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Nature Food

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https://doi.org/10.1038/s43016-021-00457-9

PERSPECTIVE
https://doi.org/10.1038/s43016-021-00457-9

nature food

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Nutrition research challenges for processed food and health

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Existing highly processed food (HPF) classification systems show large differences in the impact of these foods on biochemical risk factors for disease. If public health nutrition is to consider the degree of food processing as an important element of the link between food and health, certain gaps in research must be acknowledged. Quantifying the food additive exposure derived from HPFs is a task made challenging by the lack of data available on the occurrence and concentration of additives in food and the degree to which the natural occurrence of additives in unprocessed foods confounds exposure estimates. The proposed role of HPFs in health outcomes could also be associated with altered nutrient profiles. Differences exist within and between HPF classification systems in this regard and there are conflicting data on the impact of controlling for nutrient intake. Furthermore, research is needed on how the sensory aspects of HPFs contribute to energy intake. Current data suggest that high energy intake rate may be the mechanism linking HPFs and increased energy intake. A high priority now is to clarify the basis of definitions used to categorize foods as highly processed and, in a constructive sense, to distinguish between the contributions of nutrients, additives and sensory properties to health.

Traditionally, the association between food and health has focused almost entirely on nutrients with considerable impact on public health nutrition strategies in areas such as folic acid and neural tube defects, micronutrients and age-related macular degeneration, lipids and lipoproteins, iodine and infant cognition, sodium and hypertension, or eicosapentaenoic acid and the immune system. Beyond nutrients, growing interest has focused on patterns of food consumption such as that of the Mediterranean diet. More recently, the link between the degree of food processing and health has been supported by a growing body of research[1–5]. This research has entered the food policy arena and is now embodied in many national dietary guidelines and position papers, including the American Heart Association advice on limiting highly processed food (HPF) intake[6]. The term HPF is preferred over the term ultra-processed food (UPF) because not all food-processing classification systems use the latter term.

Several systems of classifying food according to their degree of processing have emerged (described in Table 1), and within the literature on food processing and health the focus has been on HPFs. In the case of the NOVA classification, the definition of the highest level of processing is based on the presence of cosmetic food additives designed to mask the basic ingredients and make the final product attractive to the senses, or on the use of processing ingredients normally confined to industrially prepared foods[7]. A revised version of the NOVA classification has been proposed by the University of North Carolina (UNC) in which the highest level of processing is 'multi-ingredient industrially formulated mixtures processed to the extent that they are no longer recognizable as their original plant or animal source'[8]. The European Prospective Investigation into Cancer (EPIC) defines HPFs as 'foods that have been industrially prepared, including those from bakeries and catering outlets, and which require no or minimal domestic preparation apart from heating and cooking'[9]. The International Food Information Council (IFIC) has not specifically defined 'highly' processed foods but three of its categories can be used to describe HPFs: mixtures of combined ingredients, ready-to-eat processed foods, and prepared foods and meals. These contrasting definitions highlight the different perspectives on the food properties that are believed to increase the degree of food processing[10,11]. The four classification systems have been found to yield conflicting results when compared under similar conditions for their impact on risk factors for non-communicable chronic diseases (NCCDs), and differ considerably for interrater reliability and their ability to profile the nutrient content of foods.

Comparability of classification systems

All four classification systems (NOVA, UNC, EPIC and IFIC) were applied to a Spanish cohort (PREDIMED-Plus trial) of 6,874 subjects for which extensive data on diet and on risk factors for cardiometabolic disorders were available[12]. Obesity was associated with increasing intake of HPFs according to the NOVA classification system, but not with any of the other three classification systems. Systolic and diastolic blood pressures were related to HPF intake according to the UNC system, but not with any of the others. Total cholesterol was linked to HPF intake only by the IFIC and EPIC criteria. Low-density lipoprotein cholesterol was not associated with intakes of HPFs by any of the four classification systems. Many other metabolites showed variable links across all four classification systems. In another study, the 100 most commonly consumed foods among US children were examined across three HPF classification systems (UNC, NOVA and IFIC) to determine interrater reliability, processing system agreement, and the relationship between processing category and nutrient concentration[13]. All three classification systems differed in their performance of these tasks.

Such variability across food classification systems is simply not acceptable in the complex study of food and health. If the degree of processing is a factor in the relationship between food and health, then it must be driven by an understanding of the relevant underlying biological mechanisms and not by the subjective opinions of different research groups on the definition of the degree of food

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Table 1 | Food-processing classification systems and their definitions of HPF

Classification system	Categorization of foods according to the degree of processing	Definition of HPF
NOVA	1. Unprocessed or minimally processed foods 2. Processed culinary ingredients 3. Processed foods 4. Ultraprocessed foods	Formulations of several ingredients which, besides salt, sugar, oils and fats, include food substances not used in culinary preparations. In particular, flavours, colours, sweeteners, emulsifiers and other additives used to imitate sensory qualities of unprocessed or minimally processed foods and their culinary preparations, or to disguise undesirable qualities of the final product.
UNC	Processing levels 1. Less processed 2. Basic processed 3. Moderately processed 4. Highly processed Convenience levels 1. Requires cooking 2. Ready to heat 3. Ready to eat	Multi-ingredient industrially formulated mixtures processed to the extent that they are no longer recognizable as their original plant/animal source and consumed as additions (condiments, dips, sauces, toppings or ingredients in mixed dishes).
EPIC	1. Moderately/non-processed 2. Processed staple foods 3. Highly processed foods	Foods that have been industrially prepared, including those from bakeries and catering outlets, and which require no or minimal domestic preparation apart from heating and cooking (for example, bread, breakfast cereals, cheese, commercial sauces, canned foods including jams, commercial cakes, biscuits and sauces).
IFIC	1. Minimally processed foods 2. Foods processed for preservation, nutritional enhancement or freshness 3. Mixtures of combined ingredients 4. Ready-to-eat processed foods 5. Prepared foods and meals	HPF is not specified in the IFIC category but categories 3–5 can be assumed to correspond to HPFs.

processing. There are three areas that merit consideration for aligning the degree of processing of foods with their potential impact on health: the influence of processing on (1) the nutritional profile of a food; (2) the sensory aspects of foods; and (3) the allied exposure to non-nutrients elements such as food additives.

HPFs and nutrient intakes

In any field of scientific research, repeated demonstration that a particular hypothesis is valid gives some comfort to those using this hypothesis as a basis for policy. That is certainly the case with HPFs and their role in diminishing the nutritional quality of the diets of high consumers of these foods, with particular emphasis on the role of high intakes of HPFs in increasing dietary intakes of saturated fatty acids and sodium[14]. However, if there are anomalous data, as is the case with HPFs, then such data cannot be ignored. Several studies using national food intake data (from the United Kingdom, the United States, Brazil and Canada, France) of NOVA-defined HPFs have failed to show an association of increasing HPF intake with increasing intakes of sodium, saturated fatty acids and total fat[15–19]. These anomalies may be due to different interpretations of the guidelines issued by the different classification systems, but merit consideration given the importance attached to these nutrients in NCCDs in most dietary guidelines.

Although such anomalies should be systematically examined, the single most important question is whether the putative role of HPFs in health outcomes is due to a deterioration in diet quality or to non-nutritional factors. Four studies have examined the relationship between HPF intake and health outcomes by means of a multivariate model controlled for nutrient intake. Three of these studies showed that when the model controlled for nutrient intake, the correlation of HPF intake with disease outcome (all-cause mortality, breast cancer and chronic lymphocytic leukaemia) remained[4,20,21]. This led the authors of these papers to speculate about the role of food additives, packaging material and phytochemicals as possible active factors driving the HPF–disease link. However, another study showed that higher HPF intake led to increased cardiometabolic risk factors, although this linkage ceased when the authors controlled for diet quality[22]. Clearly, this is an area that must be prioritized for further research.

Allied to that, studies on HPF intake and obesity must control for energy density. As HPF intake increases, there is a parallel increase in the energy density of the diet[23], and energy density has been shown to be a major driver of excess energy intake and subsequent development of obesity[24]. If, having controlled for energy density in multivariate regression models, HPF intake is still associated with obesity, then attention can turn to the exploration of the role of HPFs in altering the sensory aspects of food and the role of non-nutrients such as food additives.

Non-nutrients and the role of HPFs in health

Several papers have nominated specific additives that might play a causative role of HPFs in a given NCCD[4,25,26].This is unhelpful given that the main regulatory authorities across the globe consider the totality of all relevant published toxicology data from in vitro research, animal models and human studies. Estimating human exposure to food chemicals such as additives is extremely challenging. To begin with, food composition tables almost never contain data on the additives present in a given food. Such data can be obtained online from supermarket chains or in rare instances from specially constructed databases such as the US Branded Food Database or the ab initio collection of ingredient data as part of national dietary surveys[27,28]. Even if such data are available, data on the concentration of an additive used in a food are even more difficult to attain and may rely on data available from public analyst laboratories. A recent study has used such analytical data to assess food additive intake in 106,000 French adults and has presented data on the mean daily intake of 90 food additives[29]. However, many of the additives used in industrially produced goods are also found as natural components of everyday foods. Table 2 compares the level of human exposure to several additives from

Table 2 | Additives from processed foods and natural sources: a comparison of the estimated intake of selected additives

Food additive	Estimated exposure (mean daily intake) from processed foods in French adults	Possible exposure from naturally occurring sources	Intake from naturally occurring sources (mg)
Lecithin	54 mg	One large egg	147
Citric acid	2 g	100 ml of orange juice	16
Ascorbic acid	16 mg	One orange	70
Sodium nitrite	<1 mg	Mean daily intake of vegetables (conversion from nitrates)	10
Pectin	200 mg	One Golden Delicious apple	811
Carotene	2 mg	One serving of cooked spinach	14

the French study with intakes from natural resources, including lecithin in eggs[30], citric acid in orange juice[31], ascorbic acid from oranges[32], sodium nitrite from the conversion of vegetable nitrate to nitrite[33], pectin from apples[34] and carotene from spinach[35]. In all instances, the intake from natural sources exceeds those from processed foods.

Many preservatives used as food additives (sorbic acid, benzoic acid, propionic acid, nitrite and nitrate) are naturally present in many foods. Benzoic acid is found in many soft fruits, herbs and spices[36] and high levels of benzoate are also found in fermented milks and hard cheeses[37]. Similar issues arise for colourants, with almost half of all European Union (EU)-approved food colours, for example, cumin, riboflavin, carotenes, canthaxanthins, caramels, beetroot and chlorophylls, appearing as natural components of everyday foods.

For the regular consumption of an additive or group of additives to be causally linked to an NCCD and thus considered harmful, it is first necessary to establish common biochemical pathways of action or mechanisms by which they can disrupt normal metabolic function. The possibility that the effects of individual food chemicals might be additive poses a very considerable challenge. The French study on food additive intake identified clusters of additives that are frequently consumed together. One such cluster identified comprised iron oxide, ascorbic acid, sodium erythorbate (a stereoisomer of sodium ascorbate) and sodium nitrite. Taking into account the opinions of the European Food Safety Authority, the fact that iron oxides are very poorly absorbed[38], that the absorption, distribution, metabolism and excretion of sodium erythorbate is no different from that of ascorbic acid[39], the only remaining systemic effect might come from sodium nitrites: relaxation of smooth muscle, vasodilation and consequent lowering of blood pressure, and methaemoglobinaemia[40]. Thus for this cluster of additives, it is difficult to find any common site of action or any common effect that might justify the study of this cocktail using expensive high-throughput toxicological analysis. Indeed, the assessment of the toxicology of co-exposure to multiple compounds or the entire food exposome is a very challenging task[41]. It should be noted that HPFs have been linked to a wide range of NCCDs with markedly different pathologies, including heart disease[42], cancers[4], gut disorders[43], frailty[44], depression[45], bone health[46], dental caries[47], hypertension[48], asthma[49], redox status and inflammation[50,51], obesity[52] and macular degeneration[53]. It will be challenging to propose a biological link between an individual additive or groups of additives to such a range of complex pathologies.

If the putative role of food additives as active agents of HPFs is to be investigated, the preferred route might be through total diet studies where the food categories for analysis are specifically designed to reflect different sources of HPFs, which can capture and separate exposure from industrial use and natural occurrence.

Physical and sensory aspects of HPFs

The physical and sensory properties of HPFs have been implicated as having a causal role in disrupting metabolic responses and promoting higher energy intakes in diets high in HPFs. These include alteration of the physical properties of foods, increased palatability and energy intake rate, decreased satiety and the disruption of taste–nutrient relationships. Food form is known to influence intakes: the physical form of food can strongly influence energy intake, satiety and nutrient bioavailability[54]. Extensive processing and deformation can damage the structural integrity of the food matrix, and has been proposed as another mechanism by which processed foods can affect health. Foods with weaker structures can deform more readily during consumption and are consumed at a faster rate, often producing higher postprandial glucose and lipid responses.

Those investigating the link between food processing and health argue that HPFs are designed to be highly palatable and low in satiety, and thus drive food intake upwards. One recent randomized controlled trial (RCT) study examined appetite before and after each meal in a randomized controlled, cross-over metabolic ward study, comparing diets high and low in HPFs[55]. Energy-intake-adjusted scores for hunger, fullness, satisfaction and capacity to eat did not differ across diets and participant ratings revealed no difference in 'pleasantness' or 'palatability' between diets. In general, research shows that foods that are 'liked' more are consumed to a greater extent[56], although to date there is no evidence that the influence of liking has a strong impact on the intake of HPFs. Within the RCT, liking increased energy intake across all meals and contributed equally to intake within both diets. Furthermore, even the most appealing foods decrease in their hedonic valence during consumption through a process known as 'sensory-specific satiety'[57]. Similarly, there is no evidence that the onset of sensory-specific satiety differs between unprocessed and HPFs, or that consumers demonstrate a supranormal hedonic response to the sensory properties of HPFs.

In the RCT comparing energy intake from unprocessed and HPF diets, one important factor that was shown to promote higher energy intakes was the rate of energy intake within the meals in the HPF arm. On average, the energy intake rate was more than 50% higher in the HPF arm than in the unprocessed arm (48 versus 31 kcal min^{-1})[55]. This suggests that the differences between the processing levels of the two diets were due to large differences in food texture and energy density, and that the increase in energy intake observed in the HPF diet arm may have been related to the softer texture/faster eating rate and higher energy density of foods in the HPF diet. Although eating rate has been found to increase across foods classified as unprocessed, processed or highly processed, there are wide variations in eating rate and energy intake within each processing category, and a food can be processed to increase or decrease the rate of energy intake within meal[58]. Food texture moderates eating rate and can influence the rate and extent of food intake within and across meals[59,60]. Beyond food processing, consuming diets that have a higher energy intake rate (kcal min^{-1}) has been shown to produce a considerable increase in average daily energy intakes and is associated with higher adiposity, independently of the degree of processing[61].

The taste quality and intensity of a food perceived during consumption are associated with its nutrient and energy density, and are thought to help guide food choices and serve to counteract

Table 3 | A research roadmap for HPFs and health: summary of the challenges facing studies of the role of putative UPF active agents in health and some proposals for research to address these challenges

Challenges	Possible research areas to address such challenges
Lack of a clear policy objective for the construction of any food-processing classification system	In advance of any attempt to develop a food-processing system, the intended food policy objectives of the system must be clearly established, for example, to drive reformulation, to direct regulatory aspects of the sale of foods, such as fiscal or advertising measures.
Lack of transparency of existing systems for the classification of foods according to their degree of processing	In the development of any food-processing classification system, the inclusion or exclusion of a food from any list of HPFs should take account of the contribution of that food to overall nutrient intake.
Absence of data on the occurrence of UPF active agents in food composition databases	Data on the occurrence of putative UPF active ingredients should be made publically available and incorporated into food composition tables.
Absence of concentrations of UPF active agents in food composition tables	Specially designed total diet studies should be commissioned with sufficient detail to estimate exposure to a range of chemicals in foods with different degrees of processing.
Clarification of the role of nutrients in UPF–health outcome associations	All studies associating UPFs with disease outcomes should control for nutrient intake to ascertain if the observed associations are of nutrient or non-nutrient origin. Studies linking obesity to processed food intake should include energy density as a mediating factor.
Clarification of the role of physical and sensory properties in UPF–health outcome associations	Studies that seek to compare energy intakes from diets that differ in degree of processing should control for known covariates including food form/texture (eating rate) and energy density of the diets. There is a need to ascertain if HPFs produce a hyperpalatable response that is discernibly greater than the established relationship between a higher 'liking' and increased intake. To link specific matrix effects and taste–nutrient relationships to food processing, there is a need to explore sensory and metabolic responses to foods that have equivalent nutrients but differ in their degree of food processing.

dietary imbalances[62]. Another mechanism proposed to explain higher energy intakes from modern processed foods is that processing and formulation disrupts these natural relationships between a food's nutrient content and its sensory perception, and how this information is conveyed to the brain[63]. In this way, it could be that foods high in mono- or disaccharides do not elicit a sweet taste intensity, making it possible to passively overconsume higher calories by disrupting a natural ability to regulate food intake within meals[64]. Recent data demonstrate that a food's predominant taste quality remains a predictor of its macronutrient content, and these 'taste–nutrient' relationships are well maintained across different degrees of food processing, as defined by NOVA[65].

The available evidence suggests energy intake rate as a putative mechanism linking the physical and sensory properties of HPFs to higher energy intakes and diet-related chronic conditions. Key research areas that now need to be addressed in relation to the manner in which HPFs influence the sensory aspects of food include: (1) an increased understanding of the impact of food processing on the rate of energy intake and on metabolic responses for the same nutrient load; (2) a rigorous appraisal of the hypothesis that sensory properties increase the palatability of HPFs; and (3) further clarification of whether a high degree of processing changes taste–nutrient signals in processed foods.

First, do no harm

Any attempt to construct a classification system for food processing must first establish filters for those industrially prepared foods that make a substantial contribution to nutrient intake. The NOVA classification system, which advocates the complete removal of all HPFs, includes in its list of foods breads, breakfast cereals, spreadable fats, flavoured milks and all infant and toddler prepared foods, and all diet sodas. Ample evidence exists to show that there are no differences in postprandial glucose or insulin response following the ingestion of breads, varying from wholegrain to white and to those with and without additives[66,67]. Similarly, studies show that the nutrient intakes of infants fed on home-prepared infant and toddler foods are not materially different to those of infants fed on industrially prepared products with the exception of sodium, which was higher in the infants fed with home-prepared foods[68]. Breakfast cereals, normally served with milk, make a very important contribution to micronutrient intake[69]. The advent of low-fat spreads optimized for fatty-acid profile have contributed to a substantial reduction in the intake of saturated fatty acids[70]. Beverages sweetened with artificial sweeteners help reduce the intake of added sugars. These filters should also include foods that are generally regarded as 'treats' that have a negligible population impact on nutrient intake (for example, ice cream and chocolate). For example, a study of chocolate intake in 11 European countries showed that the contribution of chocolate to added sugar intake averaged 5% (ref. [71]). Data from the Centers for Disease Control show that ice cream accounts for just 5% of the intake of added sugar in the United States[72]. Once such foods are filtered out, the classification system must be based solely on experimentally established effects of processed foods and not simply on their ingredient list. Any proposed food classification system should not be considered in isolation but should be included in a wider food classification system, such as the proposed Food Compass[73] system, which scores 54 attributes across nine health-relevant domains: nutrient ratios, vitamins, minerals, food ingredients, additives, processing, specific lipids, fibre and protein, and phytochemicals.

Conclusions

The present literature on processed foods and health outcomes shows a high degree of repetition of correlational studies—a greater emphasis on analytical studies is needed. Table 3 lists the areas where research should be prioritized to study any putative link between HPFs and NCCDs. From a policy point of view, it is essential that the design of any food-processing classification system takes into account the intended policy uses of this system. The NOVA recommendation that HPFs be avoided poses a considerable challenge, given that a wide body of evidence across the globe shows that almost two-thirds of all energy comes from HPFs. Reformulation of HPFs has been highlighted as a priority by the United Nations and the World Health Organization as an option to enhance the nutrient density of the food supply while reducing the consumption of many public-health-sensitive nutrients. Reformulating HPFs presents an opportunity to enhance the nutrient density of the food supply while reducing the consumption of many public-health-sensitive nutrients. Food-processing classification systems may be used to regulate front-of-pack labelling and food advertising, to incentivize reformulation or to introduce fiscal measures to reduce food intake, but that requires statutory establishment of a classification system. This Perspective has outlined many challenges to any agreement on such. Finally, notwithstanding the opposition of NOVA to the reformulation of HPFs[74,75], the value of this approach is internationally recognized. Research on nutrient reformulation should also take account of further opportunities to reformulate the sensory and physical aspects of processed foods, to help reduce the risk of excessive intake.

Received: 3 November 2021; Accepted: 22 December 2021;
Published online: 7 February 2022

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Competing interests

M.J.G. has engaged in paid and non-paid consultancy for a wide range of food companies that manufacture processed foods. He has provided online presentations on ultraprocessed foods to the staff of Unilever and Mondelez. C.G.F. is currently a paid member of the Kerry Health and Nutrition Institute.

Additional information

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Peer review information *Nature Food* thanks Eileen Kennedy and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.