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ORIGINAL CONTRIBUTION

Prospective associations between dietary patterns and high sensitivity C-reactive protein in European children: the IDEFICS study

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Abstract

Purpose This prospective study explores high sensitivity C-reactive protein (hs-CRP) levels in relation to dietary patterns at two time points in European children.

Methods Out of the baseline sample of the IDEFICS study ($n = 16{,}228$), 4020 children, aged 2–9 years at baseline, with available hs-CRP levels and valid data from a food frequency questionnaire (FFQ) at baseline (T0) and 2 years later (T1) were included. K-means clustering algorithm based on the similarities between relative food consumption frequencies of the FFQ was applied. hs-CRP was dichotomized according to sex-specific cutoff points. Multilevel logistic regression was performed to assess the relationship between dietary patterns and hs-CRP adjusting for covariates.

Results Three consistent dietary patterns were found at T0 and T1: 'animal protein and refined carbohydrate', 'sweet and processed' and 'healthy'. Children allocated to the 'protein' and 'sweet and processed' clusters at both time points had significantly higher odds of being in the highest category of hs-CRP (OR 1.47; 95% CI 1.03–2.09 for 'animal protein and refined carbohydrate' and OR 1.44; 95% CI 1.08–1.92 for 'sweet and processed') compared to the 'healthy' cluster. The odds remained significantly higher for the 'sweet and processed' pattern (OR 1.39; 95% CI 1.05–1.84) when covariates were included.

J. M. Fernández-Alvira and L. A. M. Aznar equally contributed to this work.

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Conclusions A dietary pattern characterized by frequent consumption of sugar and processed products and infrequent consumption of vegetables and fruits over time was independently related with inflammation in European children. Efforts to improve the quality of the diet in childhood may prevent future diseases related with chronic inflammation.

Keywords Dietary patterns · Inflammation · C-reactive protein · European · Children · IDEFICS

Introduction

Chronic low-grade inflammation is related with metabolic disorders [1] and cardiovascular diseases (CVD) due to its role in the development of atherosclerosis [2]. In obese individuals, the endocrine function of the adipose tissue is impaired and it contributes to the production and release of pro-inflammatory cytokines; this condition is already observed in children [3, 4]. Among the available inflammatory biomarkers, high sensitivity C-reactive protein (hs-CRP) is the most commonly measured biomarker in clinical and epidemiologic studies and it is associated with adiposity and cardiovascular risk factors [5], even in children [6, 7].

Dietary intake, and its relation with low-grade inflammation, has been previously investigated in adults, taking into account nutrients, specific food items or dietary patterns [8–10]. In the baseline sample of the IDEFICS study, cross-sectional associations with hs-CRP were found between fatty acids intake, assessed via whole blood [11], and consumption frequencies of specific foods measured using a food frequency questionnaire (FFQ) [12] and hs-CRP. Dietary pattern analysis seems a good way to assess the diet as a whole as it considers also the possible interactions between the foods consumed and not only specific food items or isolated components. Additionally, dietary patterns could give an accurate insight into dietary behaviors in a population [13] and are useful to link specific dietary habits with chronic diseases [14].

Recent literature suggests that unhealthy patterns, i.e., those characterized by a westernized diet with high intake of animal proteins, free sugars and/or processed foods and low intake of vegetables/fruits, are positively related with inflammation while patterns with high intake of fruits and/or vegetables, i.e., plant-based patterns, are inversely associated with the inflammatory state [15–18].

Out of different approaches to derive dietary patterns, cluster analysis identifies diet patterns by grouping individuals into non-overlapping groups that reflect relatively homogeneous dietary behaviors within groups and relatively different dietary behavior between groups. Principal component analysis (PCA) is the most commonly used method to assess dietary patterns. However, PCA provides linear combinations of food, instead of referring to identifiable groups of subjects. A previous study [19] compared PCA and cluster analysis assessment methods, finding similar patterns and comparable long-term associations with coronary heart disease and stroke. Cluster analysis has been used to describe homogeneous groups of subjects with similar dietary patterns [20], it seems that this approach could be useful to give a good insight of dietary patterns. Previous longitudinal studies in adults have linked cluster analysis-derived dietary patterns and chronic diseases [21]. However, similar studies following young populations are scarce. Identifying young individuals with persistent healthy or unhealthy patterns over time may help to understand the cumulative impact of dietary habits on hs-CRP that could lead to future chronic diseases.

Thus, the first aim of this study was to describe cluster analysis-derived dietary patterns in children at two time points [baseline (T0) and follow-up (T1)] of the identification and prevention of dietary- and lifestyle-induced health effects in children and infants (IDEFICS) study. The second aim of this study was to assess the cross-sectional and prospective relationships between the identified dietary patterns and hs-CRP, as a marker of inflammation.

Materials and methods

Study design

The IDEFICS study is a multicentre population-based study of European children between 2 and 9 years old at time of recruitment in schools of eight countries: Belgium, Cyprus, Estonia, Germany, Hungary, Italy, Spain and Sweden. The general design and main procedures of the IDEFICS study have been described in detail elsewhere [22]. Two main surveys were performed in the present study: baseline (T0) and follow-up (T1) 2 years later. Children of pre-school and first or second grade of primary education were included at baseline. The baseline survey was performed between September 2007 and May 2008 and included 16,228 children from 2 to 9 years, while the follow-up survey performed between September 2009 and May 2010 included 11,038 children aged 4–11 years (overall response rate of 68%).

Authorization was obtained from the ethics committees of all participating countries. Parents provided written informed consent and children provided oral consent. The

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study was performed according to the ethical guidelines of the Edinburgh revision of the 1964 Declaration of Helsinki (2000).

Study sample

8754 children from the baseline sample of the IDEFICS study had data on hs-CRP and less than 50% of missing values in the food frequency questionnaire (FFQ). On the other hand, 6688 children from the follow-up sample of the IDEFICS study had the already mentioned data. Out of the total baseline and follow-up sample, 4174 children had less than 50% of missing values in the food frequency questionnaire (FFQ) and hs-CRP measured, at T0 and T1.

Then, children with hs-CRP concentrations higher than 10 mg/dL and those who took any medication the previous 24 h to blood collection that could potentially affect the hs-CRP values, i.e., anti-inflammatory drugs, steroids and/or corticoids, were excluded from the present analysis. Finally, 4020 children were included in the present analysis.

Measurements

The FFQ for obtaining the dietary data was the Children's Eating Habits Questionnaire FFQ (CEHQ-FFQ) [23, 24], a validated screening tool where the parents recorded their children's frequency of consumption of specific food items during the previous 4 weeks. The CEHQ-FFQ which comprised 43 food items within 14 food groups and was not designed to provide an estimate of total energy intake or total amount of food but to reflect dietary habits. Responses included seven frequency categories of consumption: 'never/less than once a week,' '1–3 times per week,' '4–6 times per week,' '1 time per day,' '2 times per day,' '3 times per day' and '4 or more times per day'. Also 'I have no idea' was a possible answer. Frequency categories were converted into times per week, represented by a number ranging from 0 to 30. Multiple imputation was applied to estimate missing values using gender, age, BMI and country as predictors for the rest of missing values and the pooled data from the imputed databases was retrieved.

Children were asked to participate in fasting blood collection, on a voluntary basis. A description of blood sampling and analytical procedures in the IDEFICS survey has been published elsewhere [25]. The hs-CRP concentrations were measured in a central laboratory with a high-sensitivity assay using latex-enhanced nephelometry (BN2-Nephelometer, Siemens, Deerfield, IL, USA) and the lower limit of detection of the assay was 0.02 mg/dL.

Parental education level (the highest level of both parents) was categorized according to the International Standard Classification of EDucation (ISCED) [26]. As the previous 24 h medication intake was recorded for the day of the blood collection, the type of medication, other than the medication mentioned as exclusion criteria, was used as confounder in the analysis as a categorical variable.

Finally, trained staff performed the anthropometric measurements, at T0 and T1, following standardized procedures. Body height was measured with bare feet in a portable stadiometer (SECA 225). Weight was measured in a child-adapted Tanita BC 420 SMA with the children in fasting status. BMI was calculated as the ratio between weight (kg) and squared height (m^2).

Statistical analyses

K-means cluster analysis was performed to identify clusters of children with similar dietary patterns [27]. The same procedures as in a previous IDEFICS study were followed [28]. Out of the 43 food items included in the FFQ, 'meat replacement products' were excluded from the analysis as more than 95% of the subjects reported to consume: 'never/less than once per week'. Correlations between the single items were calculated to assess multi-collinearity, showing no redundant variables. For the 42 food items, relative frequencies of consumption were calculated: the frequency of consumption of each one was divided by the sum of the consumption of all food items for each subject. *Z* scores of the relative frequencies of each food item were calculated to standardize values and to avoid large differences between food items [29]. The k-means algorithm was applied with a pre-defined maximum of 100 iterations, generated until no changes in the centroids were shown, to create cluster solutions for two to six clusters. Several solutions were obtained with different starting seeds to find stable cluster patterns. Randomly splitting the database in two halves to repeat the same procedure in baseline and follow-up datasets was used to examine the stability of the final solution both in baseline and follow-up datasets. Cohen's kappa values for the selected solution were 0.892 and 0.963 for baseline and follow-up, respectively.

The criteria to choose the clusters were based on stability of the cluster solution and interpretability. The clusters were labeled based on the corresponding *z* score values of the types of foods they included. Three clusters over time were found: 'healthy', 'animal protein and refined carbohydrate' and 'sweet and processed'. In addition, radar plots showing the maximum and minimum *z* score values in comparison with the other clusters were created to identify and to describe visually each cluster at each time point.

Distribution of children in different clusters was calculated, stratified by gender, age, BMI status and country at baseline and follow-up. Cluster memberships at baseline and follow-up were cross tabulated, to assess the percentage of children characterized by persistent dietary patterns and of those who changed dietary pattern from T0 to T1.

The distribution of hs-CRP was skewed as approximately a third of the sample had the value 'under detection limit': 0.02 mg/dL, in T0 and T1. Thus, subjects were allocated into two groups or categories, i.e., the first and second sex-specific hs-CRP tertiles vs. the third sex-specific tertile.

For the prospective analysis, each possible combination of dietary patterns over time was treated as a separate category. For example, being allocated in the 'sweet and processed' in T0 and 'healthy' in T1 was considered one category. Those children who stayed in the 'Healthy pattern' over time, at T0 and T1, were considered as the reference category. In addition, being persistently allocated to the same cluster at baseline and follow-up was considered as additional categories.

Finally, multilevel logistic regression (levels: country and school) was performed using the hs-CRP at both time points as dependent variable to assess the odds ratio (OR) for having a higher inflammatory status when presenting a specific dietary pattern at baseline and follow-up separately. Additionally, ORs for having a high inflammatory state when being persistently allocated to the same cluster at baseline and follow-up (i.e., 'animal protein and refined carbohydrate', 'sweet and processed' or 'healthy') or when changing from one of the three clusters to another were calculated. The 'healthy' cluster was always considered as the reference. Two models with different covariates were applied. Model 1 was adjusted by levels: country and school, while model 2 was additionally adjusted for age, gender, study region (intervention vs. control), parental education level, BMI and medication. These covariates were assessed at both time points, T0 and T1. The analysis with the combination of T0 and T1 patterns included: hs-CRP of T1 as dependent and was adjusted for age at T1, gender, study region (intervention vs. control), parental education level at T1, BMI at T1, hs-CRP at T0 and medication.

The analyses were performed using Statistical Package for the Social Sciences (version 21.0; SPSS, Inc.) and Stata (version 13.0) for the multilevel logistic regression. The radar plots were performed with Excel (Microsoft).

Results

Based on the food items and their z score values, a three-cluster solution was considered the most interpretable and stable. The following names were assigned to the clusters: 'healthy' ($n=1245$ at T0 and $n=1335$ at T1), 'sweet and processed' ($n=1472$ at T0 and $n=1306$ at T1) and 'animal protein and refined carbohydrate' ($n=1303$ at T0 and $n=1379$ at T1).

Tables 1 and 2 present the z scores of the 42 food items and standard deviations for each cluster. The cluster solutions obtained were similar in terms of interpretability at both time points. The mean relative frequency of the majority of the food items differed significantly between the three clusters (Tables 1, 2).

At both time points, the 'animal protein and refined carbohydrate' cluster presented higher relative frequencies of consumption of water, sweetened fruit, white bread, pasta, rice and also foods like sweetened milk, sweet yogurt, fish (fresh or fried), meat and fried eggs. Food items such as whole bread, spreads, cold cuts, fried meat, plain milk, hamburgers or sweetened and diet drinks scored lowest. In contrast, 'the sweet and processed' cluster had consistently higher relative consumption frequencies for sugar-rich products such as fruit juices, sweetened drinks, diet drinks, sweetened breakfast cereals, chocolate/nut-spread, ketchup, chocolate-candy bars, candies, biscuits/pastries and ice-cream. Also, at both time points, this cluster had higher relative frequencies for fried potatoes, cold cuts, fried meat, mayonnaise and hamburgers/hot dogs/kebabs, whereas food items such as cooked vegetables, fresh fruit, water, muesli, plain yogurt, fresh fish, cheese or pasta scored the lowest. Finally, the 'healthy' cluster presented at both time points higher relative consumption frequencies for cooked vegetables, raw vegetables, fresh fruits, muesli, plain milk, plain yogurt, boiled eggs, reduced-fat products on bread, whole-meal bread, dish of milled cereals and nuts/seeds. Food items such as fried potatoes, fruits with added sugar, sweetened breakfast cereals, sweetened milk, sweet yogurt, fried eggs, mayonnaise, chocolate/nut spreads, white bread, pizza as main dish, crisps, savoury pastries, chocolate/candy bars or biscuits scored the lowest.

Table 3 shows the main characteristics of the participants in the three clusters. The percentage of girls in the 'healthy' cluster was slightly higher than in the other clusters, while a higher percentage of boys were observed in the 'sweet and processed' and 'animal protein and refined carbohydrate' cluster. Also, age differences by cluster are presented. A higher percentage of older children in T0 and T1 were allocated to the 'sweet and processed' cluster compared to the other clusters. Regarding BMI differences, the 'animal protein and refined carbohydrate' cluster included a higher percentage of overweight and obese children compared with the other two clusters. In contrast, the 'healthy' cluster had lower percentages of obese children compared with the 'animal protein and refined carbohydrate' or 'sweet and processed' cluster over time. There were also differences between the distributions by country per cluster, i.e., certain countries allocated subjects up to 51.7% on one cluster. The 'animal protein and refined carbohydrate' cluster was mainly represented by Spain and Italy; the 'sweet and processed' cluster by Hungary, Belgium, Estonia and Germany while the 'healthy' cluster predominated in Sweden, Estonia, Hungary and Germany.

Table 1 *Z* scores of relative consumption frequencies in the three clusters at baseline [mean values and standard deviation (SD)]

Food items	Animal protein and refined carbohydrate ($n=1303$)		Sweet and processed ($n=1472$)		Healthy ($n=1245$)	
	Mean	SD	Mean	SD	Mean	SD
Cooked vegetables, potatoes, beans	-0.07^{b}	0.96	$-0.14^{b,*}$	0.92	$0.24^{a,\dagger}$	1.07
Fried potatoes, potato croquettes	0.02^{c}	0.93	$0.27^{a}\dagger$	1.17	$-0.35^{b,*}$	0.67
Raw vegetables	$-0.40^{b,*}$	0.70	-0.25^{c}	0.74	$0.72^{a,\dagger}$	1.12
Fresh fruits without added sugar	0.11^{c}	1.07	$-0.42^{b}*$	0.72	$0.38^{a,\dagger}$	1.01
Fresh fruits with added sugar	$0.11^{a,\dagger}$	1.17	0.06^{a}	1.01	$-0.18^{b}*$	0.73
Water	$0.76^{a,\dagger}$	0.76	$-0.52^{b,*}$	0.89	-0.17^{c}	0.83
Fruit juices	-0.17^{b}	0.76	$0.30^{a,\dagger}$	1.21	$-0.17^{b}*$	0.83
Sweetened drinks	$-0.30^{b,*}$	0.39	$0.46^{a,\dagger}$	1.43	-0.22^{b}	0.04
Diet drinks	-0.15^{b}	0.37	$0.26^{a,\dagger}$	1.54	$-0.15^{b,*}$	0.36
Breakfast cereals, muesli, sweetened	-0.08^{c}	1.01	$0.29^{a,\dagger}$	1.10	$-0.26^{b,*}$	0.74
Porridge, oat meal, gruel, cereals, muesli, unsweetened	-0.21^{c}	0.91	$-0.30^{b}*$	0.54	$0.58^{a,\dagger}$	1.23
Plain unsweetened milk	$-0.41^{b,*}$	0.83	-0.09^{c}	0.87	$0.54^{a,\dagger}$	1.05
Sweetened milk	$0.63^{a,\dagger}$	1.22	-0.13^{c}	0.78	$-0.51^{b,*}$	0.48
Plain unsweetened yogurt or kefir	-0.16^{b}	0.84	$-0.18^{b}*$	0.68	$0.38^{a,\dagger}$	1.31
Sweet yogurt, fermented milk beverages	$0.27^{a,\dagger}$	1.23	-0.10^{b}	0.81	$-0.16^{b,*}$	0.85
Fresh or frozen fish, not fried	$0.53^{a,\dagger}$	1.15	$-0.50^{b,*}$	0.63	0.02^{c}	0.87
Fried fish, fish fingers	$0.23^{a,\dagger}$	1.16	$-0.16^{b,*}$	0.88	-0.05^{c}	0.89
Cold cuts, preserved, ready to cook meat products	-0.12^{c}	0.86	$0.36^{a,\dagger}$	1.07	$-0.29^{b,*}$	0.90
Fresh meat, not fried	$0.31^{a,\dagger}$	1.11	$-0.13^{b,*}$	0.92	-0.16^{c}	0.87
Fried meat	$-0.22^{b,*}$	0.92	$0.14^{a,\dagger}$	1.05	0.05^{a}	0.96
Fried or scramble eggs	$0.30^{a,\dagger}$	1.09	-0.06^{c}	0.95	$-0.24^{b,*}$	0.85
Boiled or poached eggs	$-0.19^{b,*}$	0.86	-0.12^{b}	0.91	$0.35^{a,\dagger}$	1.13
Mayonnaise, mayonnaise-based products	-0.16^{b}	0.74	$0.34^{a,\dagger}$	1.32	$-0.23^{b,*}$	0.58
Cheese	-0.07^{a}	0.95	$-0.05^{b,*}$	0.96	$0.06^{a,\dagger}$	1.08
Jam-honey	$-0.29^{b,*}$	0.74	$0.16^{a}\dagger$	1.02	0.11^{a}	1.12
Chocolate or nut based spreads	0.06^{c}	0.87	$0.29^{a}\dagger$	1.20	$-0.42^{b,*}$	0.65
Butter, margarine on bread	$-0.56^{b,*}$	0.34	0.25^{c}	1.04	$0.29^{a,\dagger}$	1.14
Reduced-fat products on bread	$-0.46^{b}*$	0.31	0.07^{c}	0.97	$0.39^{a,\dagger}$	1.27
Ketchup	$-0.31^{b,*}$	0.83	$0.22^{a}\dagger$	1.09	0.06^{c}	0.96
White bread, white roll, white crispbread	$0.34^{a,\dagger}$	1.09	0.13^{c}	0.97	$-0.51^{b,*}$	0.65
Wholemeal bread, dark roll, dark crispbread	$-0.50^{b,*}$	0.61	-0.02^{c}	0.94	$0.56^{a,\dagger}$	1.09
Pasta, noodles, rice	$0.26^{a,\dagger}$	1.23	$-0.30^{b,*}$	0.70	0.07^{c}	0.92
Dish of milled cereals	$-0.27^{b,*}$	0.41	-0.01^{c}	0.88	$0.29^{a,\dagger}$	1.40
Pizza as main dish	$0.35^{a,\dagger}$	1.34	-0.04^{c}	0.85	$-0.31^{b,*}$	0.47
Hamburguers, hot dogs, kebabs, wraps, falafel	$-0.35^{b,*}$	0.52	$0.35^{a,\dagger}$	1.28	-0.05^{c}	0.84
Nuts, seeds, dried fruits	$-0.06^{b,*}$	0.91	-0.06^{b}	0.90	$0.15^{a,\dagger}$	1.16
Crisps, maize (corn) crisps, popcorn	$0.16^{a,\dagger}$	1.13	0.07^{a}	1.01	$-0.25^{b,*}$	0.74
Savoury pastries, fritters	0.01^{c}	1.06	$0.17^{a,\dagger}$	1.12	$-0.23^{b,*}$	0.66
Chocolate, candy bars	-0.12^{c}	0.84	$0.38^{a,\dagger}$	1.24	$-0.32^{b,*}$	0.59
Candies, loose candies, marshmallows	-0.13^{b}	0.83	$0.26^{a,\dagger}$	1.29	$-0.17^{b}*$	0.62
Biscuits, packaged cakes, pastries, puddings	0.02^{c}	0.99	$0.19^{a,\dagger}$	1.20	$-0.26^{b,*}$	0.58
Ice cream, milk- or fruit-based bars	$-0.30^{b,*}$	0.76	$0.29^{a,\dagger}$	1.24	-0.02^{c}	0.77

*The lowest mean value within a row

†The highest mean value within a row

[a,b,c]Mean values within a row with unlike superscript letters were significantly different ($p<0.05$)

Table 2 *Z* scores of relative consumption frequencies in the three clusters at follow-up [mean values and standard deviation (SD)]

Food items	Animal protein and refined carbohydrate ($n=1303$)		Sweet and processed ($n=1306$)		Healthy ($n=1335$)	
	Mean	SD	Mean	SD	Mean	SD
Cooked vegetables, potatoes, beans	0.02^{c}	1.01	$-0.15^{b,*}$	0.93	$0.12^{a,\dagger}$	1.04
Fried potatoes, potato croquettes	-0.07^{c}	0.94	$0.42^{a,\dagger}$	1.12	-0.33^{b*}	0.74
Raw vegetables	-0.25^{c}	0.78	-0.41^{b*}	0.61	$0.66^{a,\dagger}$	1.15
Fresh fruits without added sugar	0.20^{a}	1.07	-0.46^{b*}	0.73	$0.24^{a}\dagger$	0.98
Fresh fruits with added sugar	$0.13^{a,\dagger}$	1.26	-0.01^{c}	0.85	-0.13^{b*}	0.78
Water	$0.69^{a,\dagger}$	0.81	$-0.43^{b,*}$	0.94	-0.29^{c}	0.82
Fruit juices	$-0.08^{b,*}$	0.88	$0.15^{a,\dagger}$	1.16	-0.06^{b}	0.91
Sweetened drinks	$-0.26^{b,*}$	0.41	$0.49^{a,\dagger}$	1.52	-0.21^{b}	0.44
Diet drinks	$-0.16^{b,*}$	0.34	$0.29^{a,\dagger}$	1.58	-0.11^{b}	0.53
Breakfast cereals, muesli, sweetened	0.08^{b}	1.09	$0.13^{a,\dagger}$	1.03	$-0.21^{a,*}$	0.81
Porridge, oat meal, gruel, cereals, muesli, unsweetened	-0.26^{b}	0.74	$-0.28^{b,*}$	0.61	$0.55^{a,\dagger}$	1.26
Plain unsweetened milk	$-0.41^{b,*}$	0.76	-0.18^{c}	0.81	$0.60^{a,\dagger}$	1.08
Sweetened milk	$0.55^{a,\dagger}$	1.17	-0.08^{c}	0.90	$-0.49^{b,}{}_{*}$	0.47
Plain unsweetened yogurt or kefir	-0.11^{b}	0.91	$-0.17^{b,}{}_{*}$	0.72	$0.29^{a,\dagger}$	1.22
Sweet yogurt, fermented milk beverages	$0.19^{a,\dagger}$	1.14	-0.04^{c}	0.92	$-0.15^{b,*}$	0.86
Fresh or frozen fish, not fried	$0.57^{a,\dagger}$	1.08	$-0.47^{b,*}$	0.71	-0.12^{c}	0.84
Fried fish, fish fingers	$0.08^{a,\dagger}$	1.10	0.02^{a}	1.01	$-0.10^{b,*}$	0.84
Cold cuts, preserved, ready to cook meat products	$-0.21^{b,*}$	0.84	$0.28^{a,\dagger}$	1.08	-0.05^{c}	0.99
Fresh meat, not fried	$0.42^{a,\dagger}$	1.01	-0.16^{c}	0.98	$-0.27^{b,*}$	0.85
Fried meat	$-0.23^{b,*}$	0.86	$0.20^{a,\dagger}$	1.05	0.04^{c}	1.02
Fried or scramble eggs	$0.20^{a,\dagger}$	1.03	0.05^{c}	1.05	$-0.25^{b,*}$	0.84
Boiled or poached eggs	$-0.22^{b,*}$	0.83	-0.02^{c}	1.01	$0.25^{a,\dagger}$	1.09
Mayonnaise, mayonnaise-based products	-0.18^{b}	0.74	$0.46^{a,\dagger}$	1.33	$-0.25^{b,*}$	0.61
Cheese	$0.07^{a,\dagger}$	1.06	$-0.08^{b,*}$	0.97	0.01^{b}	0.94
Jam-honey	$-0.25^{b,*}$	0.82	0.07^{c}	0.96	$0.19^{a,\dagger}$	1.13
Chocolate or nut based spreads	-0.02^{c}	0.81	$0.44^{a,\dagger}$	1.26	$-0.40^{b,}{}_{*}$	0.62
Butter, margarine on bread	$-0.49^{b,*}$	0.47	$0.11^{a,\dagger}$	0.97	0.40^{c}	1.18
Reduced-fat products on bread	$-0.39^{b,*}$	0.41	0.03^{c}	0.91	$0.37^{a,\dagger}$	1.31
Ketchup	$-0.30^{b,}{}_{*}$	0.75	$0.37^{a,\dagger}$	1.27	-0.05^{c}	0.78
White bread, white roll, white crispbread	$0.34^{a,\dagger}$	1.13	0.06^{c}	0.94	$-0.41^{b,}{}_{*}$	0.71
Wholemeal bread, dark roll, dark crispbread	$-0.49^{b,}{}_{*}$	0.58	-0.05^{c}	0.91	$0.57^{a,\dagger}$	1.12
Pasta, noodles, rice	$0.19^{a,\dagger}$	1.23	$-0.18^{b,*}$	0.81	-0.02^{c}	0.84
Dish of milled cereals	$-0.28^{b,}{}_{*}$	0.37	-0.03^{c}	0.91	$0.32^{a,\dagger}$	1.36
Pizza as main dish	0.13^{a}	1.06	$0.18^{a,\dagger}$	1.21	-0.32^{b*}	0.49
Hamburguers, hot dogs, kebabs, wraps, falafel	$-0.32^{b,}{}_{*}$	0.54	$0.31^{a,\dagger}$	1.28	0.02^{c}	0.94
Nuts, seeds, dried fruits	-0.07^{b}	0.91	$-0.08^{b,}{}_{*}$	0.87	$0.15^{a,\dagger}$	1.16
Crisps, maize (corn) crisps, popcorn	-0.13^{c}	0.89	$0.38^{a,\dagger}$	1.19	$-0.24^{b,}{}_{*}$	0.75
Savoury pastries, fritters	-0.06^{c}	0.91	$0.31^{a,\dagger}$	1.24	$-0.24^{b,}{}_{*}$	0.68
Chocolate, candy bars	-0.22^{b}	0.77	$0.50^{a,\dagger}$	1.24	-0.25^{b*}	0.72
Candies, loose candies, marshmallows	$-0.26^{b,}{}_{*}$	0.72	$0.39^{a,\dagger}$	1.34	-0.11^{c}	0.68
Biscuits, packaged cakes, pastries, puddings	-0.12^{c}	0.87	$0.35^{a,\dagger}$	1.28	$-0.21^{b,}{}_{*}$	0.64
Ice cream, milk- or fruit-based bars	$-0.25^{b,}{}_{*}$	0.85	$0.28^{a,\dagger}$	1.21	-0.01^{c}	0.83

*The lowest mean value within a row

†The highest mean value within a row

^{a,b,c}Mean values within a row with unlike superscript letters were significantly different ($p<0.05$)

Table 3 Description of the included study population by cluster membership at baseline (T0) and follow-up (T1)

	Animal protein and refined carbohydrate				Sweet and processed				Healthy				Total T0	
	T0		T1		T0		T1		T0		T1			
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Total	1303		1379		1472		1306		1245		1335		4020	
Gender														
Boys	666	51.1	708	51.3	766	52.0	683	52.3	605	48.6	646	48.4	2037	50.7
Girls	637	48.9	671	48.7	706	48.0	623	47.7	640	51.4	689	51.6	1983	49.3
Age														
<6 years	522	40.1	220	16.0	566	38.5	148	11.3	526	42.2	202	15.1	1614	40.1
≥6 years	781	59.9	1159	84.0	906	61.5	1158	88.7	719	57.8	1133	84.9	2406	59.9
BMI status														
Underweight	97	7.4	90	6.5	212	14.4	179	13.7	160	12.9	157	11.7	469	11.8
Normal weight	833	63.9	859	62.3	1074	73	879	67.3	933	74.9	964	72.2	2840	70.6
Overweight	234	18.0	295	21.4	117	7.9	179	13.7	113	9.1	161	12.1	464	11.5
Obese	139	10.7	135	9.8	69	4.7	69	5.3	39	3.1	53	4.0	247	6.1
Country														
Italy	497	38.1	458	33.2	91	6.2	133	10.2	30	2.4	27	2.0	618	15.4
Estonia	10	0.8	15	1.1	280	19	208	15.9	218	17.5	285	21.4	508	12.6
Cyprus	4	0.3	7	0.5	30	2.0	26	2.0	15	1.2	16	1.2	49	1.2
Belgium	54	4.1	58	4.2	339	23.1	324	24.8	100	8.1	111	8.3	493	12.3
Sweden	5	0.4	17	1.2	30	2.0	45	3.4	537	43.1	510	38.2	572	14.2
Germany	11	0.8	13	1.0	176	12	140	10.7	99	8.0	133	10.0	286	7.1
Hungary	49	3.8	133	9.6	472	32.2	364	27.9	196	15.7	222	16.6	719	17.9
Spain	673	51.7	678	49.2	52	3.5	66	5.1	50	4.0	31	2.3	775	19.3

Table 4 Cross tabulation between the cluster memberships of children at baseline (T0) and follow-up (T1). (Number of participants and percentages)

Cluster membership at T1	Cluster membership at T0						Total, *n*
	Animal protein and refined carbohydrate		Sweet and processed		Healthy		
	n	%	*n*	%	*n*	%	
Animal protein and refined carbohydrate	1056	76.6	187	13.6	136	9.9	1379
Sweet and processed	183	14.0	964	73.8	159	12.2	1306
Healthy	64	4.8	321	24	950	71.2	1335
Total	1303	32.4	1472	36.6	1245	31.0	4020

Table 4 summarizes the percentages of children allocated to the same, or different, clusters at baseline and follow-up. The cluster presenting the highest stability was the 'animal protein and refined carbohydrate' pattern with 76% of the children being allocated there both in T0 and T1. 73.8% of the children remained in the 'sweet and processed' cluster over time while 71.2% remained in the 'healthy' cluster from T0 to T1. Table 5 summarizes the percentages of children allocated in the different categories of hs-CRP over time. Most of the children, 79.9%, remained in the lowest category of the hs-CRP at both time points, i.e., were in the first or second tertile of the hs-CRP.

Table 5 Cross tabulation between the high sensitivity C-reactive protein (hs-CRP) categories at baseline (T0) and follow-up (T1). (Number of participants and percentages)

hs-CRP categories at T1	hs-CRP categories at T0				Total, *n*
	Category I		Category II		
	n	%	*n*	%	
Category I	2618	79.9	658	20.1	3276
Category II	540	72.6	204	27.8	744
Total	3158	78.6	862	21.4	4020

Category I being in the first or second tertile of hs-CRP by gender

Category II being in the highest tertile of hs-CRP by gender

In contrast, 27.8% remained in the highest tertile of hs-CRP over time.

Finally, Table 6 shows the OR and 95% CI for the associations between the hs-CRP categories and the identified dietary patterns.

In the cross-sectional analyses, there were no associations of diet with CRP at T0. When diet assessed at T1 was compared to hs-CRP at T1, children allocated to the 'sweet and processed' cluster had a 28% higher probability of being in the upper category of hs-CRP compared with those allocated in the 'healthy' cluster (OR = 1.28; 95% CI 1.03, 1.61) in the full-adjusted model. In the analysis of the cluster combinations, children allocated to the 'animal protein and refined carbohydrate' or to the 'sweet and processed' cluster at both times presented, respectively, a 47% (OR = 1.47; 95% CI 1.03, 2.09) and a 44% (OR = 1.44; 95% CI 1.08, 1.92) higher probability of being in the upper hs-CRP category compared with those allocated to the 'healthy' cluster both times in the unadjusted model. When all the co-variables were included in the analyses, those allocated in the 'sweet and processed' cluster still presented significantly higher odds of being in the highest hs-CRP category (OR = 1.39; 95% CI 1.05, 1.84) compared to those in the 'healthy cluster'.

The *z* scores of the relative frequency of the food items that defined the clusters, i.e., the highest or lowest z value from Tables 1 and 2 in comparison with the other patterns over time, are presented as radar plots in the supplementary material (Supplementary Figs. 1–12).

Discussion

This study in European children identified three dietary patterns at two time points (T0 and T1) using cluster analysis. The so-labeled 'animal protein and refined carbohydrate' pattern was characterized for having a relatively

Table 6 Associations between high sensitivity C-reactive protein (hs-CRP) in each time point and cluster membership in each time point (T0 and T1)* and the combinations of clusters over time

	hs-CRP		hs-CRP	
	Model 1		Model 2	
	OR**	95% CI	OR**	95% CI
T0				
Healthy cluster	1		1	
Animal protein and refined carbohydrate	1.21	0.96, 1.52	1.19	0.95, 1.50
Sweet and processed	1.11	0.90, 1.35	1.10	0.90, 1.35
Animal protein and refined carbohydrate or sweet and processed	1.14	0.95, 1.38	1.14	0.94, 1.37
T1				
Healthy cluster	1		1	
Animal protein and refined carbohydrate	1.25	0.93, 1.67	1.22	0.95, 1.56
Sweet and processed	**1.28**	**1.02, 1.61**	**1.28**	**1.03, 1.61**
Animal protein and refined carbohydrate or sweet and processed	**1.27**	**1.02, 1.59**	**1.26**	**1.02, 1.54**
Cluster combinations over time†				
Healthy at two time points ($n = 950$)	1		1	
Animal protein and refined carbohydrate cluster at two time points ($n = 1056$)	**1.47**	**1.03, 2.09**	1.13	0.97, 1.76
Sweet and processed cluster at two time points ($n = 964$)	**1.44**	**1.08, 1.92**	**1.39**	**1.05, 1.84**
Animal protein and refined carbohydrate or sweet/processed to healthy cluster, ($n = 385$)	1.25	0.88, 1.79	1.12	0.78, 1.60
Healthy cluster to sweet/processed and animal protein and refined carbohydrate ($n = 295$)	1.19	0.82, 1.73	1.12	0.76-1.63
Animal protein and refined carbohydrate or sweet/processed to animal protein and refined carbohydrate or sweet/processed, ($n = 370$)	1.42	0.98, 2.04	1.28	0.90, 1.81

All models of the multilevel logistic regression include random effects (country, school) to account for the study design

Model 1: unadjusted multilevel logistic regression

Model 2: multilevel logistic regression adjusted for age, gender, study region (intervention vs. control), parental education level, BMI and medication

Bold value indicates $p < 0.005$

*T0: baseline, T1: follow

**Odds for being allocated to the highest hs-CRP tertile

†Model 1 and Model 2 for the cluster combination included hs-CRP of T1 as dependent variable. Model 1 was unadjusted, while Model 2 was adjusted for age at T1, sex, study region (intervention vs. control), parental education level at T1, BMI at T1, hs-CRP at T0 and medication

high frequency of protein foods, water and some carbohydrate foods; the 'sweet and processed' pattern showed a high relative frequency of both sweet products and sweet drinks and a low relative frequency of fruit and vegetables, whereas the named 'healthy' pattern showed high relative frequency of fruits and vegetables, whole grain foods and low consumption of sweet products. These patterns were consistently similar at both time points, which allowed us to explore the associations of persistency/changes of dietary patterns in children and hs-CRP.

Although dietary patterns are dependent on the specific study group sample and not comparable between studies, it should be mentioned that a previous dietary patterns analysis in the IDEFICS cohort was performed; similar patterns were found using PCA [30]. In the previous study, similar 'animal protein and refined carbohydrate', 'healthy' and 'sweet and processed' patterns were found but were allocated to different names. In addition, they identified a fourth pattern named 'snacking' which was not identified in our analysis and this could be due to the different statistical approach or the different sub-sample. Nevertheless, other studies have obtained similar dietary patterns using different assessment methods in the same sample of adults [31, 32], and even in children [33]. Also, another study performed with IDEFICS data [28] found a similar 'healthy' dietary pattern using cluster analysis. This study also obtained a 'processed' cluster and a 'sweet' cluster, with similar characteristics as the 'sweet and processed' pattern found in this study, whereas no pattern related with protein intake was found. This could be due to the differences in sample size and characteristics: 9301 children were included in that analysis compared with 4020 children included in the present study. Importantly, these studies found persistent patterns in both time points.

In the current study, lower percentages of obese children were included in the 'healthy' pattern in comparison with the proportion of children in the other two patterns. In contrast, higher percentages of overweight and obese children were observed in the 'animal protein and refined carbohydrate' pattern when compared to both 'sweet and processed' and 'healthy' patterns.

The present study also found positive associations between the 'sweet and processed' pattern and inflammation at T1 as compared to the 'healthy' pattern. In the literature, a review identified the western-type diet, characterized by a high consumption of meat, as the dietary pattern more related with inflammation, while the 'healthy' pattern with high consumption of fruits and vegetables was inversely related with inflammation [10]. However, this review included only cross-sectional observational studies. It seems that westernized dietary patterns characterized by higher intakes of red and processed meats, sweets, desserts, fried foods, and refined grains are positively related to an increase of inflammation molecules, endothelial adhesion molecules and atherogenic promoters [34, 35]. Also another review found similar results regarding the western dietary pattern comparing studies using different ways to obtain the dietary patterns [36]. Another study [37] found that the 'eggs and sweets' pattern was associated with high levels of CRP, as well as the 'pasta and meat' pattern, while the 'olive oil and vegetables' pattern was negatively associated with CRP. Therefore, results from literature suggest that the relationship between unhealthy dietary patterns and inflammation is not as consistent as for the 'healthy' pattern. This could be explained because the statistical approach is *a posteriori* method, meaning that different clusters could appear in different samples. In addition, the definition of an unhealthy pattern is wider than for the 'healthy' pattern, often characterized for a high consumption of vegetables and fruits. The beneficial combination of antioxidant vitamins or compounds, fiber and other anti-inflammatory phytochemicals, which are contained in vegetal foods, may underlie the inverse association with CRP, or inflammation [38].

Results from the present study regarding the 'sweet and processed' pattern, in comparison with other studies, could be explained by the population sample, as children are more likely to eat sweet products than adults in a regular basis. Also, soft drinks or sugar-rich foods are associated with glycemic spikes that may contribute to oxidative stress and both to acute and chronic inflammation even in lean subjects [39]. Also the 'animal protein and refined carbohydrate' cluster included foods with high glycemic index, which also have been related with inflammation. However, the 'sweet and processed' pattern was also characterized by a low relative frequency of vegetables and fruits. Therefore, the combination of these frequencies of consumption of these specific foods could explain the relationship between this pattern and inflammation, measured by the hs-CRP.

The present study is subject to a number of limitations. The CEHQ-FFQ was not designed to capture total food intake but to record information on parent-supervised meals. However, the CEHQ-FFQ has previously been shown to give reproducible estimates of the frequency of food group consumption in European children [23, 24]. Also, the number of meals under parental control varied between countries, which could partially explain the differences observed in dietary patterns between countries. In addition, hs-CRP was the only inflammatory marker measured in the IDEFICS study; more markers could have provided a better insight of their effect in the inflammatory process. Moreover, recent Mendelian randomization studies with genetic CRP marker data do not support a causal role for CRP in the etiology coronary heart disease [40]. Also, in cluster analysis, clusters are not exactly the same at different time points, although in the present study we

found high similarities at both time points for each cluster. Finally, the FFQ covered the 4 previous weeks; therefore, potential differences due to seasonality could not be considered in our analysis. However, the measurements of the subjects were performed in the same period over time. On the other hand, this study also presents some strengths: Firstly, the use of standardized and harmonized information from eight European countries and the use of a validated dietary instrument, providing reproducible estimates of food frequency consumptions. Secondly, the multilevel design, which takes into account differences by country and schools adjusting for a set of relevant confounders such as BMI. Finally, the prospective design of the analysis is a strength as it gives a better insight of a long-term behavior such as diet consumption and its relation with inflammation.

To our knowledge, this is the first prospective study to assess the association between dietary patterns and inflammation, measured by hs-CRP, in a sample of European children. In conclusion, this study shows that a 'sweet and processed' pattern was associated with hs-CRP cross-sectionally and over time. It seems that a long-term pattern characterized by a high relative consumption frequency of sugar and processed products and a low relative consumption frequency of vegetables and fruits is independently related with inflammation already in childhood. Efforts to reduce the frequency of sugar and processed products consumption and to increase the frequency of fruits and vegetables consumption should be undertaken in children, to avoid potential future diseases related with chronic inflammation. These results provide further insight to better understand the association between dietary patterns and inflammation.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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