Ultra-processed foods and human health: from epidemiological evidence to mechanistic insights

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Epidemiological studies have suggested a role for ultra-processed foods in numerous chronic inflammatory diseases such as inflammatory bowel diseases and metabolic syndrome. Preclinical and clinical studies are accumulating to better decipher the effects of various aspects of food processing and formulation on the aetiology of chronic, debilitating inflammatory diseases. In this Review, we provide an overview of the current data that highlight an association between ultra-processed food consumption and various chronic diseases, with a focus on epidemiological evidence and mechanistic insights involving the intestinal microbiota.

Lancet Gastroenterol Hepatol 2022

Published **Online** August 8, 2022 https://doi.org/10.1016/S2468-1253(22)00169-8

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Introduction

Since the dawn of humankind, humans have built and used a variety of techniques to process their food. From hunter-gatherer, to pastoral-migrant, to peasant-agri-cultural lifestyles, these tools have evolved over hundreds of thousands of years. After the building of towns and cities, humans needed to provide their homes with food, usually obtained from the neighbouring countryside, with sun drying, salting, pickling, and smoking of foods used for preservation when they could not be freshly consumed. Over time, more sophisticated methods were developed, mainly to preserve foods or to exploit cereals (eg, by use of mills to process flour to be mixed with water afterwards to create wheat bread).[1] During the industrial revolution, processing technologies were invented, enabling larger scale production of culinary ingredients, such as oils, animal fats, sugars, flour, and salt.[2] Nearly a century later, due to industrial processing techniques, a wide range of products with guaranteed microbiological safety, that are easy to preserve, practical, and convenient to consume in various social contexts, became accessible and affordable to most populations in high-income countries. Mechanical and physical techniques (eg, roller milling, pressure rendering, and extrusion) and chemical techniques (eg, hydrogenation and hydroxylation) were developed, through the use of artificial flavours, preservatives, and other additives. These techniques allowed large-scale production and manufacturing of massively produced processed foods, making them available throughout the year. These processed products are time-saving as they require less preparation than fresh products—something that has become increasingly valued in high-income societies over the past few decades. Processed foods are also microbiologically safe, widely accessible and affordable to a growing population, and can contribute to food waste reduction as they have a longer shelf life than fresh foods. Moreover, some industrial processes—eg, those used in tomato sauce preparation—might be beneficial as they could lead to enhanced bioaccessibility of antioxidants.[3]

Although this massive shift from artisanal food to processed products occurred in high-income countries first, middle-income and low-income populations and countries have followed suit. Highly processed foods started to occupy supermarket shelves worldwide at the same time as a rise in the incidence of chronic inflammatory diseases, such as metabolic syndrome and inflammatory bowel disease (IBD). This correlation has led scientists worldwide to start investigating whether a link exists between this increasing degree of food processing and the risk of chronic diseases. In this Review, we study the most commonly used classification for processed foods, consider the various prospective epidemiological studies linking ultra-processed foods (UPFs) to human health, and describe recent mechanistic studies linking UPFs to chronic diseases, with a focus on the role played by the intestinal microbiota. We also discuss implications for future research, public dietary policies, and food manufacturing practices.

Food processing in modern societies

UPFs: definition and classifications

Several classification systems for foods and beverages have been proposed,[4–8] with the NOVA classification being most extensively used in nutritional surveys and aetiological studies.[6] NOVA was developed by scientists from the University of São Paulo, and categorises foods and beverages into four groups according to their degree of processing.[9] Group 1 of the NOVA classification consists of unprocessed or minimally processed foods, including fresh, dried, ground, chilled, frozen, pasteurised, or fermented staple foods (eg, fruits, vegetables, pulses, rice, pasta, eggs, meat, fish, or milk). Group 2 of NOVA consists of processed culinary ingredients, including salt, vegetable oils, butter, sugar, and other substances extracted from foods and used in kitchens to transform unprocessed or minimally processed foods into culinary preparations. Group 3 of NOVA comprises processed foods, including canned vegetables with added salt, sugar-coated dry fruits, meat products only preserved by salting, cheeses, freshly made unpackaged breads, and other products manu-factured with the addition of salt, sugar, or other substances in group 2 to items that are in group 1. Finally, products in the most processed group (group 4), called UPFs, include all foods that undergo intense industrial physical, chemical, or biological processes, including hydrogenation, hydrolysis, extruding, and pre-processing

by frying. The UPF group also generally contains industrial substances that are not usually found in domestic kitchens (eg, maltodextrin, hydrogenated oils, or modified starches) and flavouring agents and cosmetic additives (eg, dyes, emulsifiers, and artificial sweeteners). Examples of UPFs include reconstituted meat products transformed by the addition of preservatives other than salt (eg, nitrites), fish and chicken nuggets, instant noodles and dehydrated soups, chocolate and energy bars, carbonated drinks (sodas), vegetable patties (ie, meat substitutes) containing food additives, so-called slimming products and other foods marketed as healthy products—eg, powdered or fortified meal replacement shakes or snacks—and foods containing various food additives.[9,10]

UPFs: an increasing contribution to energy intake in high-income countries

UPF consumption has been increasing worldwide in both adults and children over the past few decades.[11–15] For example, representative studies published since 2016 have shown that UPFs contributed up to 31·1% of daily caloric intake in France,[16] 56·8% in the UK,[17] and 57·9% in the USA (figure 1).[18] Consequently, exposure to numerous food additives has followed the same upwards trend, with the likes of dietary emulsifiers used in foods and beverages seeing annual sales constantly increasing.[19]

UPF and human health: an epidemiological point of view

UPF consumption and links to human health

Numerous studies have shown a correlation between UPF consumption and the prevalence or incidence of numerous chronic inflammatory diseases (eg, metabolic syndrome, IBD, and various cancers). To our knowledge, at the time of writing this Review, 48 prospective studies investigating the associations between UPF consumption and health status, chronic diseases, or mortality have been published, as summarised in the table. One of the most comprehensive tools used to measure UPF consumption is a set of detailed and repeated 24-h dietary records, especially when merged with extensive food composition databases. This tool also offers the opportunity to collect data about specific consumed brands within one generic food item, allowing for a more accurate UPF categorisation. When 24-h dietary records are not available, food frequency questionnaires, with a large number of items, can also be used to measure UPFs in diet; however, they are less accurate than 24-h dietary records. The largest number of prospective studies addressing the relationship between UPFs and health was conducted using the French NutriNet-Santé cohort (using repeated 24-h dietary records)[68] and the Spanish SUN cohort (using a 136-item food frequency questionnaire),[69] and some of these studies were summarised in six meta-analyses.[70–75] Numerous cross-sectional studies have also been published, but as they convey a lower weight of evidence than prospective studies due to their non-prospective design, they will not be included in this Review.

Among the 48 prospective studies, six in the general population and one in patients with cardiovascular disease —all conducted in Spain, France, Italy, and the USA— have suggested an association between consumption of UPFs and risk of all-cause mortality, with hazard ratios (HRs) ranging from 1·26 to 1·62 for the highest versus lowest UPF consumption categories.[21–27] With regards to cardiovascular and cerebrovascular disease and mortality, five studies investigated the potential link between UPF consumption and cardiovascular disease and mortality, in both the USA and Europe, and showed a significant increase in risk.[22,31–33,35] Four European studies (in the NutriNet-Santé, SUN, UK Biobank, and Lifelines cohorts) have shown direct associations between UPF consumption and the risk of type 2 diabetes, with HRs ranging from 1·26 to 1·53 and an odds ratio (OR) of 1·80.[61–64] One prospective study found a significant association between UPF consumption and the risk of gestational diabetes in a Spanish population.[42] Moreover, a Brazilian study suggested an association between consumption of UPF during pregnancy and gestational weight gain.[43]

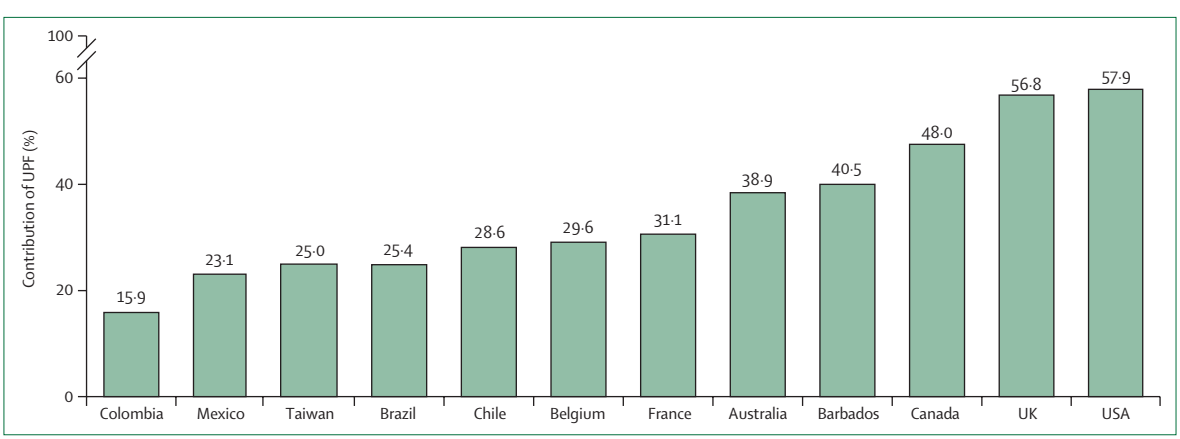

Figure 1: **Contributions of ultra-processed foods to daily energy intakes in several countries, based on dietary intake nationally representative surveys**
Data are numerical values.

	Country	Sample size	Study population	Outcome	Risk estimates: highest category of UPF *vs* lowest
Sandoval-Insausti et al (2020)[20]	Spain	652	Older adults (mean age 67·1 years; Enrica study)	Abdominal obesity	OR 1·62 (1·04–2·54)
Bonaccio et al (2022)[21]	Italy	1171	Older adults with history of cardiovascular disease (mean age 67·0 years; Moli-sani study)	All-cause and cardiovascular disease mortality	HR 1·38 (1·00–1·91) for all-cause mortality and 1·65 (1·07–2·55) for cardiovascular disease mortality
Bonaccio et al (2021)[22]	Italy	22 475	Adults (Moli-sani study)	All-cause and cardiovascular disease mortality	HR 1·58 (1·23–2·03) for cardiovascular disease mortality and 1·26 (1·09–1·46) for all-cause mortality
Kim et al (2019)[23]	USA	11 898	Adults (NHANES III)	All-cause mortality	HR 1·31 (1·09–1·58)
Schnabel et al (2019)[24]	France	44 551	Adults (NutriNet-Santé cohort)	All-cause mortality	HR 1·14 (1·04–1·27) per 10% increase in UPF
Rico- Campà et al (2019)[25]	Spain	19 899	Adults (SUN cohort)	All-cause mortality	HR 1·62 (1·13–2·33)
Romero Ferreiro et al (2021)[26]	Spain	4679	General population (DRECE cohort)	All-cause mortality	HR 1·15 (1·03–1·27) per 10% increase in UPF
Blanco-Rojo et al (2019)[27]	Spain	11 898	Adults (Enrica study)	All-cause mortality	HR 1·44 (1·01–2·07)
Melo et al (2018)[28]	Brazil	109 104	Adolescents (National Survey of School Health)	Asthma	OR 1·27 (1·15–1·41)
Machado Azeredo et al (2019)[29]	Brazil	2190	Children (Pelotas cohort)	Asthma	OR 0·84 (0·58–1·21)
Fiolet et al (2018)[30]	France	104 980	Adults (NutriNet-Santé cohort)	Cancer (overall and by site)	Overall cancer, HR 1·21 (1·06–1·38); and postmenopausal breast cancer, 1·39 (1·07–1·82)
Srour et al (2019)[31]	France	105 159	Adults (NutriNet-Santé cohort)	Cardiovascular disease	HR 1·23 (1·04–1·45)
Zhong et al (2021)[32]	USA	91 891	Adults (PLCO Cancer Screening Trial)	Cardiovascular disease mortality	HR 1·50 (1·36–1·64)
Du et al (2021)[33]	USA	13 548	Adults (Atherosclerosis Risk in Communities)	Coronary artery disease	HR 1·19 (1·05–1·35)
Lo et al (2021)[34]	USA	245 112	Adults (Nurses' Health study II and Health Professionals' follow-up study)	Crohn's disease and ulcerative colitis	Crohn's disease, HR 1·70 (1·23–2·35); and ulcerative colitis, HR 1·20 (0·91–1·58)
Juul et al (2021)[35]	USA	3003	Adults (Framingham Offspring cohort)	Cardiovascular disease and cardiovascular disease mortality	Cardiovascular disease, (one additional serving), HR 1·05 (1·02–1·08); and cardiovascular disease mortality, 1·09 (1·02–1·16)
Gómez-Donoso et al (2019)[36]	Spain	14 907	Adults (SUN cohort)	Depression	HR 1·33 (1·07–1·64)
Adjibade et al (2019)[37]	France	26 730	Adults (NutriNet-Santé cohort)	Depressive symptoms	HR 1·31 (1·16–1·47)
Donat-Vargas et al (2021)[38]	Spain	1082	Older adults (mean age 68·0 years)	Dyslipidaemia	OR 2·66 (1·20–5·90)
Costa et al (2021)[39]	Brazil	4231	Children (Pelotas cohort)	Fat-mass index	β (100 g contribution in UPF) 0·14 kg/m^2
Sandoval-Insausti et al (2020)[40]	Spain	1822	Older adults (mean age 68·7 years; Enrica study)	Frailty	OR 3·22 (1·79–5·79)
Zhang et al (2021)[41]	China	5409	Adults	Grip strength	β (for 10% increase in UPF) –0·0057 (–0·0086 to –0·0029) kg/kg
Leone et al (2021)[42]	Spain	3730	Pregnant women	Gestational diabetes	OR 2·05 (1·03–4·07)
Gomes et al (2021)[43]	Brazil	259	Pregnant women	Gestational weight gain	β (for 1% increase in UPF) 4·17 (0·55–7·79) g
Scaranni et al (2021)[44]	Brazil	8754	Adults (ELSA-brazil)	Hypertension	OR 1·23 (1·06–1·44)
Mendonça et al (2017)[45]	Spain	14 790	Adults (SUN cohort)	Hypertension	HR 1·21 (1·06–1·37)
Rezende-Alves et al (2021)[46]	Brazil	1221	Adults (Cohort of Universities of Minas Gerais)	Hypertension	RR 1·35 (1·01–1·81)
Monge et al (2021)[47]	Mexico	64 934	Women (Mexican Teacher's cohort)	Hypertension	Incidence RR 0·96 (0·79–1·16)
Vasseur et al (2021)[48]	France	105 382	Adults (NutriNet-Santé cohort)	Inflammatory bowel disease	RR 1·44 (0·70–2·94)
Narula et al (2021)[49]	Muticentric	116 087	Adults from different countries worldwide (PURE cohort)	Inflammatory bowel disease	HR 1·82 (1·22–2·72)
Leffa et al (2020)[50]	Brazil	308	Children (age range 3–6 years; Porto-Alegre)	Lipid profile	β (total cholesterol) 0·22
Rauber et al (2015)[51]	Brazil	345	Children (age range 3–8 years; San Leopoldo)	Lipid profile	β (total cholesterol) 0·430, and β (LDL cholesterol) 0·369
Zhang et al (2021)[52]	China	16 168	Adults (TCLSIH cohort study)	Non-alcoholic fatty liver disease	HR 1·18 (1·07–1·30)
Rauber et al (2021)[53]	UK	22 659	Adults (UK Biobank)	Obesity	HR 1·79 (1·06–3·03)
de Melo et al (2021)[54]	Brazil	196	Breastfed infants	Overweight associated with maternal consumption of UPF while breastfeeding	HR 3·02 (1·28–7·13)

(Table continues on next page)

	Country	Sample size	Study population	Outcome	Risk estimates: highest category of UPF *vs* lowest
(Continued from previous page)					
Li et al (2021)[55]	China	12 451	Adults (China Nutrition and Health Survey)	Overweight or obesity	OR 1·45 (1·21–1·74)
Canhada et al (2019)[56]	Brazil	11 827	Adults (ELSA-brazil cohort)	Overweight or obesity	HR 1·20 (1·03–1·40)
Beslay et al (2020)[57]	France	110 260	Adults (NutriNet-Santé cohort)	Overweight or obesity	HR 1·26 (1·18–1·35)
Mendonça et al (2016)[58]	Spain	8451	Adults (SUN cohort)	Overweight or obesity	HR 1·26 (1·10–1·45)
Cordova et al (2021)[59]	Multicentric	348 748	European adults (EPIC cohort)	Overweight or obesity	HR 1·15 (1·11–1·19)
Rey-García et al (2021)[60]	Spain	1312	Older adults (mean age 67·0 years)	Renal function decline	OR 1·74 (1·14–2·66)
Srour et al (2020)[61]	France	104 707	Adults (NutriNet-Santé cohort)	Type 2 diabetes	HR 1·26 (1·01–1·57)
Llavero-Valero et al (2021)[62]	Spain	20 060	Adults (SUN cohort)	Type 2 diabetes	HR 1·53 (1·06–2·22)
Levy et al (2020)[63]	UK	21 730	Adults (UK Biobank)	Type 2 diabetes	HR 1·44 (1·04–2·02)
Duan et al (2022)[64]	Netherlands	70 421	Adults (Lifelines cohort)	Type 2 diabetes	OR 1·80 (1·47–2·20)
Konieczna et al (2021)[65]	Spain	1485	General population (PREDIMED-PLUS)	Visceral fat and total fat	β (visceral fat) 0·13, and β (total fat) 0·15
Costa et al (2019)[66]	Brazil	307	Children (age range 3–6 years; San Leopoldo)	Waist circumference and glucose metabolism	β (waist circumference) 0·07, not significant for glucose metabolism
Chang et al (2021)[67]	England	9025	Children (Avon Longitudinal Study of Parents and Children)	Weight trajectories	β (body-mass index) 0·06, and β (waist circumference) 0·17

HR=hazard ratio. OR=odds ratio. RR=rate ratio. UPF=ultra-processed food.

Table: **Prospective studies investigating the associations between ultra-processed foods and risks of weight gain, overweight, chronic diseases, and mortality**

Additionally, four prospective studies done in Brazil, Spain, and Mexico explored the associations between UPF and the risk of hypertension.[44,46,47,76] Although three of these studies (done in men and women) found direct significant associations,[44,46,76] with association measures (ie, HRs, ORs, or risk ratios) ranging between 1·21 and 1·35, the Mexican study (done only in women) found no significant association (table).[47] The magnitude of all the aforementioned association measure estimates are similar to that typically observed in nutritional epidemiology studies,[77–81] reflecting a substantial number of additional individuals with chronic diseases and premature deaths.[82]

To date, only one prospective cohort study, conducted within the NutriNet-Santé cohort, explored the association between UPF and cancer risk, showing an association with overall cancer risk and breast cancer risk.[30,83] Several prospective studies have observed associations between UPF consumption and increased risks of overweight or obesity (or both).[20,53,55–57,76] The summarised ORs from the most recent meta-analysis published in 2021 were 1·55 (95% CI 1·36–1·77) for obesity, 1·36 (1·14–1·63) for overweight, and 1·41 (1·18–1·68) for abdominal obesity.[73] In children, several prospective studies have shown associations between increased consumption of UPFs and increases in weight, waist circumference, fat-mass index, and worse lipid profiles.[50,51,66,67] Hence, accumulating evidence suggests an association between UPF consumption and various debilitating chronic inflammatory diseases.

Data from the 2021 multicentric international Prospective Urban Rural Epidemiology (PURE) cohort showed an association between UPF consumption and an increased risk of IBD,[49] and a follow-up study showed that these associations were significant for Crohn's disease but not for ulcerative colitis.[34] There was no evidence for a significant association between UPF and IBD in the French NutriNet-Santé cohort, but there were few IBD cases available for analysis at the time of the study.[48] Other prospective studies have observed associations between consumption of UPFs and increased risk of depression or depressive symptoms,[36,37] dyslipidaemia,[38] renal function decline,[60] frailty,[40] decreased grip strength,[84] and non-alcoholic fatty liver disease.[52]

Importantly, and despite careful adjustment, residual confounding cannot be ruled out in observational studies. With this limitation in mind, several independent studies in diverse populations worldwide are accumulating and presenting consistent results for various outcomes, strengthening the association between UPF consumption and risk for various chronic disorders. Although it is not possible for obvious ethical reasons and practical constraints to set up long-term randomised trials with endpoints such as the onset of chronic diseases, short-term randomised intervention trials are possible on intermediate health events, providing useful and complementary mechanistic insights. For example, a randomised trial performed by Hall and colleagues[85] included 20 participants admitted as inpatients for the purpose of the trial to the Metabolic Clinical Research Unit at the National Institutes of Health Clinical Center, USA, who were allocated to either an ultra-processed or unprocessed diet for 2 weeks, which was then immediately followed by the alternative diet for a further 2 weeks. This approach showed that the ultra-processed diet led to an increased energy intake (508 [SD 106] kcal per day during the ultra-processed diet), which was highly correlated with weight gain (0·8 kg [0·3], p=0·01), versus a mean weight loss of 1·1 kg (0·3) during the

unprocessed diet. Other short-term randomised trials are ongoing (eg, NCT04280146 and NCT04308473).

UPF and chronic diseases: mechanistic insights

As summarised in the table, a consensus has emerged regarding the associations between UPF consumption and the incidence of various chronic conditions. A UPF-rich diet could affect human health by a number of mechanisms (figure 2).

A poorer nutritional quality on average

UPFs often have a lower nutritional quality than unprocessed foods, with higher content of saturated fat, added sugar, energy density, and salt, along with a lower fibre and vitamin content, which can all be important factors in driving their detrimental impact on health.[4,8,15,17,19,86–92] Importantly, the nutritional content of a food product and its degree of processing are two different dimensions that might be related but are not colinear. A large proportion of commercialised packaged food products with a low-relative caloric content are ultra-processed, and conversely some unprocessed foods might have high-caloric content.[93] For example, diet carbonated drinks contain no or very low calories and, therefore, have a better caloric value than natural fruit juice, but are nonetheless considered UPFs since they contain artificial sweeteners. As shown in the appendix (p 2), of the 220 522 UPF products available on the French Open Food Facts database in 2020, 46 310 (21%) had a good nutritional score according to the validated Nutri-Score front-of-package label—a nutritional rating system selected by the French government in March, 2017, and by six other European countries since then, to be displayed on food products to summarise their nutritional quality.[94] In almost all of the previously mentioned epidemiological studies, statistical analyses accounted for energy intake and nutritional quality of the diet. However, the associations between UPF and health outcomes persisted, suggesting that factors beyond nutritional aspects have a role in these associations.

Contaminants from processes or packaging

Food processing can result in the production of potentially toxic compounds, such as furans, heterocyclic amines, polycyclic aromatic hydrocarbons, acrolein, advanced glycation end products, industrial trans-fatty acids (from hydrogenation of oils) or acrylamide (from high temperature cooking of foods containing starch and asparagine, such as French fries, crisps, and biscuits).[95–97] Although some contaminants are not specific to UPFs (eg, acrylamide is also produced during domestic cooking), increased concentrations of several of these contaminants have been observed in industrially processed products.[98] Another hypothesis suggests that contaminants (eg, phthalates, bisphenols, mineral oils, and microplastics) migrate from contact packaging to foods. This migration might occur during prolonged exposure times, which is often the case for UPFs with extended shelf lives. For example, UPF consumption was associated with increased urinary phthalate concentrations in the US National Health and Nutrition Examination Survey study.[98,99] Previous studies in humans have suggested that contaminants, such as acrylamide, heterocyclic amines, polycyclic aromatic hydrocarbons, and acrolein, might have carcinogenic properties,[100] increase cardiovascular disease risk[95,101] and insulin resistance.[102,103] Furthermore, bisphenols were associated with increased risks of cardiovascular disease,[104] cancer,[105] type 2 diabetes,[106] and obesity.[107] Substitutes for bisphenol A, such as bisphenol S, also lead to increased internal exposure to an endocrine-active compound that would be of concern for human health.[108] Despite the scarce literature in human studies, a few food toxicology studies have suggested that microwave heating could increase migration of bisphenols from polycarbonate containers,[109] or the formation of acrylamide when heating at a high power.[110] Even though these risks are not specific to UPFs, most ready-to-eat meals are classified as UPFs, and they often require microwave heating.

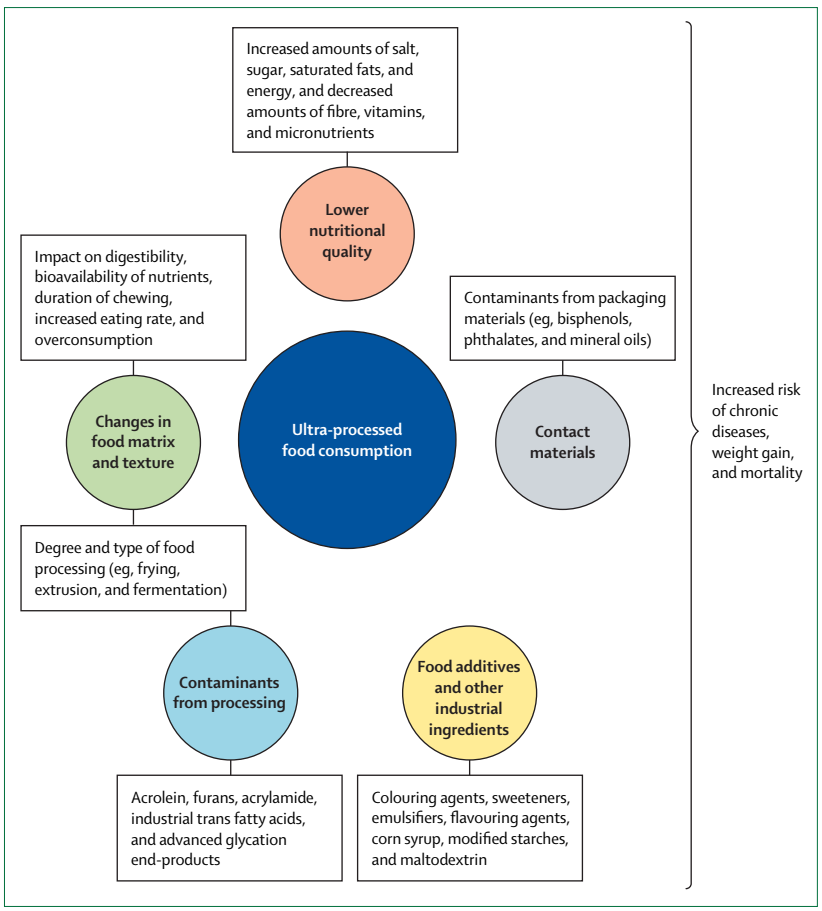

Figure 2: **Possible mechanisms underlying the associations between ultra-processed foods and chronic diseases risk**

See **Online** for appendix

Disruption of food matrices

Changes to the food matrix (ie, the structure defining how the various compounds in a food interact) during processing could also affect satiety, transit time, digestibility,[111] bioavailability of ingested nutrients,[112] and the rate of food ingestion and duration of chewing, because UPFs seem to have a faster rate of energy intake (in kcal per min) than unprocessed foods do.[113] Although models in prospective studies were adjusted for energy and nutrient intakes and BMI, the fact that the associations between UPFs and chronic diseases persisted in the studies means that these factors only partly explain the observed associations. The impact of food structure and matrix on nutrient bioavailability in the occurrence of chronic diseases has been, to our knowledge, rarely explored so far.

Use of food additives

About 330 food additives are currently approved to be used in the EU under the European Food Safety Authority regulation. Most of them probably have no effect on health, and some might even have beneficial effects (eg, antioxidants and polyphenols). However, several studies published in 2021, including preclinical and clinical studies, have suggested a potential effect of various food additives, such as emulsifiers, sweeteners and colorant, in the etiology of chronic inflammatory diseases.[114–116] Many of these studies on UPFs in general—and on additives in particular—have suggested that the microbiota is involved in mediating the potential effects of these additives on human health.

UPF and chronic diseases: a central role for the intestinal microbiota?

As discussed, UPF consumption is associated with several adverse health effects and pathologies, which have serious epidemiological implications given the prevalence of UPFs in diets globally.[117] Hence, numerous research efforts have focused on better understanding the mechanisms behind UPF's effects on health. These efforts have brought to light the potential central role played by the intestinal microbiota in connecting UPF and host health. The human intestinal microbiota consists of trillions of microorganisms that have co-evolved with their host for millennia and now perform core functions, such as food digestion and maturation of host immunity and metabolism.[118,119] A combination of laboratory-based preclinical research, epidemiological studies, and clinical trials suggest that UPFs affect human health through alterations of the intestinal microbiota composition and function.

Seminal works from Jeffrey Gordon's group, published in 2006–08, showed microbiota composition alterations in murine models of obesity and in individuals with obesity. These studies also showed that microbiota transplantation from mice with diet-induced obesity to lean germ-free recipients on a healthy diet was sufficient to promote fat deposition in the recipient animals.[120–121] This work established a causal link between diet-induced alterations of microbiota and altered host metabolism in mice. Mechanistically, functional microbiota analysis revealed an increase in features, such as import and processing of simple sugars by members of the microbiota in the presence of a high-fat diet, suggesting that the microbiota's ability to extract calories from ingested food affects diet-induced metabolic dysregulation (figure 3).[120,123] Another hallmark of metabolic dysregulation is the presence of chronic low-grade inflammation and alterations in microbiota composition and function, which lead to an increase in the systemic concentrations of bacterial products, such as lipopolysaccharides.[124–126] Lipopolysaccharides derived from the outer cell membrane of Gram-negative bacteria contain a molecular structure known as lipid A and are able to cross the gastrointestinal mucosa via various mechanisms—eg, chylomicron-mediated transport—ultimately reaching the systemic circulation.[127] Once in the circulation, lipopolysaccharides infiltrate tissues (eg, the liver and adipose tissues) and trigger inflammation-related processes that associate with metabolic pathologies, such as obesity and insulin resistance.[128,129] Work by Hotamışlıgil and colleagues illustrated the concept of metainflammation, a metabolic inflammatory state defined by low-grade chronic inflammation created by metabolic cells and stress sensors.[130–132] Metainflammation was shown to contribute to obesity and insulin resistance over time in both mice and humans, through the infiltration of immune cells and the secretion of inflammatory cytokines in the tissue environment, which progressively interfered with—and even inhibited—insulin signalling.[130] The demonstration that the immune system and metabolism were connected opened a new field of study in metabolic diseases, ultimately leading to the investigation of anti-inflammatory therapies as a treatment for obesity and metabolic diseases.[132] Moreover, intestinal microbiota are also highly regulated in their ability to produce metabolites, mainly through modulation of gene expression by the intestinal environment, including diet.[133,134] Hence, UPFs also have the capacity to alter the metabolomic capacities of the intestinal microbiota in a way that can substantially affect host health.[135] For example, both human and animal studies have shown that microbiota members can respond to compounds present in UPFs by increasing their expression of virulence factors, consequently increasing the inflammatory potential of the microbiome.[136,137] UPFs might also contribute to chronic inflammation by altering the production of beneficial bacterial metabolites such as short-chain fatty acids by the intestinal microbiota.[138–140] Another example that highlights the importance of UPF–microbiota interactions in various chronic diseases relates to the increased consumption of refined sugar.[141,142] In particular, Montrose and colleagues showed that the administration of a high-fructose diet to mice induced atypical microbiota encroachment to the gut epithelium,

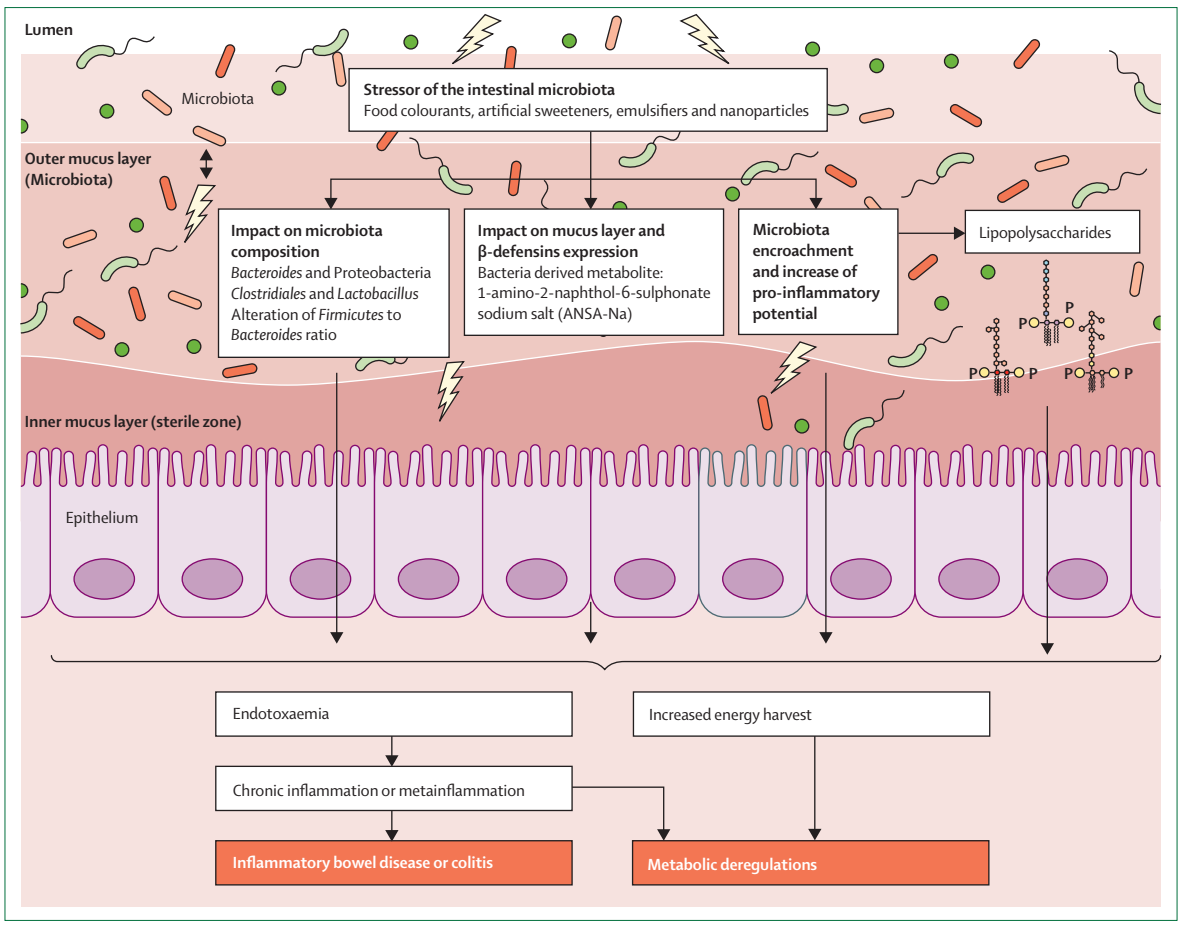

Figure 3: **The intestinal microbiota in chronic inflammatory conditions**

reduced mucus layer thickness, and altered intestinal microbiota composition.[142] Moreover, Arnone and colleagues reported intestinal microbiota dysbiosis in mice consuming a high-fat and high-sucrose diet, which was associated with a predisposition to dextran sulfate sodium-induced colitis.[141] Thus, UPFs disturb numerous mechanisms that are important for the maintenance of energy balance and immune homoeostasis, ultimately leading to metabolic and inflammatory diseases.

Finally, two studies from 2016 in rodents showed that dysbiosis induced by a diet typical of industrialised, high-income countries can be transferred to later generations, possibly inducing inheritable metabolic changes.[143,144] Ultimately, all of these diet–microbiome–host interactions could have a role in the development of chronic diseases.

Artificial sweeteners

Non-caloric artificial sweeteners (NAS) are among the most commonly used food additives due to their ability to enhance sweetness with a low or non-caloric intake. Some examples used by the food industry are sucralose, saccharine, and aspartame. Despite their low or non-caloric intake, Suez and colleagues previously reported that NAS could affect glucose tolerance in both rats and humans, with a central role played by the intestinal microbiota.[145] This study reported the over-representation of *Bacteroides* and the under-representation of *Clostridiales* following NAS consumption, an imbalance notably associated with type 2 diabetes in humans.[145] When saccharin was administered to individuals that normally do not consume NAS, glucose tolerance was affected in a subset of participants who had alterations in their microbiota composition after NAS consumption. Faecal microbial transplantation from these participants into germ-free mice showed that the microbiota played a central role in driving insulin resistance.[145] Another study from Palmnäs and colleagues reported hyperglycaemia and an impaired ability to respond to insulin in rats after aspartame consumption, which is probably linked to increased propionate production that enhanced gluconeogenesis.[146] This study also showed that aspartame consumption could counteract high-fat diet-induced negative effects, by decreasing adiposity, fasting insulin concentrations, body mass, and caloric consumption.[146] Hence, the exact influence of aspartame on metabolic health requires further investigation.

Food colourants

Food colourants were first introduced to the food market during the 19th century; however, despite their large consumption, their impact on the intestinal microbiota remains relatively unknown. A 2021 study showed that azo dyes red 40 and yellow 6, the most abundant colourants used by the food industry, can trigger IBD-like colitis in genetically susceptible mice.[147] This study showed that commensal bacteria such as *Bacteroides ovatus* and *Enterococcus faecalis* can metabolise food colourants and produce a metabolite known as 1-amino-2-naphthol-6- sulphonate sodium salt (ANSA-Na). This metabolite appears sufficient to induce colitis, highlighting the importance of the intestinal microbiota in driving the detrimental effects of food additives on intestinal health.[147]

Emulsifiers

Food additive emulsifiers are widely used by the food industry to improve organoleptic properties and extend shelf-life, with the most commonly used being lecithin, monoglycerides and diglycerides, guar gum, xanthan gum, carrageenan, polysorbate-80, and carboxymethylcellulose.[114,115] Since 2015, dietary emulsifiers have received particular attention due to their possible role in the pathogenesis of IBD and metabolic dysregulations.[134,148] While investigating their effect on the development of chronic inflammatory disease, several studies revealed that the administration of carboxymethylcellulose and polysorbate-80 to mice is sufficient to drive microbiota alterations in a way that increases its pro-inflammatory potential. Furthermore, emulsifier consumption is sufficient to induce microbiota encroachment, characterised by microbiota penetration of the typically sterile mucus layer that lines the intestinal mucosa. Altogether, these microbiota alterations lead to chronic intestinal inflammation that manifest as colitis in genetically susceptible hosts and as metabolic dysregulation in wild-type hosts.[114,134,149] Moreover, a 2021 double-blind controlled-feeding study investigated the effect of carboxymethylcellulose consumption on the intestinal microbiota and intestinal health in healthy human participants.[150] Results showed that carboxymethylcellulose consumption is sufficient to detrimentally alter the intestinal microbiota composition and faecal metabolome, showing the need for further studies focusing on the role played by long-term emulsifier consumption in healthy individuals and in various diseases characterised by a chronic intestinal inflammation state (eg, IBD or metabolic syndrome).[150]

Nanoparticles

Nanoparticles have unique chemical and physical properties due to their high surface-area-to-volume ratio. They are present in food products intentionally (originating from food additives or food supplements) or unintentionally (migration from food packaging).[151–153] To date, only a few studies have reported on interactions between nanoparticles and gut microbiota. In 2019, Pinget and colleagues showed how E171 (titanium dioxide), prevalent in UPFs, can alter the release of bacterial metabolites in vivo and promote biofilm formation in vitro.[154] Moreover, when relatively high levels of E171 were administered to mice, *Muc2* gene expression was reduced together with an increased expression of β-defensin, suggesting that titanium dioxide impairs the expression of some colonic key factors involved in gut homoeostasis.[154] Some studies have reported the presence of nanoparticles in colon biopsies of patients with IBD and colorectal cancer, whereas they were absent in colon biopsies of healthy patients.[155] Other studies, involving nanoparticle administration to mice, reported alteration of the *Firmicutes* to *Bacteroides* ratio, depletion of *Lactobacillus,* and enrichment of Proteobacteria in the mice's gut microbiota.[156] Another study showed that food-grade E171 impairs intestinal and systemic immune homoeostasis, initiating preneoplastic lesions in the colon and promoting aberrant crypt formation in rats.[157] Taken together, these data suggest a possible negative shift of the gut microbiota during the consumption of nanoparticles. However, more studies are needed to further characterise the mechanisms through which nanoparticles affect intestinal health and to carefully investigate the detrimental effect of doses carefully mimicking human exposure.

Conclusions

There is an urgent need for public research to explore and better understand the impact of food processing on human health, especially to identify which factors among additives and contaminants are causally involved. To

Search strategy and selection criteria

References for this narrative review were identified through searches of PubMed on Feb 10, 2022 with the search terms (with no date limitations): [((Ultraprocessed food[((Ultraprocessed food[Title/Abstract]) or (Ultra-processed food[Title/Abstract])) AND ((risk[Title/Abstract]) or (health[Title/Abstract]) or (diseases[Title/Abstract]) or (disease[Title /Abstract]) or (obesity[Title/Abstract]) or (health[Title/Abstract]) or (cancer[Title/Abstract]) or (cardiovascular[Title/Abstract]) or (diabetes[Title/Abstract]) or (hypertension[Title/Abstract]) or (mortality[Title/Abstract]))].) or (Ultra-processed food[Title])) AND ((risk[Title/Abstract]) or (health[Title/Abstract]) or (diseases[Title/Abstract]) or (disease[Title /Abstract]) or (obesity[Title/Abstract]) or (health[Title/Abstract]) or (cancer[Title/Abstract]) or (cardiovascular[Title/Abstract]) or (diabetes[Title/Abstract]) or (hypertension[Title/Abstract]) or (mortality[Title/Abstract]))]. Articles were also identified through searches of the authors' own files, their personal network, cross-referencing, and through citations on platforms such as ResearchGate. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review. Regarding epidemiological studies, all prospective studies (cohort, nested case-control, or nested case-cohort studies) with a calculated risk estimate, identified with this strategy and meta-analyses published until Feb 10, 2022, have been listed in this Review.

tackle such challenges, large-scale programmes are needed for both the epidemiological and mechanistic aspects. Such programmes should generate crucial data in the coming years and will serve as the scientific basis to guide further regulations (eg, reduction of authorised concentrations of some substances, or their prohibition altogether) and guidelines. Such guidelines could focus on the improvement of official national recommendations and food labelling or on providing evidence-based material to food choice smartphone applications, given that such applications are extensively used by consumers nowadays. While waiting for more scientific evidence in this field, it is crucial to guide consumers and help them make healthier food purchases, by encouraging the consumption of products with a better nutritional quality (eg, low in salt, sugar, and saturated fats, and rich in dietary fibre). In addition to nutritional quality, consumers should also be advised not to ignore the degree to which foods have been processed, and to prefer non-to-minimally processed products, without unnecessary additives. The UN Food and Agriculture Organization now recommends—in line with several national dietary guidelines—limiting UPF consumption.[159] Ultimately, governments and the food industry should join efforts to establish policies fostering a healthier food environment for consumers to help fight efficiently against the rising incidence of chronic inflammatory conditions. Future policies could also include monetary regulations; for example, they could add a specific tax on UPFs and on products with a poor nutritional profile, while making less-processed and nutritionally healthy foods more available and affordable. Finally, we believe that the intestinal microbiota should now be studied as a central actor for the assessment of food quality and safety to further regulate UPF production and additive usage. Knowledge of these UPF–microbiome–host interactions will help to gain a better understanding of mechanisms involved in the development of chronic diseases. These interactions will also offer innovative avenues for future research on microbiome-based diagnostic and therapeutic strategies to help to manage these diseases and establish new regulations to help to prevent their development.

Contributors

BS drafted the epidemiology section of the manuscript, supervised by MT. MCK and EB drafted the sections on mechanistic insights and intestinal microbiota for the manuscript, supervised by BC. BS, MCK, EB, MD-T, MT, and BC provided scientific and methodological input. All authors read and revised each draft of the full manuscript for important intellectual content. BS, MCK, and EB contributed equally and share co-first authorship. MT and BC contributed equally and share co-last authorship.

Declaration of interests

BC reports honorarium and consulting fees from Nestlé, Procter and Gamble, and Qiagen. All other authors declare no competing interests.

Acknowledgments

BC is supported by a Starting Grant from the European Research Council (ERC) under the EU's Horizon 2020 research and innovation programme (ERC-2018-StG- 804135), a Chaire d'Excellence from IdEx Université de Paris (ANR-18-IDEX-0001), an Innovator Award from the Kenneth Rainin Foundation, an ANR grant EMULBIONT (ANR-21-CE15-0042-01), and the national programme Microbiote from INSERM. MCK is supported by a fellowship from the French Foundation for Medical Research (Fondation pour la Recherche Médicale, Programme généraliste, Espoirs de la recherche, SPF202.110.013914). MT is the principal investigator for the ADDITIVES project, which has received funding from the ERC under the EU's Horizon 2020 research and innovation programme (864219), the French National Cancer Institute (INCa_14059), the French Ministry of Health (decision issued on Nov 29, 2019) and the IdEx Université de Paris (ANR-18-IDEX-0001). The ADDITIVES project was awarded the NACRe (French network for Nutrition And Cancer Research) Partnership Label. None of the funders were involved in the manuscript writing, or in the decision to submit it for publication.

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