	Preserved (sodium, nitrates) meats such as bacon, sausage, hot dogs, pepperoni, salami, low-fat deli meats (e.g., chicken, turkey, ham, beef).
	Unprocessed red meats	No more than 2-3 servings per week	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

		Goal*	One Serving Equals...	Examples
				(often injected to increase succulence), cheese, processed meats, soups, canned foods.

Adapted from Mozaffarian et al., Circulation 2011;[19] and the corresponding Harvard Health Letter.[23]

*Based on a 2000 kcal/day 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; i.e., food containing at least 1 g of fiber for every 10 g of total carbohydrate. In addition, minimally processed whole grains (e.g., steel-cut oats, stone ground bread) are generally preferable to finely milled whole grains (e.g., many commercial whole grain breads and breakfast cereals) due to 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 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 use of partially hydrogenated vegetable oils through direct legislation on 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; health effects of these trace industrial trans fats require careful investigation.

Table 3

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

	Broad concordance and less† controversy and/or uncertainty	**General concordance but some remaining controversy and/or uncertainty**	**Substantial controversy and/or 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 (e.g., 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 (e.g., 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 anti-oxidant vitamins, calcium	Poultry 100% fruit juice Total protein, specific amino acids Noncaloric sweeteners	Local, organic, farmed/wild, grass fed, genetic modification

*See manuscript text for details on these topics as well as other foods and nutrients.

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

Table 4

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

Beta-Carotene	Some cohort studies have linked low serum levels or low dietary intake of beta-carotene with higher CVD risk. Trials of beta-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 utilizing 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 two meta-analyses suggest that high dose vitamin E supplements may increase total mortality.
Folic Acid, Vitamins B6, B12	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 B6 and vitamin B12 on CVD outcomes. In some trials, supplemental folic acid was associated with increased risk of CVD.
Fish Oil	Multiple cohort studies have documented 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 due to benefits in patients with prevalent CHD.
Multivitamins	While 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 multi-vitamin use in mixed populations.

Table updated from Mozaffarian et al., Circulation 2011.[19]

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 (e.g., over the next 3 months, increase fruits by one serving/day).
- **Self-monitoring.** Establish a strategy for self-monitoring, such as a dietary or physical activity diary or web-based or mobile applications.
- **Scheduled follow-up.** Schedule regular follow-up (in-person, telephone, written, and/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, and/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 other workplace, school, or community-based programs.
- **Multi-component approaches.** Combine two or more of the above strategies into the behavior change efforts.

* Examples of strategies to increase self-efficacy include mastery experiences (set a reasonable, proximal goal that the person can successfully achieve); vicarious experience (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 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, dieticians, 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.

Adapted from Spring et al., Circulation 2013.[95]

Table 7

Evidence-Based Policy Approaches to Improve Population Dietary Habits.

Media and Education	• Sustained, focused media and education campaigns, utilizing 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 multi-component strategies. *
	• On-site supermarket and grocery store educational programs to support the purchase of healthier foods.
Labeling and Information	• Mandated nutrition facts panels or front-of-pack labels/icons as a means to influence *industry* product formulations. †
Economic Incentives	• 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 which facilitates production, transportation, storage, and marketing of healthier foods.
Schools	• Multi-component interventions focused on improving both diet and physical activity, including specialized educational curricula, trained teachers, supportive school policies, a formal PE 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	• Comprehensive worksite wellness programs including dietary, physical activity, and tobacco cessation/ prevention components.
	• Increased availability of healthier food/beverage options and/or strong nutrition standards for foods and beverages served, in combination with on-site prompts, labels, or icons to select healthier choices.
Neighborhood Environment	• Increased availability of supermarkets near homes. §
Quality Standards	• 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 (e.g., sodium, partially hydrogenated oil) or beneficial (e.g. healthful fats) ingredients in foods.

Adapted from Mozaffarian et al., Circulation 2012.[11]

*Evidence for effectiveness of long-term campaigns (e.g., more than 3 years) comes mainly from multi-component 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 provision of dietary information through food product or menu nutrition labeling.[11, 401, 402]

‡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; little longitudinal data are available. Cross-sectional findings consistently show a beneficial association between 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.