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ASSOCIATION BETWEEN ULTRA-PROCESSED FOOD CONSUMPTION AND INFLAMMATION: INSIGHTS FROM THE STANISLAS COHORT

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KEYWORDS: Ultra-processed food; NOVA; Inflammation; Circulating protein; Olink; Fibroblast growth factor 19

ABSTRACT

Purpose High consumption of ultra-processed food (UPF) is associated with an increased risk of developing chronic diseases. Inflammation may be one of the underlying mechanisms behind this association. However, only a limited number of studies have investigated the association between UPF consumption and a few selected inflammation biomarkers, yielding inconsistent results. This study aimed to assess the cross-sectional association between UPF consumption (as a whole and 10 sub-categories), and 78 circulating proteins related to inflammation.

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Methods The present study included 1594 adult participants from the STANISLAS cohort. UPF consumption was estimated using the NOVA classification, and linear regression models were used to assess their association with circulating proteins.

Results UPFs accounted for 28% of the total energy intake and 5.7 servings on average per day. In the unadjusted model, 15 circulating proteins had a significant association with UPF consumption. After adjustment, only (FGF-19) was significantly associated with UPF consumption ($\beta = -0.02[-0.03; -0.003]$).

Conclusion UPF consumption was negatively associated with Fibroblast Growth Factor 19 (FGF-19) serum levels. When considering UPF sub-categories, no circulating proteins were associated with dairy products and dairy desserts. Of note, circulating proteins were differentially associated depending on the sub-category of UPF. Further studies are needed to better understand the link between UPF and inflammation.

Abbreviations

95%CI	95% Confidence intervals
ADII	Adapted Dietary Inflammatory Index
BMI	Body mass index
CRP	C -reactive protein
DASH	Dietary Approaches to Stop Hypertension
FDR	False discovery rate
FFQ	Food Frequency Questionnaire
FGF-19	Fibroblast growth factor 19
HDL	Plasma high-density cholesterol
IL	Interleukine
IPAQ	International Physical Activity Questionnaire
LDL	Plasma low-density cholesterol
NPX	Normalized protein expression
PEA	Proximity extension assay
PNNS	Programme National Nutrition Santé

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SCF	Stem cell factor
STANISLAS	Suivi Temporaire Annuel Non-Invasif de la Santé des Lorrains Assurés Sociaux
TNF-α	Tumor necrosis factor alpha
UPF	Ultra-processed food

Introduction

The past few decades have seen the global rise of ultra-processed foods (UPFs) [1, 2]. UPFs are industrial formulations, often containing additives, and undergo a series of highly denaturing technological processes [3, 4], which alter the food matrix and result in a loss of their original nutritional value [5, 6]. These convenient, ready-to-use and ready-to-eat products are highly attractive and have rapidly become part of our daily diet [1, 7]. However, their nutritional quality is low, as they contain very little vitamins and fiber, and are rich in saturated fats, salt and sugar [2, 8]. UPFs account for over one-third of the calorie intake in France [1, 9] and nearly 60% in the United States [10].

A food classification system, NOVA, developed by Monteiro et al., is now endorsed by the United Nations and the World Health Organization [3]. It categorizes food products based on their degree of processing and quality. The NOVA classification has enabled researchers to study the consumption of UPFs and their effects on health. Several studies have observed an increased risk of developing chronic diseases [11, 12], including obesity [13–17], type 2 diabetes [18, 19], cancer [20, 21], hypertension [22–24], cardiovascular disease (CVD) risk factors and CVD itself [25–29], depression [30–32], Crohn's disease [33, 34], irritable bowel syndrome [35], hyperuricemia [36] and non-alcoholic fatty liver [37], as well as a higher all-cause mortality risk [38–41]. In France, UPFs consumption has become a serious public health issue, leading the health authorities to implement into the national nutrition and health program (*Programme National Nutrition Santé 4, PNNS 4*) a recommendation that aimed at halting the rise of this consumption and reducing it by 20% between 2018 and 2021 [42]. The French Senate, alongside leading researchers, also issued a statement urging further research into the impacts of UPFs and their underlying mechanisms [43, 44].

While some underlying mechanisms have been proposed [44, 45], further studies are nonetheless needed to further explore these mechanisms. One of the underlying mechanisms may be

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inflammation. Indeed, inflammation is a catalyst for the development of chronic non-communicable diseases. Cytokines amplify the inflammatory response, increase cell proliferation, and lead to tissue degradation [46]. A more specific involvement of cytokines has also been demonstrated in cardiovascular disease [47]. One hypothesis could be that consuming UPFs leads to increased inflammation, creating a favorable environment for the development of chronic diseases.

Despite the above, only a few studies have investigated the association between UPFs consumption and certain biomarkers of inflammation, the latter of which have yielded inconsistent results [48–51]. In studies conducted in Brazilian populations, the association between C reactive protein (CRP) and UPFs consumption was not significant after adjustment for BMI in the ELSA—Brasil adult cohort study [48], while in young adults (21–23 years), interleukine (IL) 6 was significantly associated with UPFs consumption in men (Pelotas Cohort) and women (EPITeen Cohort) [51]. In another Brazilian adolescent population sample in which hsCRP, IL-6, TNF-α, adiponectin, leptin and IL-8 were investigated, only IL-8 was significantly positively associated with UPFs consumption[49]. hsCRP was also investigated in an Australian population in conjunction with the quantity of UPFs consumption in which results showed that every 100 g increase in UPFs intake was associated with a 4% increase in hsCRP [50].

This study aimed to further explore the cross-sectional association between UPFs consumption as a whole using the NOVA classification, as well as sub-categories, and circulating proteins from the Olink inflammatory panel and CRP.

Materials and methods

STUDY POPULATION

The STANISLAS (Suivi Temporaire Annuel Non-Invasif de la Santé des Lorrains Assurés Sociaux) family cohort study is a population-based study of 1,006 nuclear families consisting of 4295 participants recruited between 1993 and 1995 at the Center of Preventive Medicine. Participants were free of acute or chronic disease, were of French origin and living in the Lorraine region of France. Participants were followed every 5–10 years. The 4th visit was conducted from 2011 to 2016 and included 1705 adult participants. The details of the STANISLAS family cohort study have been published elsewhere [52].

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The present study focuses on the fourth visit in which circulating proteins were measured and food frequency questionnaire was given to estimate food intake allowing the determination of UPF intake. After excluding 10 participants without food intake data, 63 for aberrant energy intake either below 1,000 or above 5,000 kcal per day, 25 without circulating proteins data (Olink inflammatory panel), 1 without CRP serum level, and 12 without covariates data, the present cross-sectional analysis included a total of 1,594 adult participants (Fig. 1).

DATA COLLECTION

DIETARY ASSESSMENT

Dietary intake data were collected using a validated Food Frequency Questionnaire (FFQ) [53]. The participants reported their consumption frequency and portion size of 133 food and beverage items over the previous 3 months. Consumption frequency was reported using six levels in the questionnaire, ranging from "never or rarely" to "twice or more a day." The portion size of each food or beverage item was estimated using standard serving sizes and food models. Daily nutrient intakes were calculated in grams per day by multiplying the consumption frequency of each item by the nutrient content of selected portions using the French food composition database established by the French Data Center on Food Quality (Ciqual). Items were classified into four groups according to the NOVA Food Classification System [3]. Group 1: unprocessed or minimally processed foods, group 2: processed culinary ingredients, group 3: processed foods, and group 4: ultra-processed food products and beverages. Food items in group 4 were classified into ten sub-categories: Toast and breakfast cereals, Sugary products, Salty snacks, Meat and fish, Fast food and cooked dishes, Fats and sauces, Dairy products, Dairy desserts, Sugar-sweetened beverages, and Alcoholic beverages. UPFs consumption was expressed as serving per day. To obtain UPFs consumption in serving per day, the intake of group 4 in grams per day was divided by the quantity (in g) of a standard French serving size for each item [54]. We chose to use servings rather than weight in grams because UPFs are highly diverse, with portion sizes varying significantly across items (see Supplementary Table 1). Using servings provides a clearer and more meaningful approach, which has also been applied in previous study [55].

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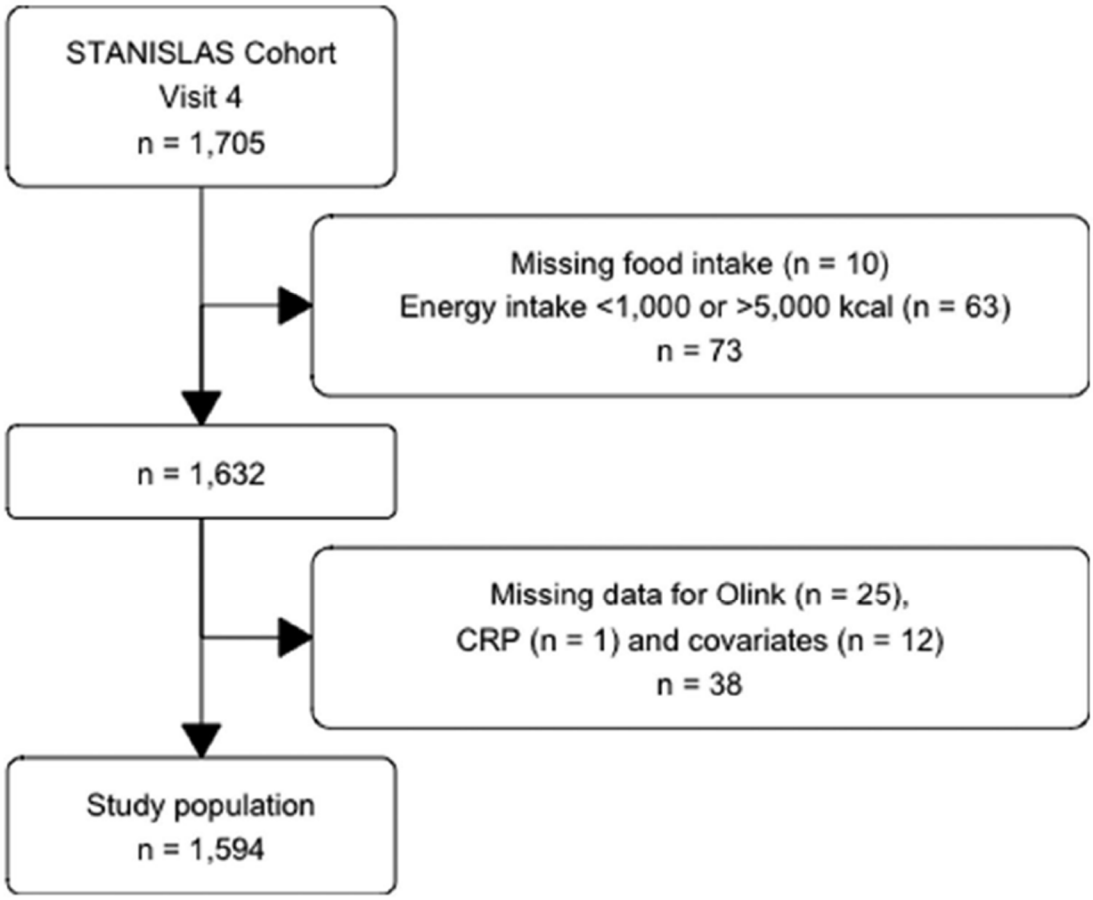
To assess the global quality of the diet, the Dietary Approaches to Stop Hypertension (DASH) score was used and calculated as the sum of 12 component scores: fruits, vegetables, grain products, whole grains products, dairy products, processed meat, fish, legumes, oils and fats, saturated fats, sugar and sweets, and sodium. Each component is assigned a value from 0 to 10 based on the DASH recommendations. The overall DASH score can range from 0 to 90, the higher the score, the better the nutritional quality of the diet [56, 57]. The Adapted Dietary Inflammatory Index (ADII) was also calculated to determine the inflammatory potential of the diet of the participants [57, 58]. The scoring system is based on the inflammatory weights of dietary components obtained based on the literature whereby an inflammatory weight is assigned to each dietary component according to their effect on biological inflammatory markers [57, 59]. A positive ADII score indicates a pro-inflammatory diet while a negative ADII score indicates an anti-inflammatory diet.

***Figure 1**: Flowchart of the study population*



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Outcome: circulating proteins

Circulating proteins were analyzed using the Olink Proseek® Multiplex inflammation panel. The Olink technique protein assay, which is based on Proximity Extension Assay (PEA) technology, allows for the simultaneous determination of 92 circulating proteins in 1µL of plasma. Briefly, samples were incubated with 92 antigen-specific antibody pairs with oligonucleotides, in which the antibody pairs bind to their antigen followed by the addition of DNA polymerase to promote extension. Formed DNA amplicons are amplified, and then quantified using a Fluidigm BioMark™ HD real-time PCR platform. The platform provides log2- normalized protein expression (NPX) data. A detailed description of the Olink technology is available in the White paper from Olink (https:// www. olink. com/ resou rces-suppo rt/ white- papers- from- olink). Circulating protein variables with more than 80% of data below the limit of detection were excluded from the statistical analysis (see Supplementary Table S2). The present analysis focused on 78 circulating proteins. CRP was measured using immunoturbidimetric methods.

Covariates

During the fourth visit, all participants underwent a clinical examination in which weight (kg), height (m) and waist circumference (cm) were measured, along with blood collection and urine sampling. Additionally, the participants completed several questionnaires assessing their sociodemographic characteristics such as education and income (€/month), medical history and treatment, as well as level of physical activity using the International Physical Activity Questionnaire (IPAQ). We considered physical activity into categories: low, moderate, high and missing. Moderate activity was defined as either: (1) 3 or more days of vigorous activity for at least 20 min/day, (2) 5 or more days of moderate activity or walking for at least 30 min/ day, or (3) any combination of activity types accumulating at least 600 MET-minutes/week. High activity was defined as either: (1) 3 or more days of vigorous activity totaling 1500 MET-minutes/week, or (2) 7 days of any combination of activities reaching at least 3000 MET-minutes/ week. Low activity included individuals who do not meet the criteria for the other two categories.

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STATISTICAL ANALYSIS

Study population characteristics were described as mean (standard deviation) or median (first quartile, 3rd quartile) as appropriate for continuous variables, while categorical variables are presented as frequencies (percentages). Linear regression models were performed to assess the association between UPFs consumption (total followed by subcategories as defined in the dietary assessment section) and circulating proteins. Regression coefficients and their 95% confidence interval are reported as ß (95% CI). Univariate analyses were first performed to identify proteins significantly associated with UPFs consumption. The resulting p-value of the association of each circulating protein was corrected for false discovery rate (FDR) using the Benjamini–Hochberg method. All significant circulating proteins with an FDR < 5% were subsequently considered in multivariable models: model 1 adjusting for sex and age, and model 2 for sex, age, metabolic syndrome, body mass index (BMI), anti-inflammatory and gastrointestinal medication intake, total energy intake, DASH score, physical activity and smoking status

The significance level was set at $p < 0.05$. All analyses were carried out using R software version 4.3.2.

Results

BASELINE CHARACTERISTICS

Table 1 describes the characteristics of the individuals included in the analyses. The study population (49% men) had a median (Q1, Q3) age of 56 (34, 60) years and a CRP level of 1.4 (0.7, 3.1) mg/L. In addition, 5% of the participants had diabetes and 25% had metabolic syndrome. UPFs accounted for an average of 28% of the daily energy intake and 5.6 servings on average per day (see supplementary Fig. 1 for distributions). The median ADII score was 0.46 (−1.6, 2.04), ranging from −16.32 to 8.09, suggesting that the diet was relatively neutral in terms of inflammation.

ASSOCIATION BETWEEN UPF CONSUMPTION AND CIRCULATING PROTEINS

In the univariate models, 15 circulating proteins were identified as significantly associated with UPF consumption (listed in Table 2). In model 1, adjusted for age and sex, five proteins remained significantly associated: CDCP1 (ß = 0.008[0.0006, 0.02]), CXCL9 (ß = − 0.01[− 0.02; −0.002]), LIF-R (ß =

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− 0.003[− 0.006; − 0.00002]), TRANCE (ß = 0.009[0.0003; 0.02]), and FGF-19 (ß = − 0.02 [− 0.03; − 0.007]) (Table 2). In the fully adjusted model, only FGF-19 was significantly associated with UPF consumption (β = − 0.02[− 0.03; − 0.003]). No interaction with BMI was found (all p-value > 0.10).

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Table 1 *Characteristics of the study population*

Characteristics	N = 1594	Q1 < 3.05 serving/day	Q2 3.05–4.8 serving/day	Q3 4.8–7.4 serving/day	Q4 > 7.4 serving/day	p-value
Socio-demographic characteristics						
Age (years)	56 (34, 60)	58(51–62)	57(37–61)	54(34–60)	38(31–57)	< 0.001
Men	774 (49%)	158 (39.3)	181 (45.1)	212 (52.9)	227 (56.5)	< 0.001
Education						
< High school degree	667 (42%)	184 (45.8)	182 (45.4)	159 (39.7)	147 (36.7)	0.014
0–2 years after high school	524 (33%)	119 (29.6)	111 (27.7)	145 (36.2)	154 (38.4)	
> 2 years after high school	402 (25%)	99 (24.6)	108 (26.9)	97 (24.2)	100 (24.9)	
Income (€/month)						
Less than 750	196 (12%)	51 (12.7)	40 (10.0)	51 (12.7)	56 (14.0)	0.324
750–1499	305 (19%)	70 (17.4)	86 (21.6)	73 (18.2)	80 (20.1)	
1500–2249	327 (21%)	74 (18.4)	75 (18.8)	87 (21.7)	93 (23.3)	
2250–2999	546 (34%)	145 (36.1)	136 (34.1)	144 (35.9)	125 (31.3)	
3000–4999	168 (11%)	51 (12.7)	50 (12.5)	33 (8.2)	34 (8.5)	
5000–10,000	47 (3%)	11 (2.7)	12 (3.0)	13 (3.2)	11 (2.8)	
Physical activity categories						
Low activity	481 (30.0)	123 (30.6)	106 (26.4)	125 (31.2)	127 (31.6)	0.388
Moderate activity	488 (30.4)	113 (28.1)	135 (33.7)	114 (28.4)	126 (31.3)	
High activity	355 (22.1)	101 (25.1)	90 (22.4)	89 (22.2)	75 (18.7)	
Missing	282 (17.6)	65 (16.2)	70 (17.5)	73 (18.2)	74 (18.4)	
Physical activity (MET-min/week)	1782 (643, 4217)	1856 (792, 4137)	1698 (530, 4068)	1864 (673, 4802)	1704 (599, 4351)	0.617
Smoking status						
Current smoker	328 (21%)	53 (13.2)	64 (16.0)	91 (22.8)	123 (30.6)	< 0.001
Never smoker	747 (47%)	205 (51.1)	203 (50.7)	169 (42.2)	173 (43.0)	
Past smoker	519 (33%)	143 (35.7)	133 (33.2)	140 (35.0)	106 (26.4)	
Clinical and biological characteristics						
BMI (kg/m^2)	25.1 (22.5, 28.4)	25 (22.7, 28.1)	25.1 (22.4, 28.5)	25.2 (22.6, 28.3)	25.1 (22.4, 28.8)	0.962
BMI in classes						
Health weight	784 (48.9)	200 (49.9)	198 (49.4)	189 (47.2)	197 (49.0)	0.486
Participants with overweight	540 (33.7)	140 (34.9)	131 (32.7)	145 (36.2)	124 (30.8)	
Participants with obesity	280 (17.5)	61 (15.2)	72 (18.0)	66 (16.5)	81 (20.1)	
Waist circumference (cm)	89 (80, 99)	88 (78, 98)	88 (79, 97.75)	90 (80, 100)	90 (81, 99)	0.157
Dyslipidemia	292 (18%)	93 (23.1)	95 (23.7)	54 (13.5)	52 (12.9)	< 0.001
Diabetes	94 (5.9%)	25 (6.2)	29 (7.2)	17 (4.2)	23 (5.7)	0.335
Pre-diabetes	551 (35%)	160 (39.8)	147 (36.7)	139 (34.7)	109 (27.1)	0.001
Hypertension	370 (23%)	114 (28.4)	106 (26.4)	85 (21.2)	68 (16.9)	< 0.001
Metabolic syndrome	394 (25%)	110 (27.4)	115 (29.0)	89 (22.4)	81 (20.1)	0.011
CRP (mg/L)	1.40 (0.70, 3.10)	1.40 (0.70, 3.00)	1.30 (0.70, 2.90)	1.50 (0.80, 3.30)	1.60 (0.72, 3.50)	0.229
Fasting glucose (g/L)	0.88 (0.83, 0.95)	0.89 (0.83, 0.96)	0.89 (0.83, 0.97)	0.88 (0.82, 0.95)	0.87 (0.82, 0.94)	0.004
HDL-C (g/L)	0.58 (0.14)	0.6 (0.5, 0.7)	0.6 (0.5, 0.7)	0.6 (0.5, 0.6)	0.5 (0.5, 0.6)	< 0.001
LDL-C (g/L)	1.34 (0.34)	1.3 (1.1, 1.6)	1.3 (1.1, 1.6)	1.3 (1.1, 1.6)	1.3 (1.1, 1.5)	0.007
Triglycerides (g/L)	0.92 (0.67, 1.26)	0.9 (0.7, 1.2)	1 (0.7, 1.3)	0.9 (0.7, 1.3)	0.9 (0.7, 1.3)	0.589
Food characteristics						
Total energy intake (kcal/day)	2236 (1751, 2850)	1801 (1400, 2239)	2042 (1651, 2443)	2290 (1859, 2802)	3005 (2471, 3546)	< 0.001

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Alcohol consumption (g/day)	5 (1, 13)	4 (1, 10)	5 (1, 13)	5 (2, 14)	6 (2, 16)	<0.001
DASH score	46.2 (7.7)	50.6 (45.9, 55.1)	48 (43.4, 52.4)	44.7 (40.6, 49.9)	41.7 (37.1, 46.3)	<0.001
ADII score	0.46 (−1.60, 2.04)	−0.1 (−2, 1.5)	0.3 (−1.7, 1.7)	0.6 (−1.3, 2.3)	1 (−1.3, 2.7)	<0.001
Dieting	145 (9.1%)	38 (9.5)	33 (8.2)	34 (8.5)	42 (10.4)	0.684
Total ultra-processed food intake (serving/day)	5.7 (3.7)	2.2 (1.5, 2.6)	3.9 (3.5, 4.3)	6 (5.4, 6.7)	9.6 (8.4, 12.2)	<0.001
Total ultra-processed food intake (g/day)	343.1 (204.2, 550.8)	149.2 (94.4, 198.9)	287.2 (221.4, 348.8)	440.2 (354.5, 543)	725.7 (558.5, 937.4)	<0.001
Total ultra-processed food intake (% of energy intake)	28.1 (20.0, 38.3)	16.3 (11.1, 22.4)	25.3 (19.9, 31.7)	32.5 (26, 39.7)	41.1 (34.2, 48.5)	<0.001
Medication intake						
Anti-hypertensive	324 (20%)	107 (26.6)	86 (21.4)	74 (18.5)	59 (14.7)	<0.001
Lipid-lowering	246 (15%)	78 (19.4)	78 (19.5)	45 (11.2)	46 (11.4)	<0.001
Anti-diabetic	60 (3.8%)	17 (4.2)	18 (4.5)	14 (3.5)	11 (2.7)	0.555
Anti-inflammatory	54 (3.4%)	14 (3.5)	10 (2.5)	13 (3.2)	17 (4.2)	0.594
Gastrointestinal	130 (8.2%)	44 (10.9)	32 (8.0)	28 (7.0)	27 (6.7)	0.110

The data are presented as median (interquartile range: Q1, Q3) or mean (standard deviation) or n (%), as appropriate

BMI Body Mass Index, *CRP* C-reactive protein, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *DASH* dietary approaches to stop hypertension, *ADII* Adapted Dietary Inflammatory Index

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Table 2 *Multi-adjusted association between ultraprocessed food consumption (1 serving/day) and circulating proteins (n = 1594)*

Circulating proteins	Model 1		Model 2	
	ß(95%CI)	p-value	ß(95%CI)	p-value
CDCP1	0.008 (0.0006, 0.02)	**0.04**	−0.002 (−0.01, 0.008)	0.69
OPG*	0.0007 (−0.004, 0.005)	0.75	0.0002 (−0.006, 0.006)	0.95
uPA**	−0.0009 (−0.005, 0.003)	0.67	−0.002 (−0.008, 0.003)	0.37
MCP 1**	0.0006 (−0.005, 0.007)	0.89	−0.004 (−0.01, 0.004)	0.3
CXCL9**	−0.01 (−0.02, −0.002)	**0.017**	−0.008 (−0.02, 0.005)	0.24
CST5*	−0.006 (−0.01, 0.0007)	0.08	−0.008 (−0.02, 0)	0.05
CCL11**	−0.0002 (−0.007, 0.006)	0.96	−0.006 (−0.01, 0.002)	0.16
FGF 5	−0.002 (−−0.005, 0.001)	0.21	−0.001 (−0.006, 0.003)	0.47
LIF R*	−0.003 (−0.006, −0.00002)	**0.049**	−0.001 (−0.005, 0.002)	0.47
TRANCE	0.009 (0.0003, 0.02)	**0.042**	0.011 (0, 0.02)	0.05
Flt3L	−0.0009 (−0.006, 0.005)	0.67	−0.004 (−0.01, 0.003)	0.31
CXCL10**	−0.008 (−0.02, 0.003)	0.16	−0.007 (−0.02, 0.007)	0.33
CCL28*	−0.0005 (−0.007, 0.006)	0.89	−0.0002 (−0.008, 0.008)	0.96
FGF 19	−0.02 (−0.03, −0.007)	**0.001**	−0.018 (−0.03, −0.003)	**0.02**
CCL25**	0.00002 (−0.007, 0.007)	0.98	−0.018 (−0.03, −0.003)	0.20

Model 1: adjusted for age and sex. Model 2: model 1 further adjusted for metabolic syndrome, BMI, antiinflammatory and gastrointestinal medication intake, total energy intake, DASH score, physical activity and smoking status.

**Anti-inflammatory*

***Pro-inflammatory*

Other proteins are involved in inflammatory processes but not directly classified as specifically anti-inflammatory or pro-inflammatory

ASSOCIATION BETWEEN UPF SUB-CATEGORIES CONSUMPTION AND CIRCULATING PROTEINS

In univariate analysis (Supplementary Table S3), no circulating proteins were associated with dairy products and dairy dessert UPFs sub-categories. Several circulating proteins had a different significant association depending on the considered UPFs sub-category. Results from the adjusted

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linear regression analysis are shown in Table 3. In the fully adjusted model, no associations were observed for toast and breakfast cereals, fast food and cooked dishes sub-categories. Foods in the sugary products sub-category were significantly associated with CRP (ß = − 0.05 [− 0.08; − 0.008]), SCF (ß = 0.03 [0.02; 0.04]) and PD-L1(ß = 0.03 [0.01; 0.05]). The salty snacks sub-category was significantly associated with IL-17A (ß = 0.4[0.2; 0.6]). The meat and fish sub-category were significantly associated with IL-12B (ß = − 0.10 [− 0.20; − 0.01]), fats and sauces sub-category with FGF-19 (ß = − 0.04[− 0.06; − 0.009]), and sugar-sweetened beverages sub-category with SCF (ß = − 0.02[− 0.04; − 0.01]). The alcoholic beverages sub-category was significantly associated with CXCL9 (ß = − 0.08[− 0.15; − 0.02]), CD6 (ß = − 0.06[− 0.11; − 0.02]), SCF (ß = − 0.05[− 0.09; − 0.02]), FGF21 (ß = 0.3[0.2; 0.4]), IL-12B (ß = − 0.08[− 0.1; − 0.03]), CD5 (ß = −0.04[− 0.07; − 0.01]), TNFRSF9 (ß = − 0.07[− 0.11; − 0.04]), TWEAK (ß = − 0.03[− 0.06; − 0.001]) and TNFB (ß = − 0.06[− 0.1; − 0.02]). SCF was common in the sugary products, sugar-sweetened beverages, and alcoholic beverages sub-categories. IL-12B in meat and fish and alcoholic beverages. Interactions with weight status were found for 10 proteins (supplementary Table 4).

Discussion

In the present cohort, UPF consumption was negatively associated with FGF-19 (β = − 0.02[− 0.03; − 0.003]). Further examination into various sub-categories revealed that some categories, i.e. ultra-processed dairy products and dairy desserts, were not at all associated with circulating inflammation proteins, while some were associated in minimally adjusted models but not in the fully adjusted models, e.g., for toast and breakfast cereals, and fast food and cooked dishes sub-categories. Other subcategories were differentially associated with circulating proteins.

ULTRA-PROCESSED FOODS AS A WHOLE AND INFLAMMATION

Compared to the limited epidemiological studies available on the relationship between UPFs and a few selected markers of inflammation, a novelty of the present study is the investigation of a large set (n = 78) of circulating proteins from the Olink inflammatory panel and CRP. Although 15 circulating proteins were identified in univariate models as significantly associated with UPFs consumption, only FGF19 remained significantly and negatively associated with UPFs consumption after adjustment for all confounders.

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FGF-19 is a postprandial enterokine [60] and plays a key role in whole-body homeostasis, regulating glucose homeostasis, glycogen and protein synthesis, and primary bile acid metabolism [60, 61]. FGF-19 is thought to be a protector in pancreatic beta-cell dysfunction [62], and in atherosclerosis in patients with type 2 diabetes [63]. Elevated FGF-19 levels are associated with reduced bile acid levels [61] and modulation of intestinal bile acid composition, protecting against intestinal inflammation and maintaining intestinal barrier integrity while influencing microbiota composition. Furthermore, there is evidence of a negative correlation between FGF-19 levels and obesity, with lower circulating FGF-19 levels observed in patients with obesity [64].

UPFs consumption has been linked to an increased risk of developing obesity [13–17] and type-2 diabetes [18]. FGF19 may hence be an underlying mechanism between UPFs consumption and these diseases. To our knowledge, our study is the first to highlights UPFs consumption as being associated with a decreased rate of FGF-19, thereby suggesting that FGF-19 may represent a propitious therapeutic avenue in a number of diseases. Further studies are warranted to validate and expand upon these findings.

The few existing studies assessing the association of UPFs consumption and inflammation biomarkers were predominantly focused on a limited number of circulating proteins such as CRP, IL-6, TNF-α, adiponectin, leptin or IL-8 [29, 48, 4951]. CRP was not associated in fully adjusted models in these studies [48, 49]. IL-6 was found associated with UPFs in a Brazilian study involving young adults [51], but not in similar Brazilian study involving adolescents [49]. In this latter study, IL-8 was found associated with UPFs consumption whereas TNF-α, adiponectin, and leptin were not [49]. No association was found in the present study between UPFs and CRP or IL-6, indicating that the relationship between UPF and typical inflammatory biomarkers is not clear-cut and requires further investigation. It should be noted that our population was relatively exempt from inflammation as evidenced by a median CRP of 1.4 and ADII score of 0.45, suggesting a relatively neutral diet with regard to inflammation. Furthermore, in our population, UPFs contributed to 28% of the total energy intake which is slightly less compared to other French populations, namely 31% in the Etude National Nutrition Santé study and 35.9% in the NutriNet-Santé study [1, 9]. This could also contribute to the fact that we did not find any association with known key mediators of inflammation such as IL6.

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SUB-CATEGORIES OF ULTRA-PROCESSED FOODS AND INFLAMMATION

UPF is often considered as a whole, although it is not clear whether each sub-category triggers the same inflammatory response. FGF-19 was found to be associated with total UPFs consumption, although it was associated only with one sub-category, i.e. fats and sauce. We did not identify common biomarker across all sub-categories, suggesting that each may have distinct effects. Salty snacks were positively associated with IL-17A. It has already been demonstrated that a high salt diet affects the endothelium of blood vessels by reducing the availability of nitric oxide, mediated by IL-17, leading to a stiffening of the blood vessels [65]. Additionally, IL-17 was found to reduce renal sodium excretion resulting in its accumulation in serum [65]. By way of these mechanisms, a high salt diet increases systemic vascular resistance, leading to hypertension.

In a study by De Koning and al., the intake of sugar sweetened beverages (not artificially sweetened) food groups was found to be associated with an increase in CRP and IL-6, while artificially sweetened beverage intake was not associated with biomarkers in men [66]. Our results on the sugar-sweetened beverages UPF sub-category, which contains artificially sweetened beverages, showed that it was not significantly associated with CRP or IL-6 in the fully adjusted model. This sub-category is composed mostly of fruit juices containing vitamin C, an antioxidant, which reduces aspects of the inflammatory response [67].

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Table 3 *Multi-adjusted association between sub-categories of ultra-processed foods consumption (1 serving/day) and circulating proteins (n = 1594)*

UPFs sub-categories	Circulating proteins	Model 1		Model 2	
		ß(95%CI)	p-value	ß(95%CI)	p-value
Salty snacks					
	IL-17A**	0.37 (0.2, 0.6)	**0.0006**	0.394 (0.2, 0.6)	**<0.001**
Sugary products					
	SCF**	0.03 (0.01, 0.04)	**8.9^{e-5}**	0.03 (0.02, 0.04)	**<0.0001**
	FGF-21	−0.04 (−0.08, −0.003)	**0.04**	− 0.04 (− 0.08, 0.003)	0.07
	CRP	−0.04 (−0.08, −0.002)	**0.04**	− 0.05 (− 0.08, − 0.008)	**0.02**
	PD-L1	0.03 (0.007, 0.04)	**0.006**	0.03 (0.01, 0.05)	**<0.01**
Sugar-sweetened beverages					
	CDCP1	0.02 (0.002, 0.04)	**0.03**	0.01 (− 0.009, 0.03)	0.29
	SCF**	−0.03 (−0.04, −0.01)	**8.7^{e-5}**	− 0.02 (− 0.04, − 0.01)	**<0.001**
	TRANCE/TNFSF11	0.02 (0.0002, 0.04)	**0.048**	0.02 (− 0.003, 0.03)	0.29
Alcoholic beverages					
	IL6***	0.1 (0.05, 0.2)	**0.0007**	0.07 (− 0.006, 0.1)	0.03
	CXCL9**	−0.1(−0.2, −0.04)	**0.003**	− 0.08 (− 0.15, − 0.02)	**0.02**
	OSM**	0.1 (0.03, 0.2)	**0.006**	0.06(− 0.02, 0.05)	0.41
	CD6	−0.07 (−0.1, −0.03)	**0.001**	− 0.06 (− 0.11, − 0.02)	**0.01**
	SCF**	−0.07 (−0.1, −0.04)	**3.1^{e-5}**	− 0.05 (− 0.09, − 0.02)	**<0.01**
	FGF-21	0.3 (0.2, 0.4)	**7.4^{e-12}**	0.3 (0.2, 0.4)	**<0.0001**
	IL-12B**	−0.1 (−0.2, −0.07)	**1.3^{e-5}**	− 0.08 (− 0.1, − 0.03)	**<0.01**
	CD5	−0.03 (− 0.06, −0.005)	**0.02**	− 0.04 (− 0.07, − 0.01)	**0.001**
	TNFRSF9**	−0.06 (− 0.1, −0.03)	**0.0002**	− 0.07 (− 0.1, − 0.04)	**<0.0001**
	TWEAK**	−0.05 (− 0.08, −0.02)	**0.0005**	− 0.03 (− 0.06, − 0.004)	**0.03**
	TNFB**	−0.07 (−0.1, −0.03)	**0.001**	− 0.06 (− 0.1, − 0.02)	**<0.01**
Toast and breakfast cereals					
	CCL4**	−0.06 (−0.1, −0.01)	**0.03**	− 0.04 (− 0.1, 0.02)	0.18
	IL-18R1**	−0.04 (−0.07, −0.0008)	**0.046**	− 0.02 (− 0.07, 0.02)	0.37
	CRP	−0.1 (−0.2, −0.03)	**0.01**	− 0.04 (− 0.1, 0.05)	0.37
	CCL3**	−0.06 (−0.1, −0.009)	**0.02**	− 0.03 (− 0.08, 0.02)	0.19
Meat and fish					
	CXCL9**	−0.1 (−0.2, −0.1)	**0.03**	− 0.07 (− 0.2, 0.04)	0.23
	IL-12B**	−0.1 (−0.2, −0.03)	**0.007**	− 0.10 (− 0.2, − 0.01)	**0.03**
	FGF-19	−0.2 (−0.3, −0.05)	**0.004**	− 0.10 (− 0.3, 0.002)	0.06
	TWEAK**	−0.06 (−0.1, −0.02)	**0.007**	− 0.03 (− 0.08, 0.02)	0.21
Fast food and cooked dishes					
	HGF	0.06 (0.01, 0.1)	**0.01**	0.02 (− 0.02, 0.07)	0.36
	CXCL10**	−0.1 (−0.2, 0.01)	**0.03**	− 0.1 (− 0.2, 0.002)	0.05
Fats and sauces					
	IL6***	0.04 (0.01, 0.06)	**0.002**	0.002 (− 0.02, 0.03)	0.88
	IL-18R1**	0.02 (0.004, 0.03)	**0.008**	0.006 (− 0.007, 0.02)	0.34
	CRP	0.05 (0.02, 0.08)	**0.002**	− 0.001 (− 0.03, 0.03)	0.93
	HGF	0.01 (8e^{-5}, 0.02)	**0.048**	− 0.005 (− 0.02, 0.008)	0.46
	FGF-19	−0.05 (−0.07, −0.02)	**0.0003**	− 0.04 (−0.06, − 0.009)	**0.01**
	TWEAK**	−0.02 (−0.03, −0.007)	**0.001**	− 0.009 (− 0.01, 0.03)	0.29

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Model 1: adjusted for age and sex. Model 2: model 1 further adjusted for metabolic syndrome, BMI, anti-inflammatory and gastrointestinal medication intake, total energy intake, DASH score, physical activity, and smoking status

[*] *Anti-inflammatory*

[**] *Pro-inflammatory*

[***] *Anti- and pro-inflammatory. Other proteins are involved in inflammatory processes but not directly classified as specifically anti-inflammatory or pro-inflammatory. The table lists only circulating proteins with a significant association in model 1*

The alcoholic beverages sub-category was negatively associated with pro-inflammatory circulation proteins like CXCL9, IL-12B, TNFRSF9, TWEAK and TNFB. In the general population from three different European countries, alcohol consumption of up to 40 g/day was associated with higher concentrations of anti-inflammatory biomarkers and lower levels of pro-inflammatory markers of systemic inflammation [68]. Some studies have also identified pro-inflammatory biomarkers as mediators in the relationship between moderate alcohol consumption and health outcomes, such as reduced frailty or depressive symptomatology [69, 70]. This evidence suggests that moderate alcohol use may confer health benefits, at least in part, by reducing pro-inflammatory biomarkers. One proposed explanation is that moderate alcohol consumption often involves drinking wine, which is rich in polyphenols, such as resveratrol and flavonoids, known for their positive metabolic effects [71]. However, in our study, ultra-processed alcoholic beverages do not include fermented drinks, which are categorized by NOVA system as processed rather than ultra-processed items [3]. This distinction suggests that other mechanisms, potentially related directly to alcohol itself may play a role. Supporting this, studies have demonstrated that in vitro and in vivo ethanol exposure can inhibit the production of the proinflammatory cytokine TNF-α while promoting the production of the anti-inflammatory cytokine IL-10 [72, 73]. Although common biomarker for all sub-categories could not be found in the present analysis, certain circulating proteins were associated with several UPF sub-categories: For instance, stem cell factor (SCF) was significantly associated with sugary products, sugar-sweetened beverages and alcoholic beverages while IL-12B was significantly associated with meat and fish and alcoholic beverages.

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SCF is a dimeric molecule that binds to the tyrosine kinase c-Kit receptor to activate a variety of biological processes such as vasculogenesis and cardiac repair [74, 75]. In a study using the Olink Cardiovascular (CVD-I) panel, participants with higher consumption of UPFs had significantly elevated SCF levels, but interestingly participants with a high level of SCF had a lower risk for cardiovascular events.[29]. In the present study, SCF was positively associated with sugary products and negatively associated with sugar-sweetened beverages, and alcoholic beverages sub-categories. We can hypothesize that an excessive sugar consumption through sugary products increases SCF. We hypothesize that bioactive compounds (e.g., flavonoids) in SSB like fruit juices [76, 77] and certain alcoholic beverages [68] like wine may reduce the pro-inflammatory effects of excess sugar. Nonetheless, to the best of our knowledge, except the study of Li et al., 2023, no studies have focused on the link between nutrition and SCF. Then, further studies are needed to clarify this association.

IL-12B is a heterodimeric pro-inflammatory cytokine subunit of IL12 and plays a key role in promoting type 1 T helper cells in host defense against infection [78, 79]. Altered expression of IL12 may also be associated with esophageal squamous carcinoma progression [80]. UPFs consumption may increase the risk of developing cancer [20, 21]. IL12B may be involved in the inflammatory responses triggered by UPFs consumption and constitute an underlying mechanism between UPFs consumption and cancer. Therefore, further studies are necessary to confirm and expand upon these findings.

Certain UPF subcategories in the present study such as dairy products and dairy desserts were notably not associated with circulating inflammation proteins. The dairy product food group is known to be anti-inflammatory [81], and our results show that ultra-processed dairy products were not significantly associated with inflammation. It may be suggested that while ultra-processing may lead to the loss of the anti-inflammatory benefit of dairy products, it does not appear to increase the inflammatory potential.

STRENGTHS AND LIMITATIONS

The present study features several strengths. The analyses were based on a large population-based cohort with detailed information on diet, lifestyle and clinical factors, as well as including a large set of circulating proteins from the Olink inflammatory panel. This is also the first study to focus on inflammation and ten UPFs sub-categories. However, certain limitations of this study should be

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acknowledged. First, the results are based on cross-sectional data and causality cannot be implied due to the study's observational nature. Second, a validated 133 items-FFQ was used, and not a specific questionnaire designed to collect data based on the NOVA classification; thus, some food items were not included (e.g. pre-prepared dishes, slimming products, etc.). In addition, the fast food and cooked dishes category included only certain items. Third, the tools used to collect dietary food, and also the way to consider UPF intake (% of energy intake, g/day and also servings/day) vary across studies and may explain between-study differences. Fourth, the PEA technology utilized for this proteomics analysis, while ensuring an elevated degree of sensitivity, provides information in terms of relative abundance (NPX values) [82] but not in terms of absolute quantity. Thus, further studies are needed to confirm these abundance data into absolute quantities by mass spectrometry techniques. Fifth, due to the limited numbers of participants with diabetes, we were unable to assess the associations between UPFs consumption and inflammatory biomarkers according to diabetes status.

Lastly, the generalizability of our results may be limited due to the inclusion of participants solely from the Lorraine region, albeit with a similar UPF intake to that of the rest of France [1]. Further studies are necessary to confirm these findings.

CONCLUSIONS

This study provides novel insight into the link between the consumption of ultra-processed food and inflammation, exploring a large set of circulating proteins related to inflammation. Our findings suggest that consumption of ultra-processed food is negatively associated with FGF-19 serum levels. In addition, our results indicate that several circulating proteins were differentially associated according to the UPFs sub-category suggesting potentially promising targets for further studies focusing on the link between UPFs consumption and inflammation as well as chronic disease.

Supplementary Information The online version contains supplementary material available at https://d oi.org/1 0 .1007 /s 00394-025-0 3607- y.

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Author contributions PR, NG, and JMB designed the fourth visit of the STANISLAS cohort. CL managed the samples of the cohort. Food data were verified and corrected by LV, SW, J-AN, and AH. LM performed the data Management. SW, JMB, NG, and LLCHX designed the present research. LLCHX performed the statistical analysis with the assistance of ZL and KD. LLCHX and SW drafted the first version of the manuscript. All authors were involved in the interpretation of the results and the critical review of the manuscript.

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Data availability The data that support the findings of this study are available upon reasonable request by contacting the corresponding author.

Declarations

Conflict of interest NG has received honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Lilly, Novartis, Novo Nordisk, Roche Diagnostics, NP Medical, and Echosens. The other co-authors declare that they have no conflict of interest.

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