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The association between ultra-processed food consumption and low-grade inflammation in childhood: A cross-sectional study

Burak Mete[1] | **Hatice Merve Sadıkoğlu**[1] | **Hakan Demirhindi**[1] | **Ebru Melekoglu**[2] | **Adnan Barutcu**[3] | **Tuba Makca**[1] | **Fatma Atun Utuk**[4]

[1]Department of Public Health, Faculty of Medicine, Cukurova University, Adana, Turkey

[2]Department of Nutrition and Dietetics, Faculty of Health Sciences, Cukurova University, Adana, Turkey

[3]Department of Child Health and Diseases, Department of Social Pediatrics, Faculty of Medicine, Cukurova University, Adana, Turkey

[4]Department of Family Medicine, Faculty of Medicine, Mersin University, Mersin, Turkey

Correspondence
Burak Mete, Department of Public Health, Faculty of Medicine, Cukurova University, Adana 01330, Turkey.
Email: burakmete2008@gmail.com

Abstract

This study aimed to investigate the relationship between the amount of ultra-processed food (UPF) in the diet and low-grade inflammation in children. This cross-sectional study was conducted in 50 healthy children recruited from children attending the Social Paediatrics Outpatient Clinic for follow-up of normal developmental stages. Low-grade inflammation was calculated by INFLA-score, dietary intake by three 24-h dietary recalls and dietary content analyses by BeBiS™ software. The mean age of the 50 children included in our study was 10.18 ± 3.98 years (5–17 years). UPF accounted for 24.5% of the total daily energy intake of children. In children with higher inflammation scores (INFLA-score ≥ 2), the amount in grams of UPF and the percentage of total energy from UPF were found to be significantly higher ($p = 0.030$ and $p = 0.015$, respectively). A weak positive correlation was found between the INFLA-score and the percentage of daily dietary energy intake coming from UPFs ($r = 0.350$, $p < 0.01$), the average daily energy intake from UPFs ($r = 0.313$, $p < 0.05$), and the average daily amount of UPF consumed ($r = 0.260$, $p < 0.05$). The linear regression model revealed that every one-unit increase (1%) in the percentage of total daily energy intake coming from UPF caused an increase in $\beta = 0.154$-unit in the INFLA-score. It was found that obesity was not a mediator in the association between the percentages of total energy intake from UPF on the INFLA-score, instead, the energy intake from UPF had a significant direct association with the INFLA-score. The average amount of UPF consumed daily showed an increasing pattern in parallel with inflammation-score quartile classes (Q1 to Q4) with 33.3% in Q1, 38.5% in Q2, 53.8% in Q3 and 66.7% in Q4 ($p = 0.049$). In conclusion, a positive association was found between low-grade inflammation and UPF consumption in children, independent of obesity.

KEYWORDS
child, food processing industry, inflammation

INTRODUCTION

Food processing is an important activity that has been carried out since prehistoric times to help people cope with food shortages. However, with the industrial revolution, the negative effects of food processing and processing techniques on healthy nutrition have come to the fore (Augustin et al., 2016). Ultra-processed food (UPF) refers to ready-to-eat industrial products made entirely or predominantly from substances derived from foods, food components or laboratory-synthesised components based on organic materials. These foods generally present an unbalanced nutrient composition and have low levels of fibre and protein

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content, lacking micronutrients and phytochemicals. They also tend to be rich in free sugars, *trans* fats and sodium (Lane et al., 2021; Marino et al., 2021; Moradi et al., 2021; Pagliai et al., 2021). UPFs are one of the cornerstones of today's Western diet and their consumption is gradually increasing, leading to various health problems (Marino et al., 2021). In many meta-analyses conducted in adults, it was found that high UPF consumption was associated with obesity, diabetes, hypertension, metabolic syndrome, cardiovascular disease, breast cancer, depression and increased risk of anxiety, with an associated rise in the risk of all-cause mortality (Fiolet et al., 2018; Lane et al., 2021; Lane, Gamage, et al., 2022; Moradi et al., 2021; Pagliai et al., 2021; Suksatan et al., 2021; Taneri et al., 2022). UPF consumption has also been found to be associated with obesity in studies conducted in children and adolescents (Costa et al., 2018). However, the mechanisms behind these observed associations are unclear and are likely to encompass a variety of behavioural and physiological factors, including palatability, nutrient composition, glycaemic index, energy density and eating rate as well as the non-nutritive components of UPF such as additives and their effects on gut health or the products of processing such as advanced glycation end-products (Tristan Asensi et al., 2023). One proposed mechanism is that increased consumption of UPF may lead to inflammation and increase the incidence of various non-communicable diseases (Monteiro et al., 2019).

The presence of low-grade inflammation modifies the communication between immune and metabolic responses by altering the homeostatic balance and this leads to chronic metabolic inflammation. This so-called 'meta-inflammation' is primarily caused by metabolic and nutrient excess and triggers the infiltration of immune cells in tissues and the release of inflammatory cytokines (Marshall et al., 2018). In general, a higher anti-inflammatory potential is reported in dietary patterns rich in vegetables, fruits and wholegrains, low in red (animal) meat, and moderate in fish and legume content, polyphenols, some vitamins, minerals and trace elements. In contrast, diets containing some macronutrients, especially in high percentages, such as diets high in carbohydrates/glycaemic index, fat, saturated or *trans* fatty acids, cholesterol or animal and meat protein are reported to be pro-inflammatory (Ramos-Lopez et al., 2022). However, the number of human studies investigating whether consumption of UPFs may increase low-grade inflammation and thus contribute to the development of non-communicable diseases is limited, particularly in children. Studies in adults trying to explain the relationship between UPF and inflammation generally focus on two issues; firstly, how excessive consumption of UPF may affect the presence of inflammation markers and secondly, how UPF may affect the development of chronic inflammation and intestinal dysbiosis (Tristan Asensi et al., 2023). In our study, we aimed to evaluate the relationship between the amount of UPF in the daily diet and low-grade inflammation in children and to explore the potential mediating effect of obesity on the effect of UPF on inflammation.

METHODS

Study design and participants

This cross-sectional study was conducted by researchers from the Department of Social Paediatrics and the Department of Public Health at Çukurova University's Faculty of Medicine, Adana, Turkey. It included healthy children aged 5 to 17 years, who applied to the Social Paediatrics Outpatient Clinic for follow-up of normal developmental stages. The sample size analysis revealed a minimum sample size to be reached as 42, with a power of 80%, a confidence interval of 99% and an effect size of $d = 0.5$. The sample was increased by 20% with a resulting number to be reached as 50 people.

Children were selected among those whose parents gave consent to participate in the study. All participants gave written informed consent to participate in the study. The ethics of data collection and analysis were approved by the Ethical Review Board for Non-interventional Studies of Cukurova University Faculty of Medicine, Adana, Turkey (Date 07.04.2023-Meeting No:132-Decree No:40).

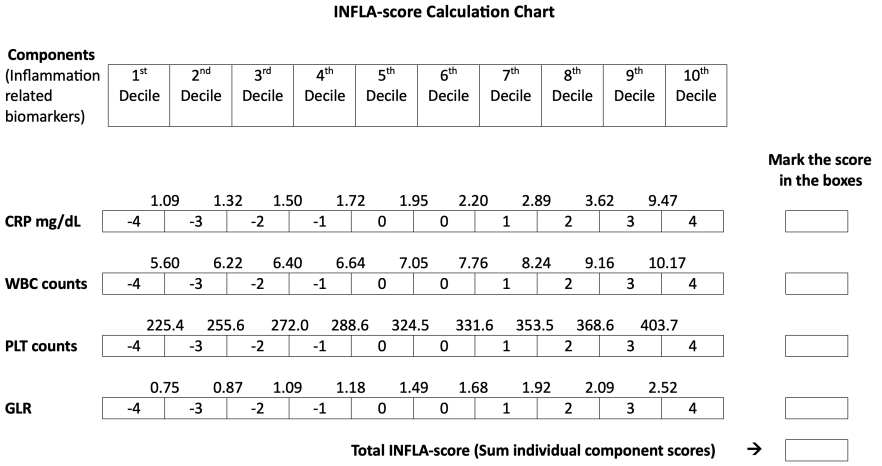
Children with a history of acute infection, surgery or chronic inflammatory disease in the last month, which might lead to changes in inflammatory parameters and those on special diets were excluded from the study. High attention was paid to the presence of infection, which is among our exclusion criteria. Any evidence of infection was checked with clinical examination, in addition to blood tests taken at the second visit. If there was a blood result indicating infection, these participants were excluded from the study. Patients with concordant clinical and laboratory results were included in the study.

Measurements and instruments

The instruments used in the study were (a) a questionnaire consisting of questions about the sociodemographic and health status of children, (b) a physical activity questionnaire (PAQ), (c) the Nutrition Information Form (NIF), (d) the NOVA-based Processed Food Frequency Questionnaire (NPFFQ) and (e) INFLA-score.

At the first visit of the participant to the polyclinic, the Socio-demographic Questionnaire and Physical Activity Questionnaire (PAQ) best fitting with the child's age (PAQ-C for children younger than 14 years or

FIGURE 1 Calculation of INFLA-score.



PAQ-A for adolescents between 14 and 20 years old) were filled face-to-face by the researchers. Following a physical examination to assess the child's basic anthropometric values such as weight, height and BMI-SDS (Body Mass Index-Standard Deviation Score), the parents were given the NIF to fill out at home. One week later, on the second visit, the NIF was taken back and the data included were input into the BeBiS™ programme (Nutrition Information System-9 Full Version) (BeBiS, 2021). Then the NOVA-based Processed Food Frequency Questionnaire (NPFFQ) was filled out face-to-face by the researchers referring also the NIF data. Data obtained by NPFFQ were input into the BeBiS™ and the amount and percentage of UPF consumed could be computed.

Physical activity questionnaire (PAQ)

The PAQ has two versions: PAQ-C for children younger than 14 years and PAQ-A for adolescents between 14 and 20 years old. The questionnaires are self-administered 7-day questionnaires developed by Kowalski et al. to assess the physical activity score of participant children (Kowalski et al., 2004). The validity and reliability study of the questionnaire for the Turkish population was conducted by Sert and Temel (2014). The form consists of nine questions to assess the physical activities performed by the participant in the last 7 days and their frequencies. The score for each question of the PAQ is between 1 and 5; therefore, the lowest and highest scores range between 9 and 45, respectively.

INFLA-score

The INFLA-score is a scoring method developed by Pounis et al. 2016 to detect low-grade inflammation reflecting the synergistic effects of four inflammatory biomarkers, which are C-reactive protein (CRP), white blood cells (WBC), platelets (PLT), granulocytes and lymphocytes. Blood samples were collected from the participants at the second visit in Becton Dickinson vacuum-gel tubes for the measurement of the inflammatory biomarkers. The blood samples were centrifuged at 4000 rpm for 10 min on the same day, using a NF1200R model device. The separated serum was portioned into Eppendorfs and stored at −80°C. When the targeted number of samples was reached, all samples were transferred to and kept in a refrigerator at 4°C for 24 h before the analysis day. The samples were brought to room temperature immediately 30 min before the analysis, which was performed manually using the BTLAB Microelisa kit test by sandwich enzyme-linked immunosorbent assay (ELISA) method and evaluated according to the kit protocols. For complete blood counts, venous blood samples taken in 2 cc EDTA tubes, were analysed on the same day, using Sysmex XN-1000 autoanalyser in the paediatric haematology laboratory of our hospital.

A chart (INFLA-score Calculation Chart) is used to calculate the total INFLA-score as illustrated in Figure 1. It gives an individual score ranging between −4 and +4 for each of the four components based on their measured laboratory values. The granulocyte (%)-to-lymphocyte (%) ratio (GLR) was calculated. The obtained levels of the four inflammation-related biomarkers (CRP, WBC, PLT and GLR) were divided into deciles. Following the methodology of Pounis et al., each decile was assigned a score between −4 and +4. For example, a CRP value <1.09 mg/dL yielded a score of −4, or CRP = 3 mg/dL yielded a score of +3. This scoring was repeated for all components and their sum yielded the INFLA-score, which can range between −16 and 16. An increase in the score represents an increase in the total low-grade inflammation status. As described by Pounis et al., the median value of the INFLA-scores of our whole study group was calculated, which was 2. The participants were divided into two groups: 'higher INFLA-score group' if their score was equal to or over the median of the study group (i.e. total

INFLA-score ≥ 2) or 'lower' if their total INFLA-score was (<2) (Pounis et al., 2016) (Figure 1).

Nutrition information form (NIF)

Food intake was assessed using 3-day nutritional information forms that were filled out on alternate days, including 1 weekend day by the participants' parents at home by 24-h recall method and presented to the researchers one week later. The reliability and validity study of NIF was performed by Sneed et al. (2023).

Three-day nutrient values were input into and evaluated by the BeBiS™. BeBiS™ is the Turkish version of EBISpro® software (Ernahrungsanamnese Beratungs- und Informations-System) (Stuttgart, Germany) (https://www.ebispro.de/) developed in 2008 (Pasifik Elektrik Elektronik Ltd. Şti., İstanbul, Turkey). It is based on Bundes-Lebensmittel-Schluessel (BLS) which is the German Food Code and Nutrient Database; Version 3.01B (http://www.bfr.bund.de/cd/801). It comprises more than 20 000 food items among which more than 400 Turkish food and ingredients are included, and more than 130 nutritional elements. It is a scientific and professional software and besides the BLS database, national and international nutrient composition tables such as USDA, TürKomp; infant formulas, enteral, dietetic and light brand products in the Turkish market, and British, Swiss, Danish and Indonesian commercial and academic resources were used in the creation of the data bank (https://bebis.com.tr/bilimsel-veri-bankalari-nelerdir).

When the portion and quantity of the food are entered digitally into the software, the software reports the number or amounts of calories, protein, carbohydrates, fat, vitamins and minerals, in addition to food components like amino acids, fatty acids, antioxidants, glycaemic index, ORAC (oxygen radical absorbance capacity) and more. Besides the total calories, the percentage of these calories derived from protein, carbohydrates or fat is also provided.

Processed food frequency questionnaire (PFFQ)

The PFFQ was used to determine UPF consumption since the BeBIS™ programme does not provide food categorisation as ultra-processed or not. The PFFQ is based on the NOVA classification (Rico-Campà et al., 2019). NOVA is a system that groups foods according to the nature, content and purpose of the industrial processes they undergo, rather than the nutrients they contain (Monteiro et al., 2018). This classification has been used in many epidemiological studies to associate food consumption with different sociodemographic parameters, diet quality, weight gain, etc. In the NOVA classification, foods are assigned to one of four groups: Group 1 includes edible parts of plants or animals taken naturally or foods taken directly from nature and slightly modified/preserved; that is, unprocessed or minimally processed food (MPF). Group 2 includes processed culinary ingredients (PCI) such as salt, sugar, oil or starch. Group 3 includes processed foods (PF) such as canned vegetables or freshly baked bread produced by combining Group 1 and Group 2 foods. Group 4 includes UPFs such as biscuits, snacks, breakfast cereals, yogurts, shop-bought bread and ready-to-heat meals, often containing little or no whole foods, usually formulated for specific industrial use and created by various industrial techniques and processes (Monteiro et al., 2019). The PFFQ was slightly modified not to dismiss frequently consumed PFs/UPFs in Turkey with the help of an additional specific Food Frequency Questionnaire including 28 food items. The data from NIFs were also checked to not miss any food items to be included in the PFFQ. Seven processed foods commonly consumed in Turkey, were included in the PFFQ; namely sausage, pastrami, frozen meatballs, frozen doner-kebab, frozen schnitzel, packaged custard and packaged puddings (Metin & Melekoğlu, 2021). Food items were categorised as 'processed' or 'ultra-processed' and the frequency of UPF consumption was classified as 'every meal', 'every day', '5–6 times a week', '3–4 times a week', '1–2 times a week', 'once every 15 days', 'once a month', 'rarely' and 'never'. Processed meat and meat products, frozen meat products, canned food, packaged milk desserts, breakfast cereals, fast-food products (nuggets, onion rings, etc.), ready-to-eat bakery products, confectionery, instant soups, fruit juices and carbonated drinks were the foods questioned.

All foods recorded in the 3-day diet form -NIF- and PFFQ were entered into the BeBiS™ and the average daily diet, calorie amount and content analyses were performed. The average energy intake of a child from the total diet content was calculated. By proportioning the two values, the portion of the total energy coming from UPF was calculated. This gave the percentage of daily energy coming from UPFs. In the second stage, UPFs were grouped according to the NOVA classification and calorie calculation was performed for these foods with the BeBiS™. The portion of the average daily total energy intake coming from UPFs was calculated with the following formula:

$$\text{Energy from UPF}\,(\%) = \frac{\text{Daily mean caloric input from UPF}}{\text{Total daily mean caloric input}} \times 100$$

Statistical analysis

SPSS™ 20.0 (IBM, U.S.A) and JAMOVI™ (Jamovi 2.3, 2023) software were used for data analysis. Shapiro Wilk test was used to test the normality. Comparisons

of normally distributed continuous variables between two groups were performed using Student's *t*-test. Associations between categorical data were tested using Pearson's Chi-square test. Associations between skewed continuous variables were tested through Spearman's rho, while those between normally distributed continuous variables were tested through Pearson correlation. A linear-by-linear association chi-square test was used to test the association between INFLA-score groups and daily average UPF amount. INFLA-score was predicted with multivariate linear regression analysis. The dependent variable in the model was INFLA-score; and the independent ones were daily total calories (kcal), energy from UPF (%), UPF amount (g), PAQ score, BMI-SDS, sex and age. Multicollinearity was evaluated using Tolerance and VIF (Variance inflation factor), with VIF <5 values admitted as an acceptable association. Mediation analysis was used to determine if and how obesity mediated the effect of the percentage of energy deriving from UPF among the total energy input on the INFLA-score. Bootstrap method (1000 samples) was used to estimate standard errors in mediation analysis. A $p < 0.05$ value was considered statistically significant.

RESULTS

The mean age of 50 children included in our study was 10.18 ± 3.98 years (5–17 years). The total daily energy intake of children derived from UPFs with a percentage of 24.5%. In children with higher inflammation scores (INFLA-score ≥ 2), the amount in grams (g) of UPF intake and the percentage of total dietary energy coming from UPFs were found to be statistically significantly higher ($p = 0.030$ and $p = 0.015$, respectively) than in children with lower inflammation scores. The effect size of these relationships was found to be moderate ($d = 0.544$ and $d = 0.637$, respectively). No significant differences were found between INFLA-score and dietary content, BMI and physical activity levels (Table 1; Figure 2).

When the correlations between the INFLA-score, UPF measurements, physical activity and BMI-SDS were analysed, a weak statistically significant positive correlation was found between the INFLA-score and the percentage of total energy intake from UPF ($r = 0.350$, $p < 0.01$), the average daily energy intake from UPF, and the average daily UPF intake ($r = 0.313$, $p < 0.05$) (Table 2; Figure 3).

It was found that the multivariate linear regression analysis to predict the INFLA-score was statistically significant (Forward model, ANOVA $p = 0.018$). The total energy percentage coming from UPF among the independent variables included in the model made a significant contribution, and a one-unit increase (1%) in the percentage of total daily energy intake coming from UPF caused a 0.154-unit increase in the INFLA-score. It was found that total daily dietary energy intake, the average amount of UPF consumed daily, physical activity level, BMI, age and sex did not make any significant contribution to the model ($p = 0.890$, 0.082, 0.606, 0.095, 0.294, respectively) (Table 3).

The percentage of UPF-derived energy among the total energy intake was found to have a significant pro-inflammatory effect (i.e. it increased the INFLA-score). This pro-inflammatory effect was direct ($p = 0.008$, estimate = 0.158), and not mediated by obesity ($p = 0.751$, estimate = −0.0046) (i.e. the increase in BMI-SDS) (Table 4; Figure 4).

There was a linear trend between the quartile classes formed according to the average amount of UPF consumed daily and the groups with high and low inflammation scores, and the percentage of those in the high inflammation class increased from Q1 to Q4 (33.3%; 38.5%; 53.8%; 66.7%, respectively, $p = 0.049$) (Table 5).

DISCUSSION

Low-grade inflammation is thought to increase the risk of chronic degenerative diseases by risk factors such as oxidative stress, obesity, diabetes, dyslipidaemia and metabolic disorders. Low-grade inflammation is also recognised as an important factor in the emergence of age-related diseases (Candore et al., 2010). It has been suggested that UPFs are related to inflammation (Monteiro et al., 2019), but there are a limited number of studies in this field, especially in children. In our study, the relationship between UPF consumption and low-grade inflammation was investigated in a group of healthy children. Approximately 25% of the daily energy intake in children was found to derive from UPFs. In our study, we found that the amount of UPF intake (expressed in grams) and the percentage of total energy from UPF foods were significantly higher in children with higher inflammation scores (INFLA-score). A positive correlation was found between inflammation score and the percentage of total energy from UPF, daily average calories from UPF and daily average amount of UPF consumed (g). It was found that a one-unit increase (1%) in the percentage of daily total UPF-derived energy was associated with a 0.154-unit increase in INFLA-score and that the direct effect of calories from UPF was significant and obesity was not a mediator. It was also found that as the amount of UPF consumed daily increased (going from lower to higher quartiles; Q1 to Q4), rates of higher inflammation scores increased.

Our findings are similar to studies in adults. In the cross-sectional analysis conducted by Lopes et al. in the *ELSA-Brasil* cohort (2008–2010), UPFs accounted for 20% of total energy intake. While no association

TABLE 1 Comparison of dietary intake, body mass index and physical activity according to inflammation groups.

	Inflammation groups			
	Low ($n=26$)	High ($n=24$)		Effect size
	INFLA-score < 2	INFLA-score ≥ 2	*p*	(Cohen's *d*)
BMI-SDS	−0.65 ± 1.38	−0.11 ± 2.03	0.275	0.312
PAQ score	23.57 ± 7.53	27.15 ± 8.04	0.110	0.460
UPF (%)	20.49 ± 11.72	28.92 ± 14.68	**0.015***	**0.637**
Total calories (kcal)	1337.65 ± 456.23	1395.25 ± 451.53	0.656	0.126
UPF calorie (kcal)	294.03 ± 241.82	401.95 ± 236.36	0.118	0.451
UPF (g)	309.13 ± 173.56	495.13 ± 459.05	**0.030***	**0.544**
Protein (%)	14.57 ± 3.59	13.70 ± 3.04	0.363	0.260
Fat (%)	38.23 ± 6.98	36.87 ± 6.38	0.478	0.202
Carbohydrate (%)	47.07 ± 6.75	56.54 ± 36.56	0.201	0.367
Protein (g)	48.96 ± 18.30	45.65 ± 17.79	0.520	0.183
Fat (g)	61.97 ± 32.19	56.51 ± 20.91	0.484	0.199
Carbohydrate (g)	162.28 ± 74.42	165.53 ± 60.68	0.867	0.047
Fibre (g)	12.57 ± 8.02	11.72 ± 4.92	0.656	0.126
Vitamin A (μg)	780.29 ± 417.70	661.65 ± 329.57	0.273	0.313
Retinol (μg)	378.85 ± 225.98	321.85 ± 167.49	0.319	0.284
Carotene (mg)	2.45 ± 2.02	1.97 ± 1.72	0.369	0.256
Vitamin D (μg)	3.54 ± 2.43	3.99 ± 2.43	0.518	0.184
Vitamin E (μg)	9.06 ± 5.96	8.50 ± 4.88	0.719	0.102
Niacin (mg)	8.50 ± 3.99	8.26 ± 3.01	0.818	0.065
Niacin equivalent (mg)	17.22 ± 7.39	16.48 ± 6.61	0.712	0.105
Vitamin B12 (μg)	3.22 ± 1.56	4.07 ± 5.98	0.491	0.196
Polyunsaturated fatty acid (g)	10.38 ± 5.47	10.41 ± 5.62	0.984	0.005
Cholesterol (mg)	310.16 ± 141.13	273.37 ± 153.16	0.381	0.250
Omega-3 (g)	1.33 ± 0.79	1.32 ± 0.70	0.950	0.017
Omega-6 (g)	8.64 ± 4.76	8.70 ± 5.02	0.965	0.012
Glycaemic index	211.81 ± 121.45	209.75 ± 97.54	0.948	0.018
Antioxidant (mmol)	2.35 ± 4.92	1.15 ± 0.72	0.246	0.332
Folate DFE (μg)	1.06 ± 1.60	2.35 ± 4.72	0.199	0.368
Copper (mg)	1.04 ± 0.49	0.96 ± 0.36	0.526	0.180
Manganese (mg)	3.02 ± 4.37	2.8083 ± 1.81465	0.821	0.064
Fluorine (μg)	364.80 ± 190.59	330.32 ± 155.27	0.489	0.197
Iodine (μg)	106.03 ± 49.77	98.84 ± 42.01	0.585	0.155
Glucose (g)	13.12 ± 9.58	9.37 ± 5.53	0.101	0.473
Fructose (g)	12.96 ± 8.85	10.45 ± 6.57	0.264	0.319
Fibre soluble (g)	4.06 ± 2.59	3.66 ± 1.68	0.522	0.182
Fibre insoluble (g)	8.34 ± 5.19	7.50 ± 3.13	0.495	0.194
Aspartame (mg)	4214.62 ± 1646.60	4173.22 ± 2438.83	0.944	0.020
Saturated fatty acid (g)	25.33 ± 14.44	26.54 ± 19.06	0.801	0.071
Oleic acid (C18:1) (g)	18.58 ± 9.97	15.96 ± 8.01828	0.313	0.288
Monounsaturated fatty acid (g)	21.18 ± 11.44	18.80 ± 8.47	0.411	0.234
Linoleic acid (C18:2) (g)	8.60 ± 5.39	7.83 ± 4.12	0.577	0.158
Linolenic acid (C18:3) (g)	1.10 ± 0.73	1.13 ± 0.71	0.856	0.051

TABLE 1 (Continued)

	Inflammation groups			
	Low ($n=26$) INFLA-score < 2	High ($n=24$) INFLA-score ≥ 2	p	Effect size (Cohen's d)
Eicosapentaenoic acid (C20:5) (g)	0.01 ± 0.04	0.00 ± 0.00	0.111	0.459
Docosahexaenoic acid (C22:6) (g)	0.19 ± 0.13	0.20 ± 0.09	0.631	0.137
Vitamin C (mg)	73.76 ± 44.50	59.69 ± 34.66	0.221	0.351
Sodium (mg)	2303.18 ± 1125.38	2021.72 ± 1028.93	0.362	0.260
Potassium (mg)	1863.02 ± 823.52	1701.84 ± 679.02	0.456	0.212
Calcium (mg)	542.33 ± 215.79	548.14 ± 268.86	0.933	0.023
Magnesium (mg)	179.54 ± 76.40	171.53 ± 60.92	0.685	0.115
Phosphorus (mg)	800.78 ± 289.34	742.82 ± 283.74	0.479	0.202
Iron (mg)	6.82 ± 3.09	6.63 ± 1.94	0.794	0.074
Zinc (mg)	6.32 ± 2.73	6.05 ± 2.12	0.693	0.112

Note: The values are means of the amounts or proportions of items consumed by children in 1 day as part of their diet; * $p < 0.05$
Abbreviations: BMI-SDS, Body mass index-standard deviation score; PAQ, Physical Activity Questionnaire; UPF, Ultra-processed food.

FIGURE 2 Distribution of the percentage of total energy deriving from ultra-processed foods (UPF) according to inflammation groups. Low inflammation group: INFLA-score < 2; High inflammation group: INFLA-score ≥ 2.

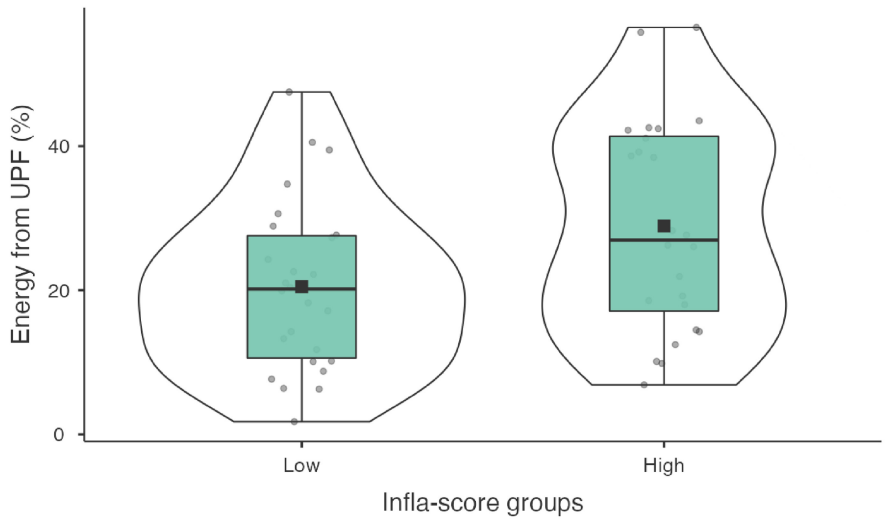


TABLE 2 Correlation matrix between the INFLA-score, ultra-processed food (UPF) measurements, physical activity and BMI-SDS (Body Mass Index-Standard Deviation Score).

	INFLA-score	BMI-SDS	Energy from UPF (%)	Total energy (kcal)	UPF energy (kcal)	UPF amount (g)	PAQ score
INFLA-score	-						
BMI-SDS	0.134	-					
Energy from UPF (%)	0.350**	0.014	-				
Total energy (kcal)	0.036	0.108	0.194	-			
UPF energy (kcal)	0.313*	0.051	0.895***	0.586***	-		
UPF amount (g)	0.260*	−0.002	0.280*	0.404**	0.395**	-	
PAQ score	0.191	−0.092	0.176	0.000	0.166	0.181	-

Abbreviation: PAQ, Physical Activity Questionnaire.
*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$ one-tailed.

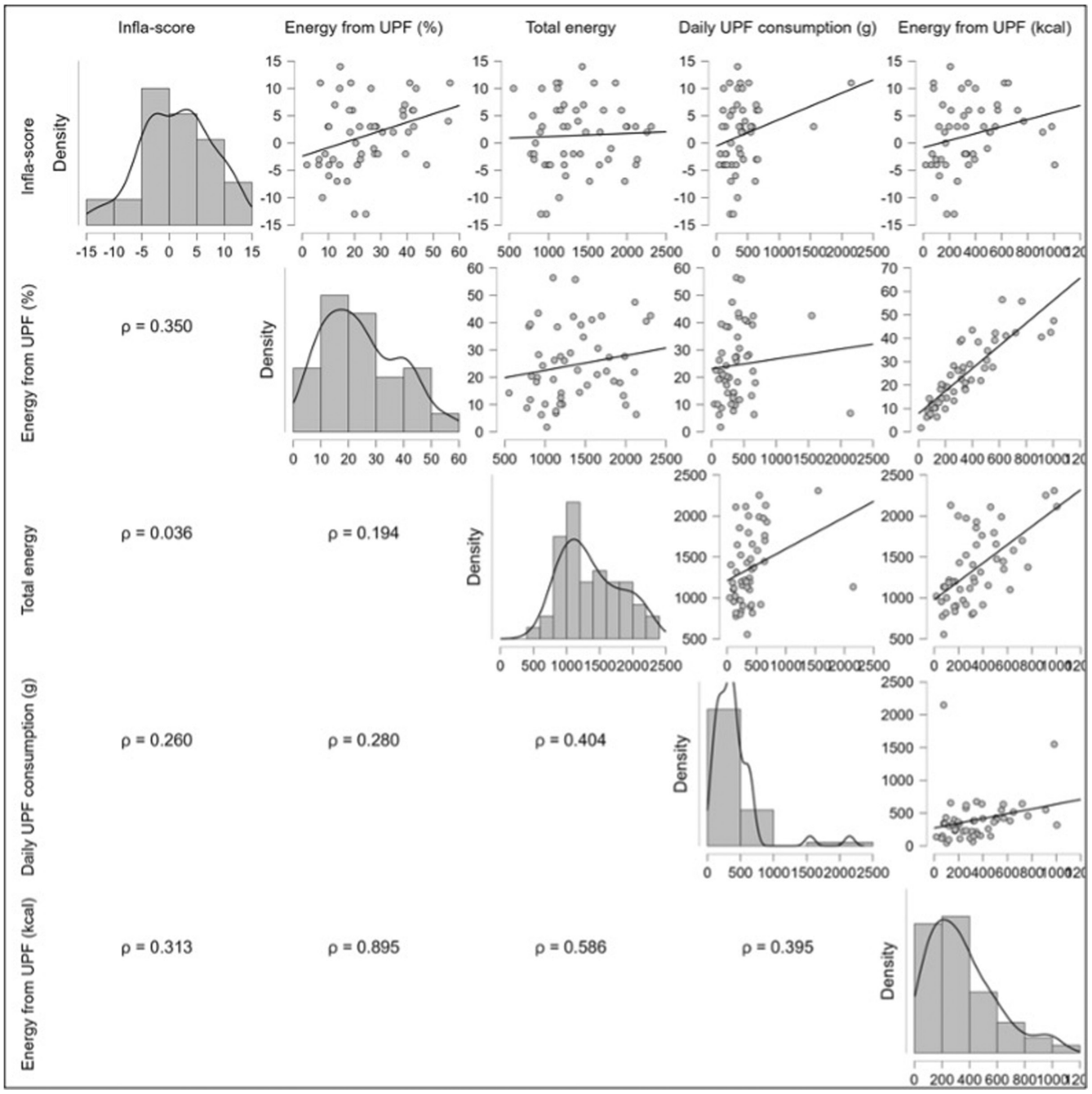


FIGURE 3 Correlations between INFLA-score and average daily consumed ultra-processed food (UPF).

was found between UPF intake and CRP levels in men, in women CRP levels were reported to be 14% higher in the group with the highest UPF intake compared to the group with the lowest UPF intake after adjustment for sociodemographic characteristics, smoking and physical activity. However, this association lost statistical significance when BMI was included in the model. They suggested that the positive association of UPF consumption with CRP levels among women may be mediated by the presence of obesity (Lopes et al., 2019). However, Lane et al. modelled UPF intake in 100 g increments and found that each 100 g increase in UPF intake was associated with a 4% increase in high-sensitivity CRP (hs-CRP) concentration (used in the assessment of cardiovascular or stroke risks) independent of BMI (Lane, Lotfaliany, et al., 2022). In a study conducted by Kelsey et al. in pregnant women, a weak positive correlation was found between UPF and CRP concentrations (Kelsey et al., 2022). In the study conducted by Martins et al. on adolescents, 26.1% of the average daily energy consumption of adolescents came from UPF. Higher serum leptin and CRP levels were found in the quartile with the highest UPF consumption. It was shown that interleukin-8 (IL-8) levels

TABLE 3 Multivariate linear regression analysis for INFLA-score prediction.

	Unstandardised coefficients			95.0% CI for B		Collinearity statistics	
Model $R^2 = 0.206$	**B**	**Std. error**	***p***	**Lower bound**	**Upper bound**	**Tolerance**	**VIF**
(Constant)	−2.386	1.772	0.184	−5.949	1.176		
Energy from UPF (%)	0.154	0.063	**0.018***	0.027	0.281	1.000	1.000

Note: Independent variables in the model: Daily total calories (kcal), energy from UPF (%), UPF amount (g), Physical Activity Questionnaire (PAQ) score, body mass index-standard deviation score (BMI-SDS), sex and age; * $p < 0.05$

Abbreviations: PAQ, Physical Activity Questionnaire; UPF, Ultra-processed Food; VIF, Variance Inflation Factor.

TABLE 4 Mediator role of obesity in the effect of ultra-processed food (UPF)-derived calories on INFLA-score.

				95% CI		
Effect (% mediation)	**Label**	**Estimate**	**SE**	**Lower**	**Upper**	***p***
Indirect (2.84%)	a×b	−0.00464	0.0146	−0.0333	0.0240	0.751
Direct (97.16%)	c	0.15894	0.0602	0.0409	0.2770	**0.008****
Total	c+a×b	0.15430	0.0618	0.0331	0.2755	**0.013***
Path estimates						
UPF-derived energy (%) → BMI-SDS	a	−0.00575	0.0178	−0.0406	0.0291	0.746
BMI-SDS → INFLA-score	b	0.80743	0.4786	−0.1307	1.7456	0.092
UPF-derived energy (%) → INFLA-score	c	0.15894	0.0602	0.0409	0.2770	**0.008****

* $p < 0.05$; * $p < 0.01$ Abbreviations: BMI-SDS, Body mass index-standard deviation score; CI, confidence interval; SE, standard error.

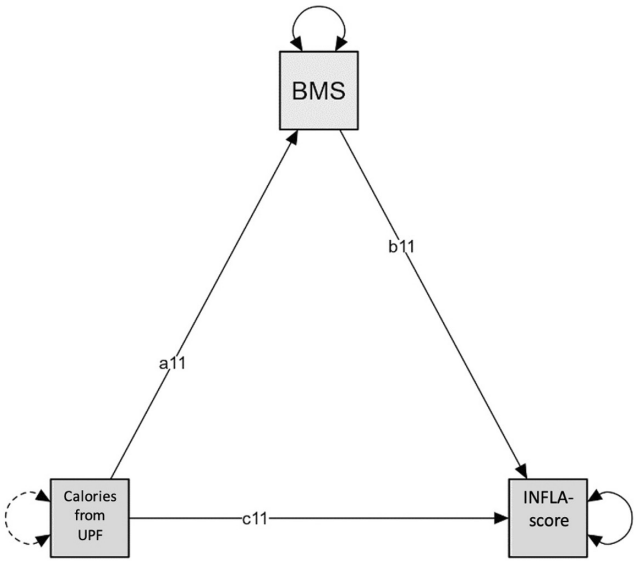


FIGURE 4 Path diagram in the mediation analysis. BMS, Body mass index-standard deviation Score; UPF, Ultra-processed food; a11, b11, c11, Paths in the mediation analysis.

were 1.79 times higher in adolescents with UPF-derived energy consumption ratio of ≥30.0% (3rd quartile of UPF intake) compared to adolescents in the first quartile (dos Martins et al., 2022). Silva et al. found that when compared to the first UPF quartile; plasma interleukin-6 (IL-6) (pg/mL) concentrations in women were 1.31 (95% CI; 0.95–1.82) times, 2.20 (95% CI; 1.60–3.01) times and 2.64 (95% CI; 1.89–3.69) times higher at the second, third and fourth UPF intake quartiles, respectively. Similar results were found among men with IL-6 levels being 1.40 (95% CI; 1.32–1.49) times at the second UPF quartile, 1.50 (95% CI; 1.41–1.59) times at the third and 1.59 (95% CI; 1.49–1.70) times higher at the fourth quartiles, compared to the first UPF quartile. The mediating effect of fat mass on this increase was found to be insignificant. UPF consumption was associated with an increase in IL-6 concentration, but this relationship was not explained by adiposity (Silva dos Santos et al., 2023). Our findings supported these results, and we also observed that there was a relationship independent of obesity.

However, it is not clear whether these findings are due to the degree of processing of UPF or to their nutrient composition and the fact that UPFs are also generally high in fat, salt and sugar. The effects of the food matrix are influenced by both the degree of processing and the nutrient composition of the food because this refers not only to the chemical and physical components of food but also to the molecular relationships that affect how food is digested and metabolised (Miller et al., 2023). In the study by Mignogna et al., in which the relationship between UPF and low-grade inflammation was examined, multivariate linear regression models revealed a positive INFLA-score association with dietary inflammatory index ($\beta = 0.15$; 95%CI; 0.10–0.19), processed foods ($\beta = 0.04$; 95%CI; 0.01–0.08) and UPFs ($\beta = 0.13$; 95%CI; 0.07–0.19);

TABLE 5 INFLA-score comparisons according to the quartile classes of ultra-processed food (UPF) amount consumed daily.

			Average amount of daily consumed UPF (g)				
			Q1 (<202.42 g)	Q2 (202.43–341.29 g)	Q3 (341.30–472.10 g)	Q4 (>472.20 g)	*p**
Inflammation groups based on INFLA-score	Low (INFLA-score < 2)	*n*	8	8	6	4	
		Column %	66.7	61.5	46.2	33.3	**0.049****
	High (INFLA-score ≥ 2)	*n*	4	5	7	8	
		Column %	33.3	38.5	53.8	66.7	

*Linear-By-Linear Association Chi-Square Test; Q1…Q4, quartile-1…quartile-4; ** $p < 0.05$

while an inverse association was observed between low-grade inflammation and minimally processed foods ($\beta = -0.09$; 95%CI; −0.13 to −0.06). Dietary inflammation score was found to be inversely associated with minimally processed food intake ($\beta = -0.40$; 95%CI; −0.41 to −0.39; for every 5% increase in the ratio of minimally processed food amount in grams among total food intake), while positively associated with processed culinary ingredients use ($\beta = 0.18$; 95% CI; 0.15–0.21 for every 1% increase), processed food intake ($\beta = 0.28$; 95%CI; 0.27–0.29 for every 5% increase) and UPF intake ($\beta = 0.34$; 95%CI 0.32–0.36 for every 5% increase). Dietary inflammation score and UPF intake explained 88.5% of the change in the INFLA-score (Mignogna et al., 2022). Silva et al. investigated the relationship between energy percentage (E%) and energy-density dietary inflammatory index (E-DII) according to the degree of industrial processing of foods during pregnancy. In linear regression models, a positive relationship with E% of UPFs in the diet ($\beta = 0.052$; 95%CI; 0.045–0.058) was reported, while an inverse relationship was found between E-DII scores and E% of minimally processed foods ($\beta = -0.049$; 95%CI; −0.055 to −0.042) (Silva et al., 2019). The authors claimed that there was a relationship between the degree of industrial processing of food and the inflammatory potential of the diet (Silva et al., 2019). While obesity (i.e. the amount of adipose tissue) could be expected to increase low-grade inflammation; based on our findings and the results of a limited number of other studies, we suggest that the relationship between low-grade inflammation and UPF is not related to obesity, but that UPF directly triggers the inflammation. These results are consistent with the idea that the direct association of food processing with low-grade inflammation is related to the high inflammatory potential of these foods and that processing alters the food composition and has effects other than just on the food matrix (Fardet, 2016, 2018).

Inflammation is one of the main factors in the development of non-communicable diseases (NCDs). Certain unhealthy dietary patterns and increasing consumption of UPF may affect the inflammation process and increase the risk of NCDs by negatively affecting the gut microbiota (Tosi et al., 2023). Considering nutrition-related diseases, further studies are required to explore any triggering effects of pro-inflammatory diets in childhood. Current evidence suggests that health professionals should consider generalised dietary patterns to provide balanced and healthy diets for children not only to provide metabolic control but also to prevent the development of NCDs in adolescence and adulthood. Personalised nutritional approaches should be encouraged and new methods should be developed to assess pro-inflammatory dietary habits in children (Tosi et al., 2023).

The limitations of our study are that it was a single-centre hospital-based study conducted in a relatively small sample, the nutrition information forms were completed by the parents (there might have been incomplete statements or they might have paid more attention to the nutritional content after the investigators' explanations (interviewer effect)) and that other factors that might affect inflammation could not be controlled. The strength of our study was that it was one of the few studies that examined the relationship between UPF and low-grade inflammation in children.

CONCLUSION

According to the results of our study, UPFs constituted a significant portion (approximately 25%) of children's diets and a positive relationship was found between low-grade inflammation and UPF consumption independent of obesity. In particular, the increase in the percentage of UPF in total daily energy intake (%) and the increase in the amount of UPF consumed daily (g) were the most important factors in the association with low-grade inflammation. Considering the relationship between low-grade inflammation and chronic degenerative diseases, children consuming more UPF may be at increased risk, and early dietary content interventions (gaining healthy eating habits, etc.) may contribute positively to the reduction of possible future disease incidence.

AUTHOR CONTRIBUTIONS

BM: Idea and Concept, Design, Analysis and Comment, Literature Review, Writing, Critical Review. HTS: Idea and Concept, Design, Data Collection, Literature

Review. HD: Idea and Concept, Design, Writing, Critical Review. EM: Idea and Concept, Design, Literature Review, Writing, Critical Review. AB: Design, Materials, Data Collection and Processing, Comment, Critical Review. TM: Design, Materials, Data Collection and Processing, Comment, Critical Review. FAÜ: Design, Materials, Data Collection and Processing, Comment, Critical Review.

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CONFLICT OF INTEREST STATEMENT
The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT
This paper reports an analysis of primary data. The ethics of data collection and analysis were approved by the Ethical Review Board for Non-interventional Studies of Cukurova University Faculty of Medicine, Adana, Turkey (Date 07 April 2023-Meeting No:132-Decree No:40). All participants gave written informed consent to participate in the study.

CONSENT STATEMENT
Consents were obtained from patients and their relatives for the data used in the study.

ORCID
Burak Mete https://orcid.org/0000-0002-0780-6176
Hatice Merve Sadıkoğlu https://orcid.org/0009-0006-7327-7387
Hakan Demirhindi https://orcid.org/0000-0001-7475-2406
Ebru Melekoglu https://orcid.org/0000-0002-2342-221X
Adnan Barutcu https://orcid.org/0000-0001-8930-1122
Tuba Makca https://orcid.org/0000-0003-1289-0701
Fatma Atun Utuk https://orcid.org/0000-0001-8804-1058

REFERENCES
Augustin, M.A., Riley, M., Stockmann, R., Bennett, L., Kahl, A., Lockett, T. et al. (2016) Role of food processing in food and nutrition security. *Trends in Food Science & Technology*, 56, 115–125. Available from: https://doi.org/10.1016/j.tifs.2016.08.005

BeBiS, 9. (2021) BeBiS Ver.9 (Nutritional Information System). Ümraniye, İstanbul, Türkiye. https://bebis.com.tr/anasayfa

Candore, G., Caruso, C., Jirillo, E., Magrone, T. & Vasto, S. (2010) Low grade inflammation as a common pathogenetic denominator in age-related diseases: novel drug targets for anti-ageing strategies and successful ageing achievement. *Current Pharmaceutical Design*, 16(6), 584–596. Available from: https://doi.org/10.2174/138161210790883868

Costa, C.S., Del-Ponte, B., Assunção, M.C.F. & Santos, I.S. (2018) Consumption of ultra-processed foods and body fat during childhood and adolescence: a systematic review. *Public Health Nutrition*, 21(1), 148–159. Available from: https://doi.org/10.1017/S1368980017001331

Lopes, A.E.D.S.C., Araújo, L.F., Levy, R.B., Barreto, S.M. & Giatti, L. (2019) Association between consumption of ultra-processed foods and serum C-reactive protein levels: cross-sectional results from the ELSA-Brasil study. *São Paulo Medical Journal*, 137(2), 169–176. Available from: https://doi.org/10.1590/1516-3180.2018.0363070219

dos Martins, G.M.S., da França, A.K.T.C., de Viola, P.C.A.F., de Carvalho, C.A., Marques, K.D.S., dos Santos, A.M. et al. (2022) Intake of ultra-processed foods is associated with inflammatory markers in Brazilian adolescents. *Public Health Nutrition*, 25(3), 591–599. Available from: https://doi.org/10.1017/S1368980021004523

Fardet, A. (2016) Minimally processed foods are more satiating and less hyperglycemic than ultra-processed foods: a preliminary study with 98 ready-to-eat foods. *Food & Function*, 7(5), 2338–2346. Available from: https://doi.org/10.1039/C6FO00107F

Fardet, A. (2018) *Characterization of the degree of food processing in relation with its health potential and effects*. (pp. 79–129) https://doi.org/10.1016/bs.afnr.2018.02.002

Fiolet, T., Srour, B., Sellem, L., Kesse-Guyot, E., Allès, B., Méjean, C. et al. (2018) Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort. *BMJ*, 360, k322. Available from: https://doi.org/10.1136/bmj.k322

Jamovi 2.3. (2023) Jamovi, 2.3 (2.3). Jamovi.org. https://www.jamovi.org

Kelsey, P.T., Papadopoulou, E., Borge, T.C., Dahl, C., Brantsæter, A.L., Erlund, I. et al. (2022) Ultra-processed food consumption and associations with biomarkers of nutrition and inflammation in pregnancy: the Norwegian environmental biobank. *Frontiers in Nutrition*, 9, 1052001. Available from: https://doi.org/10.3389/fnut.2022.1052001

Kowalski, K.C., Crocker, P.R.E. & Donen, R.M.D. (2004) *The physical activity questionnaire for older children (PAQ-C) and adolescents (PAQ-A) manual*. Saskatoon: University of Saskatchewan.

Lane, M.M., Davis, J.A., Beattie, S., Gómez-Donoso, C., Loughman, A., O'Neil, A. et al. (2021) Ultraprocessed food and chronic noncommunicable diseases: a systematic review and meta-analysis of 43 observational studies. *Obesity Reviews*, 22(3), e13146. Available from: https://doi.org/10.1111/obr.13146

Lane, M.M., Gamage, E., Travica, N., Dissanayaka, T., Ashtree, D.N., Gauci, S. et al. (2022) Ultra-processed food consumption and mental health: a systematic review and meta-analysis of observational studies. *Nutrients*, 14(13), 2568. Available from: https://doi.org/10.3390/nu14132568

Lane, M.M., Lotfaliany, M., Forbes, M., Loughman, A., Rocks, T., O'Neil, A. et al. (2022) Higher ultra-processed food consumption is associated with greater high-sensitivity C-reactive protein concentration in adults: cross-sectional results from the Melbourne collaborative cohort study. *Nutrients*, 14(16), 3309. Available from: https://doi.org/10.3390/nu14163309

Marino, M., Puppo, F., Del Bo', C., Vinelli, V., Riso, P., Porrini, M. et al. (2021) A systematic review of worldwide consumption of ultra-processed foods: findings and criticisms. *Nutrients*, 13(8), 2778. Available from: https://doi.org/10.3390/nu13082778

Marshall, J.S., Warrington, R., Watson, W. & Kim, H.L. (2018) An introduction to immunology and immunopathology. *Allergy, Asthma and Clinical Immunology*, 14(Suppl 2), 49. Available from: https://doi.org/10.1186/S13223-018-0278-1

Metin, M.M.T. & Melekoğlu, E. (2021) The relationship between stress status and consumption of fructose and processed food in university students. *Cukurova Journal of Agriculture and Food Sciences*, 36(1), 263–274. Available from: https://doi.org/10.36846/CJAFS.2021.54

Mignogna, C., Costanzo, S., Di Castelnuovo, A., Ruggiero, E., Shivappa, N., Hebert, J.R. et al. (2022) The inflammatory potential of the diet as a link between food processing and low-grade inflammation: an analysis on 21,315 participants to the Moli-sani study. *Clinical Nutrition*, 41(10), 2226–2234. Available from: https://doi.org/10.1016/j.clnu.2022.08.020

Miller, G.D., Ragalie-Carr, J. & Torres-Gonzalez, M. (2023) Perspective: seeing the forest through the trees: the importance of food matrix in diet quality and human health. *Advances in Nutrition*, 14(3), 363–365. Available from: https://doi.org/10.1016/J.ADVNUT.2023.03.005

Monteiro, C.A., Cannon, G., Lawrence, M., Costa Louzada, M.L. & Pereira Machado, P. (2019) *Ultra-processed foods, diet quality, and health using the NOVA classification system*. Rome: Food and Agriculture Organization of the United Nations (FAO).https://www.fao.org/3/ca5644en/ca5644en.pdf

Monteiro, C.A., Cannon, G., Moubarac, J.-C., Levy, R.B., Louzada, M.L.C. & Jaime, P.C. (2018) The UN decade of nutrition, the NOVA food classification and the trouble with ultra-processing. *Public Health Nutrition*, 21(1), 5–17. Available from: https://doi.org/10.1017/S1368980017000234

Moradi, S., Hojjati Kermani, M.A., Bagheri, R., Mohammadi, H., Jayedi, A., Lane, M.M. et al. (2021) Ultra-processed food consumption and adult diabetes risk: a systematic review and dose-response meta-analysis. *Nutrients*, 13(12), 4410. Available from: https://doi.org/10.3390/nu13124410

Pagliai, G., Dinu, M., Madarena, M.P., Bonaccio, M., Iacoviello, L. & Sofi, F. (2021) Consumption of ultra-processed foods and health status: a systematic review and meta-analysis. *British Journal of Nutrition*, 125(3), 308–318. Available from: https://doi.org/10.1017/S0007114520002688

Pounis, G., Bonaccio, M., Di Castelnuovo, A., Costanzo, S., De Curtis, A., Persichillo, M. et al. (2016) Polyphenol intake is associated with low-grade inflammation, using a novel data analysis from the Moli-sani study. *Thrombosis and Haemostasis*, 115(2), 344–352. Available from: https://doi.org/10.1160/th15-06-0487

Ramos-Lopez, O., Martinez-Urbistondo, D., Vargas-Nuñez, J.A. & Martinez, J.A. (2022) The role of nutrition on meta-inflammation: insights and potential targets in communicable and chronic disease management. *Current Obesity Reports*, 11(4), 305–335. Available from: https://doi.org/10.1007/s13679-022-00490-0

Rico-Campà, A., Martínez-González, M.A., Alvarez-Alvarez, I., de Mendonça, R.D., de la Fuente-Arrillaga, C., Gómez-Donoso, C. et al. (2019) Association between consumption of ultra-processed foods and all cause mortality: SUN prospective cohort study. *BMJ*, 365, l1949. Available from: https://doi.org/10.1136/bmj.l1949

Sert, Z.E. & Temel, A.B. (2014) Questionnaire to Turkish Community for Elementary School Students: validity and reliability study. *Dokuz Eylül Üniversitesi Hemşirelik Fakültesi Elektronik Dergisi*, 7(2), 109–114. https://dergipark.org.tr/tr/download/article-file/753391

Silva, C.A., Santos, I.D.S., Shivappa, N., Hebert, J.R., Crivellenti, L.C. & Sartorelli, D.S. (2019) The role of food processing in the inflammatory potential of diet during pregnancy. *Revista de Saúde Pública*, 53, 113. Available from: https://doi.org/10.11606/S1518-8787.2019053001154

Silva dos Santos, F., Costa Mintem, G., Oliveira de Oliveira, I., Lessa Horta, B., Ramos, E., Lopes, C. et al. (2023) Consumption of ultra-processed foods and IL-6 in two cohorts from high- and middle-income countries. *British Journal of Nutrition*, 129(9), 1552–1562. Available from: https://doi.org/10.1017/S0007114522000551

Sneed, N.M., Ukwuani, S., Sommer, E.C., Samuels, L.R., Truesdale, K.P., Matheson, D. et al. (2023) Reliability and validity of assigning ultraprocessed food categories to 24-h dietary recall data. *The American Journal of Clinical Nutrition*, 117(1), 182–190. Available from: https://doi.org/10.1016/J.AJCNUT.2022.10.016

Suksatan, W., Moradi, S., Naeini, F., Bagheri, R., Mohammadi, H., Talebi, S. et al. (2021) Ultra-processed food consumption and adult mortality risk: a systematic review and dose–response meta-analysis of 207,291 participants. *Nutrients*, 14(1), 174. Available from: https://doi.org/10.3390/nu14010174

Taneri, P.E., Wehrli, F., Roa-Díaz, Z.M., Itodo, O.A., Salvador, D., Raeisi-Dehkordi, H. et al. (2022) Association between ultra-processed food intake and all-cause mortality: A systematic review and meta-analysis. *American Journal of Epidemiology*, 191(7), 1323–1335. Available from: https://doi.org/10.1093/aje/kwac039

Tosi, M., Montanari, C., Bona, F., Tricella, C., Agostinelli, M., Dolor, J. et al. (2023) Dietary inflammatory potential in pediatric diseases: A narrative review. *Nutrients*, 15(24), 5095. Available from: https://doi.org/10.3390/nu15245095

Tristan Asensi, M., Napoletano, A., Sofi, F. & Dinu, M. (2023) Low-grade inflammation and ultra-processed foods consumption: a review. *Nutrients*, 15(6), 1546. Available from: https://doi.org/10.3390/nu15061546

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