Great Debates in Nutrition

David S. Ludwig, Section Editor

Does the concept of "ultra-processed foods" help inform dietary guidelines, beyond conventional classification systems? YES

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ABSTRACT

The recommendation to prefer unprocessed/minimally processed foods and freshly made meals instead of ultra-processed foods (following the Nova food classification system) is being increasingly adopted in new official dietary guidelines issued by national governments and international health associations. This recommendation is supported by systematic reviews and meta-analyses of nationally representative dietary surveys and long-term cohort studies. These data show that increased intake of ultra-processed foods is associated with poor-quality diets and with increased morbidity and mortality from several chronic diseases. Various attributes of ultra-processed foods acting through known, plausible, or suggested physiologic and behavioral mechanisms relate them to ill health, and it is likely that different combinations of attributes and mechanisms affect different health outcomes. Although more research should be done to identify these mechanisms, existing evidence is sufficient to recommend the avoidance of ultra-processed foods to optimize health and policies to support and make feasible this recommendation. *Am J Clin Nutr* 2022;00:1–6.

Keywords: ultra-processed food, Nova, dietary guidelines, diet quality, obesity, noncommunicable diseases

Main argument (Monteiro)

Definition of ultra-processed food and the Nova food classification system

Nova classifies all foods and food products, according to the extent and purpose of the industrial processing they undergo, into 4 groups: unprocessed or minimally processed foods, processed culinary ingredients, processed foods, and ultra-processed foods (UPFs) (1).

Unlike minimally processed and processed foods, UPFs are not simply modified whole foods. As defined in Nova (2), they are industrial formulations made mostly or entirely with substances extracted from foods, often chemically modified, and from additives, with little if any whole food added. Sequences of processes are and must be used to obtain, alter, and combine the ingredients and to formulate the final products (hence "ultra-processed").

Ingredients and processes used to create UPFs aim to obtain convenient (durable, ready-to-consume), tasteful (often hyperpalatable), highly profitable yet relatively affordable (low-cost ingredients) products, liable to displace all other Nova food groups. Many are designed to be consumed any time, anywhere. Branding and ownership by transnational corporations, as well as aggressive marketing, give UPFs additional market advantages (2).

Salt, sugar, and fat are common ingredients of UPFs, often in higher concentration than in processed foods. But what is characteristic of these products, and identified by Nova as markers of food ultra-processing, are food substances not traditionally in culinary use (such as plant protein isolates, mechanically separated meat, and modified starches and oils) and additives with cosmetic functions (such as colorants, flavors and flavor enhancers, emulsifiers, and nonsugar sweeteners) (2).

Ultra-processed foods include both "regular" and "diet" soft drinks; sweet or savory packaged snacks; confectioneries, mass-produced packaged breads, pastries, and cakes; margarines and other spreads; breakfast "cereals"; "milk" and "fruit" drinks; reconstituted meat products and equivalent plant-based alternatives; and varieties of ready-to-heat products (1).

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Abbreviations used: RCT, randomized controlled trial; UPF, ultra-processed food

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The concept of UPFs has achieved recognition in dietary guidelines

In 2014, the Ministry of Health of Brazil launched its Dietary Guidelines for the Brazilian Population (3) with 4 recommendations based on Nova food groups: *1*) make your diet based on *unprocessed or minimally processed foods* (mostly plants, a variety of them, and sustainably produced); *2*) season, mix, and cook these foods with small amounts of *processed culinary ingredients* (oils, fats, salt, and, occasionally, sugar) to make delicious dishes and meals; *3*) enjoy small amounts of *processed foods*, such as bread and cheese, as part of freshly prepared meals; and *4*) avoid *ultra-processed foods*.

The overall "golden rule" of the guide is "Always prefer unprocessed or minimally processed foods and freshly made meals to ultra-processed foods." This golden rule was incorporated in the 2021 Dietary Guidelines for Brazilian Children under 2 Years of Age (4) and in new dietary guidelines of Latin American countries (5) and, more recently, in those of Israel (6) and Malaysia (7). The High Council on Public Health of France includes a 20% reduction in UPF consumption as a goal for 2018–2022 (8). "Choose minimally processed foods instead of ultra-processed foods" is one of the 10 dietary pattern recommendations of the 2021 American Heart Association Scientific Statement on Dietary Guidance to Improve Cardiovascular Health (9). In 2021, the EASL-*Lancet* Liver Commission made similar recommendations for preventing liver diseases (10).

The increasingly adopted new guideline toward avoidance of UPFs is supported by scientific evidence generated in low-, middle-, and high-income countries. This evidence essentially shows that increased dietary share of UPFs is systematically associated with poor-quality diets and increased morbidity and mortality from several chronic diseases, as considered below. The global urgency of this guideline is made clear by the worldwide rapidly increasing sales of UPFs, particularly in middle-income countries (11), and also because these products already amount to 50% or more of the total dietary energy intake in some high-income countries (2), with even higher consumption among children and adolescents (12).

Consumption of UPFs is associated with poor dietary quality

The negative dietary effects of UPFs have now been made clear by many nationally representative studies using Nova to assess the relation between UPF consumption and multiple parameters of diet quality. A meta-analysis of data extracted from national studies conducted in 13 middle- and high-income countries, with mean intakes of UPF ranging from 15.9% of dietary energy (Colombia) to 57.5% (United States), showed that increased UPF consumption was associated with higher dietary free sugars and saturated fats; lower fiber, protein, potassium, and several micronutrients; and increased total energy intake (13). For instance, the predicted mean content of free sugars of diets with 15%, 50%, and 75% of total energy from UPFs was, respectively, 9.6%, 15.3%, and 19.4%, and for the dietary content of fiber was 13.1, 10.7, and 9.0 g/1000 kcal, respectively. The meta-analysis also showed an inverse linear relation between the dietary share of UPFs and of health-protective unprocessed or minimally processed foods such as vegetables, legumes, and fruit.

Analysis of nationally representative samples of children and adolescents from 8 countries found that increased dietary share of UPFs was systematically associated with dietary nutrient profiles that might predispose to obesity, including higher dietary energy density and free sugars and lower fiber (14). Analysis of the US NHANES cycles 2015–2016 and 2017–2018 identified a significant inverse dose–response association between the dietary share of UPFs and the Healthy Eating Index 2015, which reflects adherence to key recommendations in the US Dietary Guidelines for Americans (15). The same analysis revealed that across quintiles of UPF consumption, the percentage of participants with poor-quality diet (American Heart Association diet score <32 points) more than doubled in children (from 31.3% to 71.6%) and more than tripled in adults (from 18.1% to 59.7%).

Consumption of UPFs is associated with chronic disease

More than 30 cohort studies have shown prospective dose–response associations between UPF consumption and ill health (16). Two of these were multinational, conducted in 9 European countries and in 19 low-, middle-, and high-income countries, respectively. Others were conducted in Brazil, China, France, Italy, Mexico, Spain, the United Kingdom, and the United States. Disorders and diseases associated with increased dietary share of UPFs included overweight, obesity, abdominal obesity, visceral adiposity, increased adiposity from childhood to early adulthood, and type 2 diabetes, hyperuricemia, hypertension, cerebrovascular disease, dyslipidemias, coronary heart disease, breast cancer, nonalcoholic liver disease, renal function decline, Crohn disease, frailty, depression, and cardiovascular, cerebrovascular, and all-cause mortality (16). Meta-analyses of data on health outcomes for which there was >1 cohort study, most of high quality, showed significant pooled risk ratios for overweight and obesity, type 2 diabetes, depression, cardiovascular and cerebrovascular disease and death, and all-cause mortality (17–19).

To date, 1 short-term randomized controlled trial (RCT) has evaluated the health impact of UPF intake. Conducted at the US NIH, this showed that ultra-processed diets caused an increase in ad libitum calorie intake and consequent weight gain. Over a 2-wk period, 20 young adults consuming a diet with ∼83% of energy from UPFs consumed ∼500 more kcal per day than when consuming a diet with no UPFs. Participants gained 0.9 kg at the end of the 2 wk with the ultra-processed diet and lost 0.9 kg, mostly body fat, by the end of the non-ultra-processed diet (20).

Mechanisms related to UPF health harms

The persistence in several cohort studies of significant associations between UPF intake and health outcomes after adjusting risk estimates for dietary nutrient contents (16), as well as the fact that the 2 diets in the NIH trial were matched for macronutrients, sugar, sodium, and fiber (20), indicates that nonnutrient attributes of UPFs also link them to ill health. Thus, textural and structural changes to the food matrix as a result of ultra-processing enable UPFs to be consumed quickly, delaying the onset of satiation and increasing energy intake, and therefore the risk of weight gain and obesity (21). Such food matrix changes can also alter nutrient bioaccessibility and absorption

kinetics, compromising gut microbiota composition, metabolism, and cardiovascular health (22).

Other common attributes of UPFs could also play a causal role. These include the lack of health-protective nonnutrient compounds, such as phytochemicals found in whole plant foods (23); compounds generated during processing and linked to increased oxidative stress and inflammation (e.g., acrylamide and acrolein); endocrine-disrupting chemicals released from packaging materials (such as bisphenol A and phthalates) (22); and additives used to formulate UPFs for which potential adverse health effects have been suggested by recent experimental studies, such as several emulsifiers, colorants, flavor enhancers, and nonsugar sweeteners (24). These chemical "cocktails" may interact in complex and presently uncharacterized ways.

Behaviors akin to "food addiction" could also link UPF intake to disease, particularly to obesity (25). Although the ingredients or combination of ingredients responsible for higher putative addictive potential of UPFs are not yet entirely clear, a recent review of self-report studies has shown that these foods were consistently more associated with diminished control over consumption, continued use despite negative consequences, tolerance/withdrawal, craving, and impairment/distress than were minimally processed foods (26). Ultra-processed foods also appear to engage brain regions related to reward/motivation in a similar manner to drugs of abuse (26). Also of relevance are the aggressive marketing, omnipresence, large portion sizes, and the relatively low cost of leading UPFs (1), all inducing overeating and displacing unprocessed and minimally processed foods (13).

Thus, various attributes of UPFs and various known, plausible, or suggested physiologic and behavioral mechanisms may relate consumption of UPF to ill health. Indeed, it is likely that different combinations of attributes and mechanisms link UPF consumption to different health outcomes, but sufficient evidence now exists to mandate public health action.

Possible public health action to reduce the consumption of UPFs

As a start, related to the question posed in this debate, international and national organizations and governments need to review their dietary guidelines. These should emphasize the preference for unprocessed or minimally processed foods and freshly made meals, as well as make explicit the need to avoid UPFs. The reasons why, with benefits, should be explained in accessible language. Guidelines that now recommend avoidance of UPF also advocate dietary patterns mainly made up from freshly prepared meals and are designed to promote good health and well-being (3, 5–7). They also bear in mind the health of future generations and social, cultural, economic, and environmental implications, all of which need to be part of their purpose (27).

Guidelines are necessary but not sufficient. To make them feasible, national governments need to use, among other policies, fiscal measures, marketing regulations, bold mandatory front-of-pack labeling, and food procurement schemes, all designed to promote the production, distribution, accessibility, and affordability of a rich variety of unprocessed and minimally processed foods and, correspondingly, to discourage UPFs, as is now done in some countries (28). Many current national food and nutrition policies encourage food manufacturers to reformulate their products by reducing the salt, sugar, or unhealthy fats in them. There is certainly a need for such statutory measures in the case of processed foods. But, in the case of UPFs, due to their multiple harmful attributes, nutrients-to-limit reformulation will not turn them into healthy foods. Another concern with reformulated UPFs is that they may serve to legitimate, endorse, and even promote UPF consumption, particularly if they are marketed as "healthy" as they often are (29).

Encouraged by the UN and other international bodies, national policies should instead stimulate the entire food manufacturing, distribution, and catering industries to maintain, develop, and improve methods of food processing that prolong the preservation of whole foods, enhance their sensory qualities, and make their culinary preparation easier and more diverse. Ultra-processed products should be discontinued and replaced by processed foods manufactured with healthy fats and little or no added salt or sugar or preferably by minimally processed foods (30). In such ways, the food industry will protect human health and well-being.

Refutation (Astrup)

No effects beyond conventional classification systems

Monteiro provides an excellent summary of the Nova concept and evidence suggesting an adverse health effect of UPFs. However, his conclusion underscores the following issue: "This evidence essentially shows that increased dietary share of UPFs is *systematically associated* [italics added] with poor-quality diets and increased morbidity and mortality from several chronic diseases." Although I agree with this assertion, one cannot draw conclusions based on these associations. Observational studies, even those of the highest quality, cannot prove causality. Such studies involving UPFs are especially susceptible to confounding—that is, the bias resulting from the presence of factors associated with both exposures and outcomes. Various approaches can be used to account for confounding in observational studies, but it is practically impossible to completely eliminate the impact of unmeasured or unmeasurable factors (31). For obesity-related outcomes, a chief concern involves "an unhealthy cohort effect," that is, the presence among high UPF consumers of numerous factors associated with high body weight (e.g., lower socioeconomic status and education, less health-conscious behavior, depression, smoking, low physical activity, short sleep duration, and others).

In support of a causal effect of UPFs, Monteiro points to the systematic review by Dicken and Batterham (16) purporting to show independent associations between intake of UPFs and obesity after adjustment for dietary nutrients, dietary patterns, and various other relevant potential confounders. However, none of the reported studies controlled for important nondietary obesogenic factors, such as depression and short sleep duration (32). Furthermore, any imprecision or inaccuracy in dietary assessment could allow for residual confounding, a special concern with small effecsizes as in these cases (31). For these reasons, RCTs are needed.

Monteiro provides only a single RCT in support of his case (20) but—as considered in my Main Argument NO (33)—this study is too short and confounded (e.g., by energy density, added sugar, fiber type, and amounts) to allow for causal inference (33). Indeed, Monteiro explicitly recognizes that the effects of UPFs

can be explained by traditional nutritional metrics in his Main Argument, stating that "UPF consumption was associated with higher dietary free sugars and saturated fats; lower fiber, protein, potassium, and several micronutrients; and increased total energy intake" and that UPFs were "systematically associated with dietary nutrient profiles that might predispose to obesity, including higher dietary energy density and free sugars and lower fiber." Thus, there is no evidence that shows an effect of UPFs on long-term control of body weight and obesity risk beyond conventionally recognized factors, including the amount and sources of nutrients.

UPFs—a blurred definition

In addition to concerns for confounding, the utility of the concept of UPFs depends on objective definitions for terms such as "processing" and "ultra-processing." However, the Nova definition does not provide such objectively or clear distinctions to guide classification involving ingredients (34). This ambiguity is illustrated by Monteiro's repeated use of words such as "mostly," "mainly," "often," "in many cases," and "normally" and poorly defined constructs such as "highly profitable" and "hyperpalatable," impeding rigorous research by scientists and application by consumers. Moreover, meals made of similar ingredients by the same processes may be classified differently depending only on the location in which they are prepared: if preparation is industrial, then the food is considered a UPF; if preparation is at home, then it is not. The potential for such misclassifications has been considered in more details by others (34–36). This concern receives additional support from a recent study testing the interobserver reliability of >300 evaluators who were asked to use Nova to classify 231 different foods (37). Strikingly, the evaluators were highly inconsistent in their assignments; many foods were not consistently assigned to the same Nova group. Moreover, an appreciable proportion of the foods commonly classified as ultra-processed actually had acceptable nutritional quality (37).

Too many hypotheses—too little hard evidence

Monteiro offers many plausible hypotheses and speculations on putative mechanisms by which UPFs might cause excessive energy intake, weight gain, and obesity. Such ideas are important when a scientific concept is developed, but to avoid unintended adverse consequences, implementation should await experimental confirmation. With Nova, the opposite has occurred, with widespread adoption prior to robust establishment of mechanisms.

Dr. Monteiro highlights that various authorities recommend reducing UPFs, but the claim that UPF as a classification system provides information beyond conventional systems is not substantiated by scientific evidence. This is not the first time that scientists and national and international authorities have made recommendations without robust scientific evidence.

In 1990, the Dietary Guidelines for Americans advised "to avoid too much fat," and total fat was limited to 30% of calorie intake—effectively stigmatizing this macronutrient (38). In 1992, I personally recommended a low-fat, high-carbohydrate diets as a solution to the obesity epidemic (39) but later realized that this advice rested on observational studies and small trials of short duration lacking suitable controls. This focus on dietary fat reduction may have caused public health harms by inadvertently promoting intakes of high glycemic load carbohydrate and distracting from more effective measures (40). We must learn from the past and avoid premature dietary recommendations lacking rigorous experimental support.

Rebuttal (Monteiro)

Dr. Astrup says that the definition of UPF is blurred, quoting 1 online survey in which a convenience sample of evaluators were highly inconsistent in classifying foods into Nova groups (37). In fact, many studies investigating UPFs and ill health show an entirely different picture. For instance, only 4.4% of the 205 food items in the questionnaire used in Harvard cohorts were categorized as "doubtful" regarding their UPF status (41).

Based on the totality of evidence accumulated by investigators worldwide on UPF intake and ill health, I claimed that Nova with its concept of UPF helps inform dietary guidelines beyond conventional classifications that ignore how and why food was processed. This evidence included 3 meta-analyses of cohort studies demonstrating increased risk of obesity, type 2 diabetes, depression, cardiovascular disease, cerebrovascular disease, and all-cause mortality with adjustment for many potential confounders (17–19). Also, 1 systematic review restricted to cohort studies with additional adjustment for dietary nutrient contents demonstrated persistent increased risk of several diseases and disorders in 36 of 37 studies (16). In addition, 1 NIH RCT showed that ultra-processed diets increased short-term ad libitum calorie intake and weight gain despite matching with non-UPF diets for macronutrients, sugar, sodium, and fiber (20). Furthermore, there are studies on various UPF nutrient- and non-nutrient-related attributes that plausibly relate UPF intake to ill health (21–26).

Astrup discarded evidence I presented based on his belief that all observational studies involving UPFs, "even those of the highest quality," are plagued by residual confounding due to nonmeasured/measurable factors or measurement errors. This is why, he says, RCTs are needed. Yet, for him, the findings from the only RCT presently available were confounded by the imperfect nutrient matching of the 2 diets.

A serious problem with his arguments is the understanding of confounding, which, he says, is "the bias resulting from the presence of factors associated with both exposures and outcomes." Yes, but these factors, by definition, cannot be an intermediate step in the causal pathway between exposure and disease (42). When they are, statistical adjustments could produce bias rather than remove it (43). The wrong assessment of confounding led him to identify potential mediators of the UPF association with ill health, including dietary nutrient imbalances, as potential confounders.

Finally, in his considerations of what amounts to sufficient evidence, Astrup seems to want "absolute" or "final" proof. For complex biomedical problems, we may not have the luxury of awaiting absolute proof before making public health decisions (and even the choice of no action is a decision). Bradford Hill (44) has stated, "All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action it appears to demand at a given time." The

knowledge we already have on the massive ill effects of diets high in UPFs and the worldwide increasing consumption of these products certainly demand urgent public health action.

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