

Ultra-processed Foods and Cardiovascular Diseases: Potential Mechanisms of Action

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ABSTRACT

Ultra-processed foods are industrially manufactured ready-to-eat or ready-to-heat formulations containing food additives and little or no whole foods, in contrast to processed foods, which are whole foods preserved by traditional techniques such as canning or pickling. Recent epidemiological studies suggest that higher consumption of ultra-processed food is associated with increased risk of cardiovascular disease (CVD). However, epidemiological evidence needs to be corroborated with criteria of biological plausibility. This review summarizes the current evidence on the putative biological mechanisms underlying the associations between ultra-processed foods and CVD. Research ranging from laboratory-based to prospective epidemiological studies and experimental evidence suggest that ultra-processed foods may affect cardiometabolic health through a myriad of mechanisms, beyond the traditionally recognized individual nutrients. Processing induces significant changes to the food matrix, for which ultra-processed foods may affect health outcomes differently than unrefined whole foods with similar nutritional composition. Notably, the highly degraded physical structure of ultra-processed foods may affect cardiometabolic health by influencing absorption kinetics, satiety, glycemic response, and the gut microbiota composition and function. Food additives and neo-formed contaminants produced during processing may also play a role in CVD risk. Key biological pathways include altered serum lipid concentrations, modified gut microbiota and host–microbiota interactions, obesity, inflammation, oxidative stress, dysglycemia, insulin resistance, and hypertension. Further research is warranted to clarify the proportional harm associated with the nutritional composition, food additives, physical structure, and other attributes of ultra-processed foods. Understanding how ultra-processing changes whole foods and through which pathways these foods affect health is a prerequisite for eliminating harmful processing techniques and ingredients. *Adv Nutr* 2021;12:1673–1680.

Keywords: NOVA, cardiometabolic health, obesity, food additives, microbiome

Introduction

Cardiovascular diseases (CVDs) constitute the leading cause of mortality in the United States and globally, accounting for approximately one-third of all deaths (1, 2). Poor diet is the leading risk factor related to the overall CVD burden in the United States and is estimated to be associated with more than half of US deaths due to coronary heart disease (CHD) and stroke (3). Diet unequivocally plays a pivotal role in primary and secondary CVD prevention (4). Current research and practice are focusing on overall dietary patterns and quality, rather than single nutrients (4).

Food processing can profoundly influence diet quality; however, there is a broad spectrum of processing, ranging from minimal processing (e.g., frozen vegetables, dried fruits without added sugar or additives, pasteurized milk) to ultra-processing (e.g., carbonated soft drinks, fast foods, industrially produced breads, hot dogs) (Figure 1) (5). Ultra-processed foods, defined as industrially manufactured, ready-to-eat, or ready-to-heat formulations containing little whole foods (5), provide the majority of energy in the US diet (6). These foods do not only include so-called junk foods but also many foods that are marketed and perceived as healthy, such as flavored yogurts, reduced-calorie/low-fat products, breakfast cereals, and products “enriched” with beneficial nutrients (5).

While the evidence is still emerging, recent epidemiological studies suggest that higher consumption of ultra-processed foods is associated with increased risk of CVD.

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Abbreviations used: AGE, advanced glycation end-product; BPA, bisphenol A; CHD, coronary heart disease; CVD, cardiovascular disease; RCT, randomized clinical trial.

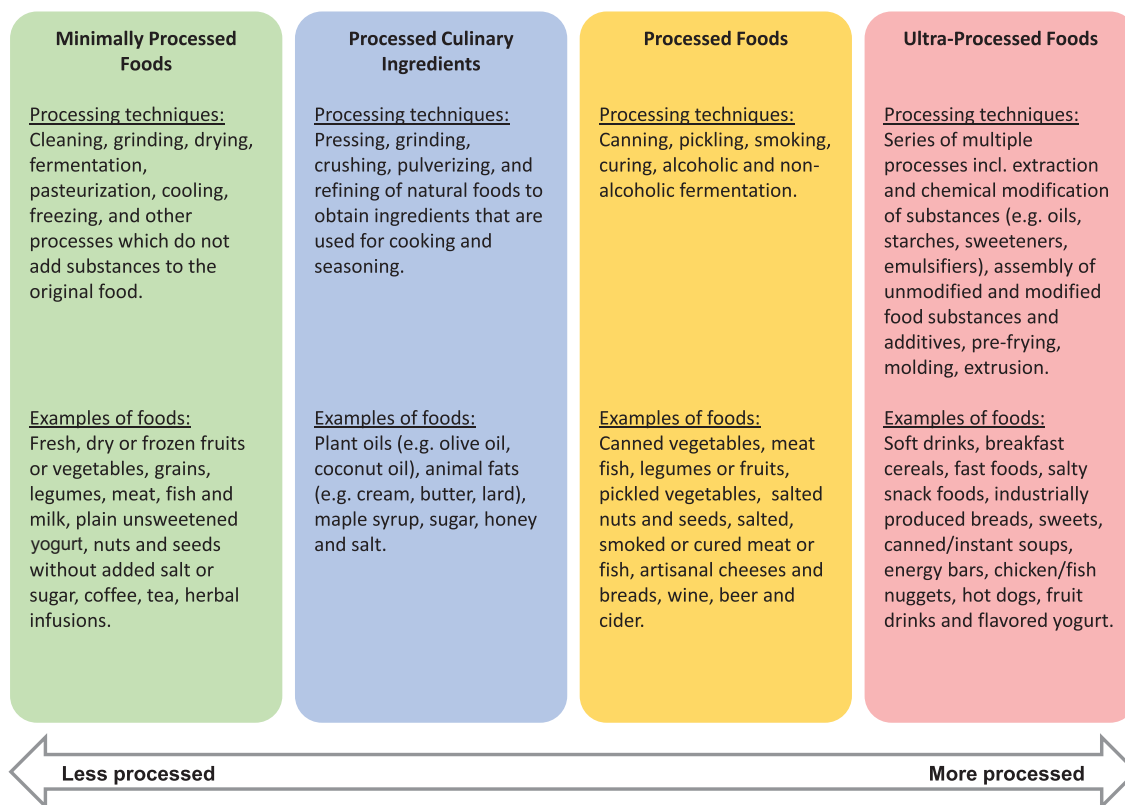


FIGURE 1 Food-processing spectrum as defined by the NOVA framework. NOVA (a name, not an acronym) classifies foods as minimally processed foods, processed culinary ingredients, processed foods, and ultra-processed foods based on the extent and purpose of industrial processing they have been submitted to (5). The figure provides examples of foods and the types of processing techniques used within each level.

In the Framingham Offspring Study, after 18 y of follow-up, each additional daily serving of ultra-processed foods was associated with a 7% increase in the risk of incident CVD (7). Likewise, increased consumption of ultra-processed foods was associated with a 12% increased risk of CVD in the French NutriNet-Santé cohort study (8). Furthermore, there is convincing evidence from meta-analyses that specific ultra-processed products (processed meat, sugar-sweetened beverages) and nutrients that are abundant in ultra-processed foods (*trans* fats, sodium) increase the risk of CVD (9). Ultra-processed foods have also been linked to multiple CVD risk factors including obesity, hypertension, and metabolic syndrome in epidemiologic studies (6, 10) The current strength and level of evidence of these associations led the American College of Cardiology/American Heart Association Guideline on the Primary Prevention of Cardiovascular Disease to recommend avoiding *trans* fats and minimizing certain ultra-processed foods (processed red meats, foods high in refined carbohydrates such as refined grain products, and sweetened beverages) (11). Nevertheless, the potential health hazards associated with a broad range of ultra-processed foods, beyond the above-mentioned products, remain largely unrecognized by clinicians and public health professionals.

A major challenge for establishing evidence in cardiovascular nutrition is the paucity of large randomized clinical trials (RCTs) with hard cardiovascular endpoints. As a consequence, in establishing causality, evidence from well-conducted prospective observational studies needs to be corroborated with criteria of biological plausibility. Key to both the theory and practice of preventive cardiology is the understanding of mechanisms of action of various food ingredients and dietary patterns embodying the human “food-ome” (12). Therefore, the objective of this review is to summarize the available evidence regarding the putative biological mechanisms underlying the associations between intake of ultra-processed foods and the risk of cardiometabolic and atherosclerotic CVDs.

Potential Mechanisms Linking Ultra-processed Foods to CVD Risk

Processing can alter the nutritional (macro- and micronutrient content), physical (food structure), and chemical (presence of artificial sweeteners, additives, and neo-formed contaminants, glycemic index and load) characteristics of foods in ways that may alter their healthfulness. Food processing may also influence long-term dietary behaviors, satiety signaling, and food reward systems. The biological

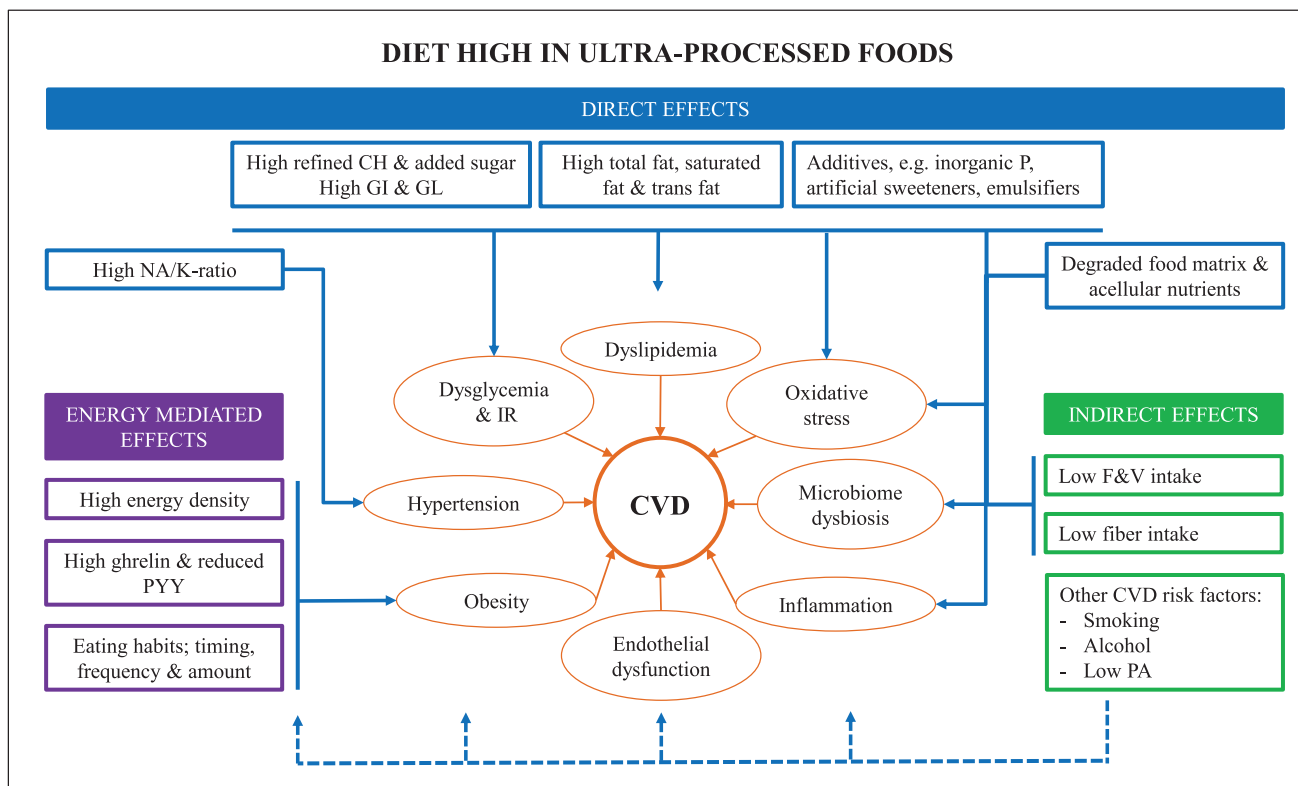


FIGURE 2 Potential biological mechanisms underlying the association between ultra-processed foods and CVD. The diagram describes plausible biological pathways through which a diet high in ultra-processed foods may contribute to CVD. Key mechanisms include altered serum lipid concentrations, modified gut microbiota and host–microbiota interactions, obesity, inflammation, oxidative stress, dysglycemia, insulin resistance, and hypertension and hormonal imbalances. Arrows indicate stimulation of a pathway. CH, carbohydrates; CVD, cardiovascular disease; F&V, fruit and vegetables; GI, glycemic index; GL, glycemic load; IR, insulin resistance; NA/K-ratio, sodium-to-potassium ratio; P, phosphorus; PA, physical activity; PYY, peptide YY.

pathways through which ultra-processed foods influence cardiovascular health may involve complex mechanisms and synergies between many compounds and characteristics of ultra-processed foods, which are not yet fully understood (Figure 2). The underlying physio-pathological interrelations in atherogenesis and CVD progression are complex and involve multiple pathways. A constellation of factors such as metabolic, proinflammatory, prothrombotic, pro-oxidative, and endothelial dysfunction coexist and potentiate each other. A myriad of nuances exist. For instance, various levels of glucose metabolism alterations activate specific inflammatory patterns (13), while immune factors interact bilaterally with gut microbiota (14). Further, most cardiovascular risk factors are playing a role in triggering endothelial dysfunction and injury, as well as maintaining a prothrombotic, proinflammatory molecular environment (15). Through these factors and via a complex network of molecular feedback loop mechanisms, atherogenesis escalates and perpetuates (16), culminating with various cardiovascular events.

Excess weight and body adiposity

Higher consumption of ultra-processed foods has been associated with excess adiposity in epidemiological and

experimental studies (6, 17–22). Notably, a recent RCT by Hall et al. (19) demonstrated that an ultra-processed diet increased ad libitum energy intake by ~500 kcal/d and caused weight gain compared with a minimally processed diet. In the prospective Seguimiento University of Navarra study and the Brazilian Longitudinal Study of Adult Health, adult participants in the highest compared with the lowest quartile of ultra-processed food intake had a 26–29% higher risk of becoming overweight over ~9 and 4 y of follow-up, respectively [HR (95% CI): 1.26 (1.10, 1.45) and 1.29 (1.08, 1.53), respectively] (17, 20). In 3 cross-sectional studies conducted in Brazil and the United States, participants with the highest compared with the lowest intake of ultra-processed foods (top vs. bottom quintile/quartile) had 31–48% higher odds of being overweight (6, 21), 41–97% higher odds of being obese (6, 21, 22), and 41–62% higher odds of abdominal obesity (defined as waist circumference ≥88/102 cm for men and women, respectively) (6, 21).

Ultra-processed foods may contribute to weight gain through their nutritional profile and by displacing low-calorie, nutritious, minimally processed foods from the diet (23). The high-intensity flavoring resulting from high levels of fat, salt, sugar, and artificial flavorings make

ultra-processed products highly palatable, for which endogenous satiety mechanisms may be superseded (23). Ultra-processed foods are, on average, more hypercaloric and less satiating than minimally processed foods and culinary preparations based on minimally processed foods (23, 24). As human satiety mechanisms are more sensitive to volume than caloric content, foods with higher energy density may facilitate excessive energy intakes (25).

The higher energy density and oro-sensory characteristics of ultra-processed foods (i.e., softer, less fibrous textures that are easy to chew) may also enable greater energy intakes in a shorter amount of time. Experimental studies suggest that increased eating rates can result in increased energy intakes, potentially due to delayed satiety signaling (26). Indeed, in the RCT by Hall et al. (19), average eating rate, measured as grams/minute and kilocalories/minute, was significantly higher during the ultra-processed diet compared with the minimally processed diet. Furthermore, higher concentrations of the appetite-suppressing hormone peptide YY were noted during the minimally processed diet compared with the ultra-processed diet (19).

Finally, the convenience, omnipresence, affordability, large portion sizes, and persuasive marketing of ultra-processed food may promote poor dietary habits, snacking, and overeating, potentially contributing to increased energy intake (27). Experimental studies indicate that visual cues and images of palatable foods, such as food advertisements, can activate brain regions that induce overeating and may encourage eating in the absence of hunger (28).

Glycemic response and related insulin dysregulation

Ultra-processed foods are the main source of total and added sugar in the US diet (29). Excessive sugar intakes, particularly in the form of sugar-sweetened beverages, are associated with multiple CVD risk factors, including overall and abdominal adiposity, hypertension, insulin resistance, type 2 diabetes, and dyslipidemia (30, 31). High-glycemic-index and high-glycemic-load diets are associated with increased risk of CHD and type 2 diabetes (9). The glycemic response to a particular food is determined by the quantity and quality of carbohydrates (source and digestibility); content of fat, protein, and fiber; food matrix structure (e.g., liquid or solid); and degree of processing (32). Experimental evidence supports that ultra-processed foods are, on average, more hyperglycemic than minimally and moderately processed foods (24). Hyperglycemia increases the risk of CVD by promoting weight gain, inflammation, oxidative stress, and endothelial dysfunction (32).

The physiological effects of low-calorie sweeteners are not well understood. Observational data from prospective studies suggest that regular consumption is associated with increased risk of type 2 diabetes (33). Animal and human experimental studies suggest that certain low-calorie sweeteners, such as sucralose, may alter glucose metabolism by influencing brain regulatory centers (34) and reduce insulin sensitivity by impairing gut–brain regulatory pathways (35).

Hypertension

Excessive dietary intake of sodium is associated with increased risk of hypertension, which is a major risk factor for CVD and stroke (9, 36). The mechanisms linking increased sodium intake and high blood pressure are complex and still not fully understood. Several pathways are implicated, including perturbed renal sodium homeostasis, extrarenal sodium handling, direct effects on vascular walls, and systemic and local neuro-hormonal pathways in conjunction with salt-sensitivity phenotypes (36, 37). Metabolic, hemodynamic, and inflammatory changes lead to volume expansion, water retention, endothelial stiffness, increased peripheral resistance, and subsequent increased blood pressure (36, 37). Epidemiological studies support that a higher sodium-to-potassium ratio (≥ 1.0) is associated with increased risk of CVD mortality, while higher potassium intakes are associated with lower risks (38). Commercially processed foods constitute the primary source of sodium in the US diet, while minimally processed foods such as milk, fruits, and vegetables are the primary dietary sources of potassium (39). A greater reliance on ultra-processed foods and lower intake of potassium-rich, minimally processed foods may therefore influence CVD risk by increasing sodium intake and altering the sodium-to-potassium ratio of the diet.

Gut microbiome

Diet is a key modulator of the gut microbiota composition and activity, with potential implications for host health (40). Alterations of the gut microbial ecosystem (changes in the relative abundance of specific microbial taxa or in gut bacterial diversity) and intestinal barrier dysfunction have been linked to excess adiposity, insulin resistance, type 2 diabetes, and CVD (40, 41). The underlying mechanisms are hypothesized to include increased bacterial production of atherogenic metabolites such as choline, trimethylamine N-oxide, and betaine; endotoxemia-induced low-grade systemic inflammation; modulation of the host immune system; and weight gain. Further mechanisms may involve increased calorie intake by the host, alterations in energy homeostasis, and hepatic lipid accumulation (40).

Modification of the food matrix and the fat and fiber content of foods, and the inclusion of certain food additives during processing, may influence gut microbiota composition, function, and bacteria–host interactions (42). Dietary fibers (primarily soluble fiber), abundant in many unrefined plant foods, provide substrate for microbial fermentation and high-fiber diets are associated with increased microbial gene richness and microbial production of SCFA fermentation end-products, which have key functions in regulating host metabolism and immune system, and may attenuate inflammation (43–45). Western dietary patterns, characterized by low fiber intake and high consumption of sugar, fat, and animal protein, are associated with a distinct and less diverse microbiotic profile compared with diets rich in minimally processed plant foods (44). Importantly, low-fiber diets shift the gut microbial metabolism toward the utilization of proteins and host mucins, resulting in

degradation of the intestinal mucus layer and increased susceptibility to chronic inflammatory diseases (44, 45). However, compared with diets based on unprocessed whole grains, high-fiber diets based on processed, extruded grains reduced bacterial diversity in animal models and led to less enrichment in beneficial butyrate-producing bacteria (46). Furthermore, evidence from animal and human studies supports that high-fat Western-type diets may promote low-grade systemic inflammation and metabolic disorders by increasing circulating concentrations of LPS derived from intestinal bacteria (metabolic endotoxemia) (47, 48). Animal studies also support that diets high in glucose or fructose may reduce gut microbiota diversity and increase intestinal permeability (49). In a human experimental study, endotoxemia increased after a meal of highly processed, high-fat, high-carbohydrate foods but not after an isocaloric meal including minimally processed whole grains, fruits, and nuts (50).

Changes to the physical structure of the food matrix during processing can alter nutrient bioaccessibility and absorption kinetics, with implications for gut microbiota composition, metabolism, and growth (42, 51). While plant-based, minimally processed foods have intact fibrous cell walls that provide substrate for fiber-degrading bacteria in the colon and ensure a slow release of nutrients along the digestive tract (52), nutrients in ultra-processed foods are largely acellular. Experimental studies suggest that the large share of acellular nutrients in ultra-processed foods leads to a high nutrient availability in the small intestine, which, in turn, promotes an inflammatory gut microbiota associated with cardiometabolic conditions (42, 51, 53).

Furthermore, accumulating evidence from animal and human studies suggests that consumption of low-calorie sweeteners may disrupt the diversity and balance of the gut microbiota and promote metabolic disorders and insulin resistance (54). Emulsifiers, used in industrial food processing, have in animal studies been shown to increase the proinflammatory potential of the microbiome by increasing microbiotic virulence factors (55).

Plasma lipid profile

Plasma lipid concentrations are influenced by the quantity and quality of dietary fats and carbohydrates, which, in turn, are influenced by food processing (56). There is scientific consensus that industrially produced *trans* fatty acids, present in partially hydrogenated vegetable oils in commercially manufactured foods, adversely affect blood lipoprotein profile and increase the risk of CHD (9, 56). As a result, the FDA has taken steps to remove partially hydrogenated vegetable oils from the US food supply (57). Evidence linking saturated fat to increased LDL cholesterol has led to longstanding recommendations to limit the intake of saturated fat (56). Major dietary sources of saturated fats include minimally processed foods, such as whole-fat dairy, processed culinary ingredients, such as cream and butter, but also ingredients primarily used in ultra-processed foods, such as palm oil and palm kernel oil (56).

However, accumulating evidence supports that the health effects of saturated fat in the diet depend on the food source, and on the interacting effects of naturally occurring food components and contaminants generated from high-heat processing of oils (58). For example, it has been shown that processed coconut oil, but not virgin coconut oil, raises serum cholesterol concentrations in rats (59, 60). Additionally, intake of full-fat dairy and unprocessed meat does not seem to increase the risk of cardiometabolic diseases (58). As a result, scholars have recommended replacing dietary saturated fat targets with food-based guidelines for saturated fat intake that take into account the whole food matrix and degree of processing (58).

Furthermore, research suggests that the influence of carbohydrates on serum lipid concentrations is also determined by their source and processing level. Intake of sugar increases serum triglycerides, while consumption of whole grains lowers total and LDL cholesterol and, to a limited extent, triglycerides (61). Consumption of minimally processed whole grains, such as oatmeal, instead of ultra-processed, high-sugar, refined grain products may therefore reduce CVD risk by promoting healthy plasma lipid concentrations.

Endocrine pathways

Concern has been raised regarding the cumulative intake of phosphorus in the US diet due to the extensive use of inorganic phosphate salts as additives in industrial food processing (62). Inorganic phosphate is absorbed to a greater extent (80–100%) than organic phosphorus that occurs naturally in foods (40–60%) (62). Epidemiological studies assessing serum phosphate and experimental studies of excess dietary phosphorus further support an association with CVD (63). These effects are possibly mediated by the disruption of hormonal regulation of extracellular phosphate through increased secretion of parathyroid hormone and fibroblast growth hormone 23, both promoters of arterial calcification (63). Elevated tissue and serum phosphate concentrations are also linked to increased oxidative stress of the endothelial cells and impaired endothelial function (63).

Industrially manufactured foods are often sold in elaborate packaging; the packaging materials may contain endocrine-disrupting chemicals, such as bisphenol A (BPA). Limited epidemiological evidence suggests that greater exposure to BPA is associated with increased prevalence of major CVD risk factors, including diabetes, overall and abdominal obesity, and hypertension (64). BPA, which is structurally similar to 17 β -estradiol, has been shown to promote insulin resistance, oxidative stress, inflammation, adipogenesis, and pancreatic B-cell dysfunction by binding to estrogen-related receptors (64). The detailed mechanisms of action remain poorly understood (64). BPA is widespread in the environment, but foods stored or reheated in BPA-lined containers are believed to constitute the primary source of human exposure (64). Although empirical evidence is limited, observational and intervention studies suggest that diets based on minimally processed and fresh foods are associated with lower urinary concentrations of BPA

(65, 66). An analysis using data from the nationally representative NHANES 2013–2014 found that greater consumption of sugar-sweetened beverages, but not ultra-processed foods overall, was associated with higher urinary concentrations of BPA (65). Although, due to safety concerns, BPA is increasingly replaced by its structurally homologous compounds (e.g., bisphenol S and bisphenol F), these may have similar endocrine-disrupting effects (67).

Other mechanisms

Extensive heat treatment during processing and preparation leads to the formation of advanced glycation end-products (AGEs), which have been linked to increased oxidative stress and inflammation and may play a role in CVD etiology (68). AGE formation is particularly high in animal foods high in protein and fat, and increases with higher temperatures, greater cooking time, and the absence of moisture (68). Dry-heat processing and deep-frying of carbohydrate-rich foods (e.g., crackers, chips, cookies, and French fries) also accelerate AGE formation (68). A full understanding of the importance of dietary AGEs in CVD development and the causal nature of the AGE–CVD link remains to be determined (69).

Observational studies suggest that fruit and vegetable intake is inversely associated with CVD, CHD, stroke, and major CVD risk factors, including type 2 diabetes (9). Available evidence also supports a protective effect against CHD and stroke (9). The beneficial effect of fruits and vegetables is attributed to their high content of fiber, micronutrients, and phytochemicals, which may reduce CVD risk through multiple mechanisms, such as reduced oxidative stress, improved insulin sensitivity and serum lipid profile, and lower blood pressure (70). It is plausible that higher intakes of ultra-processed foods increase the risk of CVD and its intermediate risk factors by displacing less-processed, more nutritious foods such as fruit and vegetables from the diet. Conversely, part of the protective effect of high fruit and vegetable consumption may be due to reduced intakes of less-healthy ultra-processed foods.

Areas for Future Research

Research is warranted to further clarify the biological mechanisms through which ultra-processed foods may influence CVD risk, and the proportional harm associated with the nutritional composition, food additives, physical structure, and other attributes of ultra-processed foods. Understanding how ultra-processing changes whole foods and through which pathways these foods affect health is a prerequisite for eliminating harmful processing techniques and ingredients and identify “optimal” levels of processing. The effects of ultra-processed foods on the gut microbiota and microbiota–host interactions constitute an area of special scientific interest, given the accumulating evidence regarding the role of the gut microbiome in cardiometabolic health and diet–disease relations. Furthermore, it is imperative to elucidate the health effects of chronic exposures to the multiple food additives and substances present in ultra-processed foods

and their packaging, as current regulations limiting the maximum levels of individual food additives do not take into account potential “cocktail effects” of combinations of compounds from various food sources.

Conclusions

Ultra-processing of foods may affect cardiometabolic health through a myriad of mechanisms, beyond the traditionally recognized individual nutrients. Research ranging from laboratory-based to prospective epidemiological studies and experimental evidence points to a network of mechanisms involving both direct and indirect effects. Ultra-processed foods not only bring poor-quality nutrients and ingredients, including refined carbohydrates and sugar, into the diet but also displace healthy whole foods, such as fruits and vegetables. Limited evidence supports that specific compounds, added or generated via aggressive processing, may also contribute to CVD development. Plausible biological pathways include increased energy intake, changes to the gut microbiome, alterations in the gut–brain satiety signaling, and hormonal effects. These chronic exposures may act as atherogenic initiators by targeting key atherogenic processes, such as dysglycemia, dyslipidemia, hypertension, obesity, inflammation, endothelial dysfunction, and oxidative stress.

Corroborated with other lines of evidence from prospective investigations, the current literature supports that consumption of ultra-processed food may be detrimental to cardiovascular health. A better understanding of the mechanisms underlying the ultra-processed food and CVD link will inform clinical practice and dietary guidance. Nutrition counseling is the cornerstone of preventive cardiology and should address ultra-processed foods, highlighting their pervasive metabolic effects, ubiquitous availability, and “hidden” sources in a variety of food formulations.

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