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## Commentary

## Ultra-processed foods and human health: What do we already know and what will further research tell us?

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Western diets are characterized by high intakes of energy-dense products, often with high amounts of sugars and sugary drinks, salt, and saturated fats, and limited amounts of fruit and vegetables, whole grains, and thus dietary fiber and vitamins. Strong scientific concordance linking these dietary factors to chronic diseases has been established and resulted in the setting of food based-dietary guidelines and tools to guide consumers towards foods and beverages of better nutritional quality (e.g. the front-of-pack nutritional label Nutri-Score, already officially adopted in seven European countries) [1]. More recently, the scientific community started to question the impact on human health of other dimensions of our diet, such as the degree of food processing. Food processing conveyed huge progresses across the last century (e.g. massive production of quick and easy to prepare foods, decrease of microbiological risk), but the question is: have we gone too far? Do these widely consumed (>50% of energy intake in the UK and the USA) “ultra-processed”/“ultra-formulated” products impact human health? Several categorization systems were proposed in order to classify foods according to their degree of processing; the most extensively used being the NOVA classification that identifies ultra-processed foods (UPF) [2]. Not only UPF have on average a poorer nutritional quality, they generally consist in products which have undergone several intense processes (e.g. molding, high-temperature extrusion) and contain cosmetic food additives and/or other industrial ingredients used to enhance the flavor and the palatability of the final product [2].

Recent systematic reviews and meta-analyses [3] show associations between UPF intake and increased risk of several chronic conditions, especially obesity and cardiometabolic outcomes (but also mortality, cancer, frailty, and depressive symptoms). These studies

were conducted in large cohorts from different countries, such as NutriNet-Santé in France [4], SUN in Spain [5], or the UK Biobank [6]. Although evidence still needs to be strengthened to establish a causal link, it is rapidly accumulating. Furthermore, while long-term randomized controlled trials (RCT) to test the impact of UPF on hard clinical outcomes are not feasible for ethical reasons, short-term RCTs on intermediate clinical endpoints can advance knowledge. One 2 × 2-week RCT [7] showed that an ultra-processed diet led to increased energy intake and weight gain compared with an unprocessed diet.

Associations between UPF and health outcomes were observed even when the overall poorer nutritional quality of UPF was fully accounted for in the models, suggesting that other factors probably play a role. Food additives (e.g. colours, emulsifiers, preservatives, ≈330 authorized in Europe) constitute one of the main hypotheses. Indeed, recently, concerning results emerged mainly from in-vitro/animal studies for several additives commonly used in thousands of foods. For instance, some emulsifiers (carboxymethylcellulose, polysorbate 80) induced metabolic perturbations, alterations to the gut microbiota, inflammation, and colon carcinogenesis in mice [8]. So far, except in particular cases, there are no human studies on additive exposure and long-term health outcomes and there is hardly no data on mixtures and their potential cocktail effects. Since 2009, the NutriNet-Santé cohort ( $n = 171,000$ ) collects repeated dietary intake data for >3500 generic foods, each displayed in tens of industrial brands. This allows capturing the huge heterogeneity in food additive content between the different commercial references at the individual level, necessary for etiological research. A multidisciplinary Europe-funded program is ongoing to investigate the links between the exposure to cocktails of food additives from UPF and chronic disease risk.

Other hypotheses pertain to substances created during food processing such as furans and trans fatty acids, and to contaminants that may migrate from packaging in contact with foods during extended durations. Phthalates and bisphenols, for instance, might have endocrine disruption functions and higher consumers of UPF in the US NHANES study had higher urinary concentrations of these compounds [9]. Effects of food matrix modification on satiety, nutrient bioavailability, transit speed and tendency of UPF to foster overconsumption are also postulated.

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There is an urgent need for public research combining epidemiological and experimental approaches to better understand the impact of food processing and formulation on health and identify which specific factors (among cocktails of additives, contaminants, etc.) are causally involved. This would be a further step forward to reach the implementation of measures at the levels of regulations (e.g., prohibition of certain substances, reduction of authorized levels), and consumers (optimization of recommendations, quality of scientific data delivered by food apps, improvement of food labeling), to positively impact human health but also environmental sustainability [10]. In the meantime, consumers should be advised to 1) choose food products of a better nutritional quality as scored by the Nutri-Score (low in salt, sugar, saturated fats and rich in dietary fiber, etc.), since this dimension of diet is the one for which health impact has the highest levels of evidence, and 2) be aware of the different yet complementary dimension of the diet related to food processing. In this context, several countries worldwide and the UN-FAO [10] now officially advise limiting UPF. Since UPF-based diets were suggested to be cheaper, policies should improve affordability and accessibility of raw/minimally-processed foods.

#### Author contributions

Dr B. Srour and Dr M. Touvier co-wrote this commentary and contributed equally to this paper.

#### Declaration of Competing Interest

The authors have no financial conflict of interest to disclose.

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