Ultra-Processed Food: Investigating Mechanisms, Prevention, and Action for Chronic Disease and Health Transformation (UPF-IMPACT) Program

Addressing Comments from Council of Councils Members

This is a revised proposed concept originally presented at the September 2025 Council of Councils meeting. Reviewers' comments (*purple italics*) and our responses to those comments are noted below.

Provide greater specificity of program goals, scope, structure, deliverables, NOFO criteria, and budget

This revised concept delineates two specific program goals and five deliverables that are achievable given the program design and budget. Additional details for a research coordinating center (RCC) and how it will coordinate the mechanistic and intervention initiatives are included. The RCC will oversee common data elements, data and biospecimen repositories, and central lab. The revised concept articulates criteria for the types of research proposals supported through the NOFOs, including possible study designs and populations, interventions, outcomes, and exploratory objectives.

Address structural barriers in the food environment and policy mechanisms to maximize public health impact

This revised concept now includes an initiative focusing on the development and testing of multi-level interventions including strategies to alter the social, physical, economic, or policy environments that shape or constrain health behaviors to reduce ultra-processed food (UPF) consumption.

Address health disparities and food access issues

This revised concept now includes a research initiative focusing on school age children and families who regularly consume UPF and are at risk for diet-related chronic diseases. The concept includes development/testing of multi-level interventions in school age children targeting social, physical, economic, or policy environments that shape or constrain health behaviors and contribute to disparities. Examples of interventions to reduce UPF consumption may include leveraging policies that affect direct marketing, pricing, labeling, and product placement.

Some investigators assert that the evidence linking UPF to chronic disease already meets the Bradford Hill criteria

While some investigators argue that existing evidence satisfies selected Bradford Hill considerations for causality, the overall body of evidence remains largely observational, heterogeneous across disease outcomes, and graded as very low to moderate for many conditions. Few studies look at specific UPF components/attributes, and thus there is insufficient evidence to demonstrate how these specific components/attributes contribute to chronic disease. The proposed concept will generate experimental evidence for plausible biological mechanisms supporting the link between UPF and disease and provide information on the dose-response relationship between UPF exposure and chronic disease.

Randomized rigorous clinical trials to ensure that UPF effects are not due to calories or potential confounders

Initiative 1 calls for rigorous, sufficiently large randomized controlled feeding trials and acute dietary interventions to examine the effects of UPF on biological markers of chronic disease, health and behavior. Mechanistic trials can be designed to examine the effects of processing while balancing the meals on nutrient profiles and total calories. Randomized parallel group designs or crossover designs used in feeding trials should more effectively balance the groups on known and unknown confounders.

How will conflicts of interest be managed and scientific independence be ensured

The original concept included a partnership component that included engaging with industry, however, this was removed to eliminate potential industry influence, reduce the risk of conflicts of interest (COI), and ensure the independence of the investigators conducting the research. Furthermore, as per normative procedures, applicants must declare all financial interests, and those will be evaluated on a case-by-case basis to ensure there are no COIs.

Scientific Independence

In accordance with the *NIH Plan to Drive Gold Standard Science* and in alignment with the NIH Director's priority to allow all science to be published, investigators will have unfettered access to their own data and research findings; and will be fully unincumbered to publish the research results from UPF-IMPACT.

Revised Concept Proposal

Background and Rationale for the Program

Diet-related chronic diseases are the leading causes of death—approximately 1 million per year—in the U.S., and 60% of the population has at least one chronic disease. Moreover, chronic diseases vary geographically and socioeconomically across the U.S., disproportionately impacting those who live in communities that face socio-economic and environmental barriers to prevention and management. The Nova 4 classification defines UPF as an industrial formulation manufactured by deconstructing foods into their component parts (such as oils, starches, and sweeteners), modifying them (for example, through enzymatic processes), and recombining them with cosmetic additives. UPF comprises ~70% of food supply and ~60% of daily caloric intake in children and adults. Profound changes to the structure and operations of global food systems, lifestyle changes, including increased demand for convenience, and lower food costs have contributed to the global increase in UPF-based dietary patterns.

Epidemiological evidence consistently links UPF-based diets to increased risks for adverse health outcomes, including obesity, type II diabetes, cardiovascular and digestive diseases, and certain types of cancer and mental health disorders. However, causal evidence on the mechanistic pathways that lead to chronic disease is lacking. Furthermore, in some studies, the association between UPF consumption and disease was independent of the nutrient content of the foods and some nutrient-dense UPF has shown no association with or decreased risks for health outcomes. Limited experimental evidence suggests that the texture, high energy density, and hyper-palatability commonly present in UPF facilitate excessive energy intake by affecting ingestive behaviors, satiety signaling, and food reward systems. Furthermore, emerging evidence suggests that non-nutritive UPF components/attributes may influence inflammatory, metabolic, and microbial pathways.

Despite the need for mechanistic trials, findings from observational studies are sufficiently strong to warrant interventions to reduce UPF consumption, particularly in vulnerable populations. UPF consumption is influenced by individual, interpersonal, community, and societal factors that limit access to healthy food. Studies suggest that environmental interventions may improve dietary patterns and associated health outcomes, and these are especially important for addressing diet-related health disparities in vulnerable populations. School age children are highly vulnerable to UPF consumption due to their developmental stage, widespread availability, and targeted marketing of low-nutrient, high-sugar products. Dietary quality also worsens and, as with adults, high UPF intake in youth is associated with metabolic dysregulation, obesity, mental health disorders, and gut microbiome dysbiosis. Children who consume more UPF have 63% higher odds of having overweight or obesity. These health conditions and dietary habits formed in childhood often track into adulthood. Thus, childhood and adolescence represent the developmental periods most critical for intervention. Multi-level interventions that act on the food environment (e.g., school meals, economic/policy measures, front-of-package labels, and marketing restrictions) could be effective public health strategies to reduce UPF consumption. Furthermore, successful nutrition interventions targeting school age children include setting family-based goals, modifying home food environment, hands-on approaches to teaching nutrition and fruit and vegetable vouchers.

Given the scientific gaps in the literature, there is a strong need to better understand and clarify the biological mechanisms through which exposures to specific UPF components/attributes may cause chronic diseases and to determine biomarkers of UPF exposure that increase risk for related health outcomes. There is also insufficient evidence to support the scale-up and broad implementation of existing interventions, especially in the U.S. Rigorously evaluated multi-level and environmental interventions are needed to identify scalable, sustainable strategies to reduce UPF consumption among school age children and families with diet-related health disparities. This proposed UPF-IMPACT program will address these gaps and opportunities to advance science and promote health in alignment with NIH's Unified Strategy to prioritize nutrition research, solution oriented-research on health disparities, and rigor and reproducibility, all aimed at reducing the burden of diet-related chronic diseases. These findings may inform food reformulation, public health programs, policies, and practices.

Program Goal: UPF-IMPACT will support research to (1) investigate biological mechanisms through which UPF consumption affects health, chronic disease, and behavior including UPF overconsumption, and to (2) develop and test real world, scalable, and sustainable interventions to reduce UPF consumption and improve health among school age children and families at risk of diet-related chronic diseases. This program is poised to support a valuable research portfolio that will move the field forward beyond observational associations toward causal mechanisms and actionable interventions for disease prevention.

1. Mechanistic Research: This initiative is anticipated to support up to 5 awards that investigate biological mechanisms by which UPF affect markers of health, chronic disease, and behavior, including UPF overconsumption. Studies should examine how attributes (e.g., food matrix, texture, and processing) and specific UPF components (i.e., nutrient profiles, additives, emulsifiers, and/or contaminants) and their dose effect on one of the following: 1) inflammatory processes and their potential interactions with changes in the microbiome and metabolic regulation, or 2) neurobiological processes and eating behavior such as stress responsivity, reward signaling, food intake rate. The latter may also examine the impact of UPF food presentation characteristics (e.g., packaging design) on UPF consumption. Trials are expected to be randomized controlled feeding trials and/or dietary challenge trials as appropriate to the research aims. The duration of exposure to UPF should be justified and endpoint dependent. Studies must be conducted with school age children and adults who regularly consume UPF (≥ 50% total daily calories) and are healthy and at risk of developing chronic diseases. NIH will prioritize proposals that address both processes.

2. Multi-level Intervention Research: This initiative is anticipated to support up to 5 awards to develop and test multi-level interventions to reduce UPF consumption and improve health among school age children (5-17 years) and families at risk of diet-related chronic diseases. At risk children and families may include but are not limited to individuals with low socioeconomic status, people living in neighborhoods with limited access to healthy food and/or individuals experiencing food insecurity. These interventions must address two or more levels of influence and include at least one environmental intervention targeting barriers to healthy eating. Environmental interventions should include strategies that alter the food environment in terms of the availability, affordability, and promotion of foods to encourage healthier and more sustainable eating (e.g., community-based nutrition education, teaching kitchens, community gardens, improvements in school meals, produce prescriptions, whole food vouchers, and UPF labeling and other state/local-level policies). Studies must include a community outreach and engagement strategy to ensure acceptability and sustainability of the proposed intervention. Studies should propose developmentally appropriate interventions for the targeted age range. Studies should enroll the primary caregivers in the home responsible for food purchasing and preparation. The primary outcome measure must be UPF consumption. Measurement of other health behaviors or clinical indicators are encouraged as co-primary or secondary outcome measures. Investigators should propose study designs most appropriate to their research, which may include but not limited to randomized controlled trials, clustered randomized, and natural experiments. NIH will prioritize applications to ensure geographic variation.

Cross-Cutting Research Objective: All studies should be adequately powered for relevant subgroup comparisons and must include an objective to identify putative biomarkers resulting from UPF exposure and their relationship to biological and behavioral outcomes under investigation. These biomarkers may be validated in future studies.

3. Research Coordinating Center (RCC): This initiative will support one award for an RCC that will provide study support, including but not limited to: 1) establishment and oversight of a central laboratory; 2) coordination with a secure controlled access biospecimen and data repository; 3) support for study harmonization and developing common data elements and measures and UPF definition; 4) expertise in statistical design and analysis; 5) participation in Common Fund Data Ecosystem, ensuring adherence to the FAIR data principles, findable, accessible, interoperable, and reusable; 6) study coordination, including support for study and Data and Safety Monitoring Board (DSMB) meetings.

Organizational Structure: The program consortium will be governed by a Program Steering Committee (PSC), composed of the principal investigators and NIH program scientists. The PSC will establish subcommittees to support core functions. Meetings will be convened to coordinate study activities, monitor study progress, and course correct as needed. The PSC and key personnel will also convene an annual in-person meeting to review progress and share findings. NIH will establish an independent DSMB, that will meet semiannually to review progress, data integrity, and participant safety. NIH will also establish an External Scientific Advisory Committee to meet annually to provide independent scientific and strategic guidance.

Deliverables: 1) causal mechanistic evidence linking specific UPF components/attributes to overconsumption and health outcomes; 2) evidence based, scalable strategies to reduce UPF consumption among children and families experiencing diet- related health disparities; 3) identification of putative biomarkers of UPF exposure and diet-related chronic disease; 4) evidence to inform public health programs, practices, and policies; 5) data to guide food reformulation efforts

Budget:

Initiatives	Lead IC(s)	FY2027	FY2028	FY2029	FY2030	FY2031	Total
RMS/NIH Program Management	TBD	$1,000	$1,000	$1,000	$1,000	$1,000	$5,000
Mechanistic Research (UG3/UH3)	TBD	$7,500	$13,500	$13,500	$13,500	$13,500	$61,500
Intervention Research (UG3/UH3)	TBD	$7,500	$14,000	$14,000	$14,000	$14,000	$63,500
Research Coordinating Center (RCC) (U24)	TBD	$3,000	$3,500	$4,000	$4,500	$5,000	$20,000
Totals		**$19,000**	**$32,000**	**$32,500**	**$33,000**	**$33,500**	**$150,000**