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ORIGINAL CONTRIBUTION

Associations between fruit and vegetable variety and low-grade inflammation in Portuguese adolescents from LabMed Physical Activity Study

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Abstract
Purpose The dietary guidelines for the consumption of a variety of fruits and vegetables have been recognized as an important factor for achieving healthy eating patterns to reduce the risk of chronic disease throughout the lifespan. Our aim is to assess the association between fruit and vegetable variety and low-grade inflammation in adolescents.
Methods This cross-sectional analysis was conducted with 412 adolescents (ages 14.4 ± 1.7 years; 52% girls). The consumption of a variety of fruits and vegetables was assessed with a food-frequency questionnaire, considering the number of individual/category of fruit or vegetable intake at least once month, and categorized into tertiles. Blood samples were collected to determine C-reactive protein (CRP), interleukin-6 (IL-6), complement component 3 (C3), and 4 (C4). We created categories of lower or higher (inflammatory state) for each biomarker, considering sex- and age-adjusted median values. Then, we computed an overall inflammatory score, by adding all points awarded wherein one point was assigned if biomarker was higher or zero if lower, and created categories of 0–1 or 2–4 biomarkers above the median. The odds ratio (OR) and 95% interval confidence (95% CI) were calculated from binary logistic regression to estimate the magnitude of association between fruit and vegetable variety and inflammatory biomarkers.
Results Adolescents with a greater variety of vegetable consumption (≥13 categories/month) had lower odds of having a higher CRP (OR 0.31, 95% CI 0.15–0.64, $p_{trend} = 0.004$) when compared to those with lower variety consumption (≤6 categories/month), independent of vegetable quantity intake. However, a greater variety of fruit consumption (≥12 categories/month) had higher odds of having a higher IL-6 (OR 4.41, 95% CI 1.67–11.71, $p_{trend} = 0.012$), C3 (OR 3.30, 95% CI 1.23–8.86, $p_{trend} = 0.047$), and inflammatory score (OR 4.90, 95% CI 1.62–14.86, $p_{trend} = 0.017$), when compared to those with lower variety consumption (≤9 categories/month), independent of fruit quantity intake, only for girls.
Conclusions The consumption of a variety of vegetables is inversely associated with lower CRP. This finding supports the current dietary guidelines regarding the consumption of a variety of vegetables. The role of fruit variety in low-grade inflammation should be further studied.

Keywords C-reactive protein · Interleukin 6 · Complement C3 · Complement C4 · Inflammatory score · Variety of diet

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Introduction

Many chronic conditions have been associated with low-grade inflammation [1–4] such as obesity [5], type 2 diabetes [5, 6], cardiovascular diseases [7, 8], and cancer [9, 10], in adulthood and seniors. It has also been reported that low-grade inflammation in children and adolescents is associated with obesity [11, 12], central obesity [13, 14], metabolic syndrome [15, 16], impaired endothelial function and atherosclerosis [17]. Low-grade inflammation is characterized by the increased concentration of inflammatory biomarkers in the bloodstream [2] and several biomarkers including cytokines, such as interleukin-6 (IL-6), and acute phase proteins, such as C-reactive protein (CRP), complement component 3 (C3) and 4 (C4), have been used to define low-grade inflammation. CRP is the most widely used indicator of low-grade inflammation, some authors have also considered IL-6 as well, but less is known about complement C3 and C4 [1]; however, there is still a lack of understanding on what should constitute the best set of biomarkers to properly describe low-grade inflammation [1–3].

Epidemiological evidence shows that fruit and vegetable intake is inversely associated with low-grade inflammation [1]. Studies have reported the importance of increased quantities of fruit and vegetable intake, but little is known about the role of fruit or vegetable variety. However, several dietary guidelines recommend a varied diet, emphasizing plant-based foods in particular [18]. The World Health Organization is very objective in its guidelines and recommends eating "a variety of vegetables and fruits" [19]. More recently, the U.S. updated its dietary guidelines to separate fruit and vegetable groups, recommending "a variety of vegetables" beyond a variety of nutrient-dense foods [20].

The contribution to disease prevention of a large variety of fruit and vegetable intake is limited and results are inconclusive. Several studies have found no relationship between fruit and vegetable variety and incidence of cardiovascular disease [21, 22], stroke [22], or bladder cancer [23], whereas other studies reported negative associations with the risk of type 2 diabetes [24], and cancer [25, 26].

A dramatic increase in chronic disease closely connected with low-grade inflammation has been observed in youth [27, 28], and these conditions can be associated with complications in adulthood, including early onset cardiovascular disease [28]. However, an increased intake of fruits and vegetables can reduce the incidence of chronic diseases, especially cardiovascular disease [29, 30]. Fruit and vegetable intake among adolescents is low [31, 32], even lower than in adults [33], and does not reflect the desired vegetable variety recommended in dietary guidelines [34]. Our aim is to study the association of fruit and vegetable variety with low-grade inflammation in adolescents, as measured by four inflammatory biomarkers and one overall score.

Subjects and methods

Study design and sampling

This is a cross-sectional analysis from the baseline (fall 2011) of the study titled longitudinal analysis of biomarkers and environmental determinants of physical activity study (LabMed Physical Activity Study), a school-based prospective cohort study conducted in five schools in the north of Portugal that have collaborative agreements previously established with our research center. A full description of the study protocol can be found elsewhere [35, 36].

Briefly, a previous sample size was estimated at 1086 subjects, considering a prevalence of 14% for the combined healthy diet/physical activity pattern exposure [40], for a power of 0.80 and two-tailed significance of 5%, and an expected dropout rate of 20%. Students from grades seven and ten were invited to participate ($n = 1678$), and the criterion for participation was that both the adolescents and their parents or legal guardian provided written informed consent ($n = 1229$). However, blood samples were collected only in subjects without known disease. All data were collected in schools.

For this cross-sectional study, the sample comprises 412 adolescents (216 girls), between 12 and 18 years old, for whom both blood sample collection ($n = 534$) and accurate dietary intake ($n = 622$) were available.

Ethical standards

All ethical issues have been guaranteed, and the study was conducted in accordance with the World Medical Association's Helsinki Declaration for Human Studies. Written informed consent was obtained from adolescents and their parents or guardians. The Portuguese Data Protection Authority (#1112434/2011), the Portuguese Ministry of Science and Education (0246200001/2011) and the Faculty of Sport, University of Porto, approved the LabMed Physical Activity Study.

Inflammatory biomarkers assessment and overall inflammatory score

After at least 10 h of fasting, participants in a sitting position donated a blood sample collected from the antecubital vein. The samples were refrigerated (4–8 °C) and sent to a laboratory to determine the inflammatory biomarkers:

high-sensitive CRP by the latex-enhanced turbidimetric assay (Siemens Advia 1600/1800, Erlangen, Germany); IL-6 by the chemiluminescence immunoassay (Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA); and C3 and C4 by the immunoturbidimetric assay (Siemens Advia 1600/1800, Erlangen, Germany).

An elevation in the concentration of inflammatory biomarkers can be minimal or absent in low-grade inflammation [10], and no accepted international cut-points have been defined for adolescents. Therefore, we have decided to consider the inflammatory biomarkers' sex- and age-adjusted median values to create two groups of participants: lower or higher (inflammatory state). The final median values for each category (lower/higher) were 0.11/0.92 mg/L for CRP, 1.90/4.20 ng/L for IL-6, 107.00/127.00 mg/dL for C3, and 17.00/25.55 mg/dL for C4.

We have also calculated an overall inflammatory score, assigning one point to subjects who were above the sex- and age-adjusted medians and zero to those who were below, for each inflammatory biomarker and totaled all points assigned. The overall inflammatory score varies from zero to four points. Two categories were defined: 0–1 (49.9%) and 2–4 (50.1%) inflammatory biomarkers above the median.

Physical activity and sedentary time assessment

GT1M Actigraph accelerometers (ActiGraph, Pensacola, Florida, USA) were used to assess physical activity and sedentary time. This is a lightweight, biaxial monitor that adolescents wore attached tightly at the hip on the right side of the body with the notch facing upwards. It was used during all waking hours and removed during water-based activities for five consecutive days (three weekdays and two weekend days). The epoch length was set to 2 s to allow a more detailed estimate of physical activity intensity.

An automated data-reduction program (ActivLive 6.12, ActiGraph, Pensacola, Florida, USA) was utilized to analyze accelerometer data from individual participants. Non-wearing time was considered when 60 min of consecutive zeros were flagged. A valid day was considered to consist of at least 8 h of accelerometer use. The participants had to have at least three valid days to be included (two weekdays and one weekend day).

After screening, the cut-points proposed by Evensons et al. [37] were used to determine physical activity intensities according to the raw activity counts. Physical activity was expressed in mean counts min^{-1} and also in estimates of the time spent in moderate-to-vigorous physical activity and sedentary time, using min day^{-1}. A total of 83 children did not meet the accelerometers criteria.

Dietary intake assessment

A self-administered, semi-quantitative food-frequency questionnaire validated for a Portuguese population [38] and adapted to adolescents [39] was used to assess dietary intake in the previous 12 months. The food-frequency questionnaire lists 91 food and beverage items or categories with a standard portion size, nine response options (from never or less than once per month to six or more times per day), and a seasonal alternative. Blank lines were included for participants to add any food that was not listed. The portion size in grams was multiplied by the multiple/fraction of daily frequency intake and by a seasonality variation factor for each option selected, and dietary intake was estimated. The Food Processor Plus program version SQL (ESHA Research, Salem, OR, USA), supplemented with the Portuguese food-composition databases [40, 41], was used to convert food to energy and nutrient intakes.

We included only accurate food-frequency questionnaires, using the Goldberg cut-off method [42] adapted by Black [43], for the determination and exclusion of dietary assessment misreporting. Thus, we calculated the basal metabolic rate using the Schofield equation [44], considering sex and age, and a ratio energy intake/basal metabolic rate to compare with 95% confidence limits (cut-offs). The cut-offs for our sample were determined using the following: mean physical activity level, number of days of dietary assessment, within-subject coefficient of variation in energy intake, between-subject variation in physical activity, and variation in basal metabolic rate. The mean physical activity level was 1.23, calculated using accelerometer data (counts min^{-1} and daily use time) per the Trust equation [45]. We considered 21 days of dietary assessment, according to Black, for the food-frequency questionnaire [43]. The within-subject coefficient of variation in energy intake was calculated considering mean and standard deviation of energy intake in our sample and the number of dietary assessments. The between-subject variation in physical activity was calculated considering the mean and standard deviation of physical activity level in our sample. A figure of 8.5% was used for the coefficient of variation of repeated basal metabolic rate measurements, as Black suggested [43]. The cut-offs achieved were 0.61 and 2.48; therefore, adolescents with energy intake/basal metabolic rate outside of this range were considered to have misreported dietary assessment, and 150 adolescents were excluded from the statistical analysis.

The variety of intake of fruits and vegetables was defined by scores considering the total number of unique individual/categories of fruits or vegetables consumed at least once per month over the past 12 months; no point was attributed for consumption <once per month, while 1 point was given for an intake of $\geq$1 time per month. For the fruit variety,

the score considered a maximum of 12 categories, as follows: apple/pear, orange/tangerine, banana, kiwi, strawberry, cherry, peach/plum, melon/watermelon, persimmon, fig/medlar/apricot, grape, and papaya/mango; it excluded candied fruit and fruit juices because their sugar content is unknown and also to avoid replicating the same fruit variety listed above. For the vegetable variety, the score considered a maximum of 15 categories, as follows: white/savoy cabbages, bunch/Portuguese cabbages, curly kale, broccoli, cauliflower/Brussels sprout, turnip sprout/turnip greens/spinach, green bean, lettuce/watercress, onion, carrot, turnip, tomato, pepper, cucumber, pea/broad bean; it excluded starchy vegetables such as potatoes and dried pulses because their starch content is very different from other foods and because there is no consensus about the inclusion of these foods in the vegetable category [46, 47].

Adolescents were classified as having low-, medium-, and high-variety intake, according to the tertiles of the fruit and vegetable variety scores, considering the following: 1st tertile ≤6 categories/month, 2nd tertile 7–12 categories/month, and 3rd tertile ≥13 categories/month for vegetable variety; and for fruit variety, 1st tertile ≤9 categories/month, 2nd tertile 10–11 categories/month, and 3rd tertile = 12 categories/month.

Anthropometric data

Weight and height were measured with a scale (TANITA Inner Scan BC532, Tokyo, Japan) and a stadiometer (SECA 213, Hamburg, Germany), respectively, with the adolescent standing upright, lightly dressed, and without shoes. We calculated the body mass index from the ratio of weight (kg) to height squared (m^2), and adolescents were classified according to Cole's body mass index categories [48].

Pubertal stage

Adolescents self-reported their pubertal stage (from 1 to 5) relatively to secondary sex characteristics, according to the criteria of Tanner and Whitehouse [49]. Briefly, Tanner A indicates the stage of breast development in girls and genitalia development (penis size and testicular volume) in boys; and Tanner B indicates the stage of public hair distribution in both sexes.

Socio-economic status

Socioeconomic status was measured by the family affluence scale [50], from 0 to 9 points; a lower score indicates a lower socioeconomic status. This scale is a self-reported questionnaire, was developed specifically to measure children and adolescents socio-economic status in the context of school, and considers items about adolescents' family such as number of car, bedrooms, vacations, computers, and others.

Smoking habits

Adolescents self-reported their smoking habits and were classified according to the World Health Organization's criteria [51] as: non-smokers, former smokers (individuals who had stopped smoking for at least 6 months), occasional smokers (individuals who smoked, on average, less than one cigarette a day), and current smokers (individuals who smoked at least one cigarette a day).

Statistical analyses

Participants' characteristics are presented for the whole sample and by sex as percentages for categorical variables and as medians and 25th and 75th percentiles for continuous variables. To assess the sex differences for each characteristic, the Mann–Whitney *U* test was used for continuous variables and a Chi-square test for categorical variables.

We performed a Chi-square test to study the difference between inflammatory biomarker categories across the variety of fruit and vegetable intake (in tertiles).

To study the association between fruit and vegetable variety tertiles and inflammatory biomarker categories, we constructed binary logistic regression models. There were nine models for each inflammatory biomarker and for the overall inflammation score, as dependent variables, and fruit or vegetable variety tertiles as predictors, using the first variety tertiles as reference: adjusted models 1, 2 and 3; for overall sample, for girls, and for boys. Models 1 were sex-adjusted for overall sample or crude models for girls and boys. Models 2 were adjusted for sex (only for overall sample), age, pubertal stage (Tanner A and B), body mass index, energy intake, socioeconomic status, sedentary time, moderate-to-vigorous physical activity, and smoking habits. Models 3 were adjusted for the same variables as models 2 plus for the quantity of fruit on the fruit variety model or the quantity of vegetable on the vegetable variety model. A multicollinearity diagnosis between independent variables was conducted and nothing was detected.

Post hoc power calculations were conducted considering the smaller sample size ($n = 329$), the smaller odds ratio for fully adjusted model (OR 0.3), a null hypothesis value of 0.5, a significance level of 0.05, and we achieved a power of >0.80.

A 0.05 level of significance and 95% CI (confidence interval) were considered. Data analysis was performed using the statistical package SPSS®, version 21.0 (SPSS Inc., Chicago, IL, USA), and power analysis was performed using G*Power, version 3.1 (Faul, Erdfelder, Lang, and Buchner, 2007).

Table 1 Participants' characteristics of Portuguese adolescents from the LabMed Physical Activity Study

	All[a] ($n = 412$)	Girls[a] ($n = 216$)	Boys[a] ($n = 196$)	p value[b]
Age (years)	14.9 (12.6–15.7)	14.9 (12.6–15.6)	15.0 (12.7–15.8)	0.143
Pubertal stage (Tanner A)				
2	7.2%	33.3%	11.7%	**0.001**
3	33.0%	54.6%	36.2%	
4	47.1%	12.0%	38.8%	
5	12.6%	2.8%	13.3%	
Pubertal stage (Tanner B)				
2	7.0%	22.7%	11.7%	**<0.001**
3	20.6%	46.8%	18.4%	
4	50.2%	27.8%	54.1%	
5	22.1%	3.2%	15.8%	
Body mass index				
Underweight	3.6%	3.7%	3.6%	0.574
Normal weight	66.7%	65.3%	68.4%	
Overweight	22.1%	21.8%	22.4%	
Obese	7.5%	9.3%	5.6%	
Socioeconomic status	6.0 (5.0–8.0)	6.0 (6.0–8.0)	6.0 (5.0–8.0)	0.416
Sedentary time (min day^{-1})[c]	667.4 (619.4–725.3)	678.4 (632.8–734.1)	645.9 (607.5–713.2)	**0.003**
Moderate-to-vigorous physical activity (min day^{-1})[c]	51.0 (39.1–65.3)	45.5 (35.1–59.5)	56.7 (43.0–71.5)	**<0.001**
Smoking habits[d]				
Current smokers	1.0%	0.9%	1.0%	**0.037**
Occasional smokers	1.7%	1.4%	2.0%	
Former smokers	7.8%	4.6%	11.2%	
Non-smokers	89.6%	93.1%	85.7%	
Energy intake (kcal day^{-1})	2 063 (1 598–2 593)	2 016 (1 559–2 404)	2 123 (1 648–2 730)	**0.005**
Vegetable intake				
Quantity (g/day)	107.4 (47.0–180.3)	95.8 (40.8–177.4)	120.7 (55.3–183.5)	0.264
Variety (categories/month)	10.0 (5.0–13.0)	9.0 (5.0–12.0)	10.0 (6.0–14.0)	**0.004**
Variety tertiles				
1st: ≤6	33.3%	38.4%	27.6%	**0.012**
2nd: 7–12	36.9%	37.5%	36.2%	
3rd: ≥13	29.9%	24.1%	36.2%	
Fruit intake				
Quantity (g/day)	192.7 (115.0–307.8)	204.4 (113.4–320.7)	188.9 (119.3–290.4)	0.735
Variety (categories/month)	10.0 (7.0–11.0)	10.0 (7.0–11.0)	10.0 (8.0–12.0)	**0.016**
Variety tertiles				
1st: ≤9	43.7%	47.7%	39.3%	**0.009**
2nd: 10–11	34.7%	36.6%	32.7%	
3rd: =12	21.6%	15.7%	28.1%	
CRP (mg/L)	0.20 (0.11–0.77)	0.11 (0.11–0.49)	0.34 (0.11–1.26)	**<0.001**
IL-6 (ng/L)	1.90 (1.90–3.40)	1.90 (1.90–3.40)	1.90 (1.90–3.35)	0.561
C3 (mg/dL)	116.0 (107.0–126.5)	119.0 (107.0–127.0)	115.0 (106.5–126.0)	0.888

Table 1 continued

	All[a] ($n = 412$)	Girls[a] ($n = 216$)	Boys[a] ($n = 196$)	p value[b]
C4 (mg/dL)	20.0 (16.0–24.0)	20.0 (16.0–25.0)	20.0 (17.0–24.0)	0.561
Overall inflammatory biomarker score[e]	1.78 (1.00–3.00)	1.79 (1.00–3.00)	1.77 (1.00–3.00)	0.884

Bold values mean that there is a statistically significant difference between the sexes

CRP C-reactive protein, *IL-6* Interleukin-6, *C3* complement component 3, *C4* complement component 4

[a] The data shown column percentage for categorical variables and median (25th–75th percentiles) for continuous variables

[b] p value was calculated based on Qui-squared test for categorical variables and Mann–Whitney U test for continuous variables

[c] It was considered $n = 329$ (55.9% girls), because there is some missing values in sedentary time and moderate-to-vigorous physical activity variables

[d] Qui-squared test performed with "Current smokers" and "Occasional smokers" together to improve power of test

[e] Overall inflammatory biomarker score were designed summing the inflammatory biomarkers (CRP, IL-6, C3 and C4) categories, wherein for each category was assigned one point if the biomarker was above the median adjusted by age and sex or zero if below the median

Results

The sample characteristics are presented in Table 1. On average, boys presented a higher variety of fruit and vegetable intake and higher levels of CRP than girls ($p < 0.05$ for both).

A descriptive analysis between fruit and vegetable varieties and inflammatory biomarkers is presented in Table 2. Adolescents within the 3rd tertile of vegetable variety (higher variety) had a higher prevalence of a lower level of CRP, IL-6, C3, and the overall inflammatory score than adolescents within the 1st or 2nd tertiles. In respect to fruit variety, no differences were observed.

The magnitude of association between vegetable variety and inflammatory biomarkers, in adjusted for confounders, is shown in Table 3. We found an inverse

Table 2 Differences between inflammatory biomarkers categories across fruit and vegetable variety tertiles

	Vegetable variety (categories/month)				Fruit variety (categories/month)			
	1st tertile: ≤6 (%)	2nd tertile: 7–12 (%)	3rd tertile: ≥13 (%)	p[a]	1st tertile: ≤9 (%)	2nd tertile: 10–11 (%)	3rd tertile: =12 (%)	p[a]
CRP (mg/L)								
Lower	**50.7**	**43.7**	**69.9**	**<0.001**	47.6	55.6	61.0	0.123
Higher	**49.3**	**56.3**	**30.1**		52.4	44.4	39.0	
IL-6 (ng/L)								
Lower	**65.4**	**56.3**	**71.5**	**0.003**	69.9	59.9	62.2	0.161
Higher	**34.6**	**43.7**	**28.5**		30.1	40.1	37.8	
C3 (mg/dL)								
Lower	**55.9**	**41.7**	**58.5**	**0.010**	52.4	52.4	48.8	0.840
Higher	**44.1**	**58.3**	**41.5**		47.6	47.6	51.2	
C4 (mg/dL)								
Lower	54.4	45.7	58.5	0.091	56.6	49.2	53.7	0.398
Higher	45.6	54.3	41.5		43.4	50.8	46.3	
Overall inflammatory biomarker score[b]								
Biomarkers above median								
0–1	**44.9**	**35.8**	**56.1**	**0.003**	46.2	43.3	46.3	0.840
2–4	**55.1**	**64.2**	**43.9**		53.8	56.7	53.7	

Bold values mean that there is a statistically significant difference between the variety tertiles

CRP C-reactive protein, *IL-6* Interleukin-6, *C3* complement component 3, *C4* complement component 4

[a] The p value was calculated based on Qui-square test

[b] Overall inflammatory biomarker score were designed summing the inflammatory biomarkers (CRP, IL-6, C3 and C4) categories, wherein for each category was assigned one point if the biomarker was above the median adjusted by age and sex or zero if below the median

Table 3 Association between vegetable variety and inflammatory biomarkers categories

	All sample				Girls				Boys			
	Vegetable variety: OR (95% CI)				Vegetable variety: OR (95% CI)				Vegetable variety: OR (95% CI)			
	Continuous	Tertiles (1st tertile ≤6: OR = 1.00)			Continuous	Tertiles (1st tertile ≤6: OR = 1.00)			Continuous	Tertiles (1st tertile ≤6: OR = 1.00)		
		2nd tertile 7–12	3rd tertile ≥13	p_{trend}		2nd tertile 7–12	3rd tertile ≥13	p_{trend}		2nd tertile 7–12	3rd tertile ≥13	p_{trend}
CRP models[a]												
Adjusted 1	**0.95 (0.91–0.99)***	1.33 (0.84–2.13)	**0.42 (0.25–0.71)****	**0.004**	0.97 (0.91–1.02)	1.22 (0.66–2.24)	**0.42 (0.20–0.88)***	**0.017**	**0.93 (0.87–0.99)***	1.51 (0.74–3.10)	**0.45 (0.22–0.92)***	**0.002**
Adjusted 2[b]	**0.93 (0.88–0.98)****	1.14 (0.65–1.99)	**0.32 (0.17–0.61)*****	**0.002**	0.95 (0.88–1.02)	1.14 (0.54–2.41)	**0.30 (0.11–0.77)***	**0.012**	**0.90 (0.83–0.98)***	0.99 (0.39–2.51)	**0.30 (0.11–0.78)***	**0.015**
Adjusted 3[b]	**0.93 (0.88–0.99)***	1.23 (0.63–2.02)	**0.31 (0.15–0.64)****	**0.004**	0.95 (0.87–1.03)	1.11 (0.51–2.40)	**0.28 (0.10–0.78)***	**0.014**	**0.90 (0.82–1.00)***	1.04 (0.39–2.78)	**0.32 (0.10–0.98)***	**0.039**
IL-6 models[a]												
Adjusted 1	1.01 (0.95–1.04)	1.53 (0.95–2.47)	0.79 (0.46–1.34)	0.538	**1.07 (1.01–1.14)***	**2.28 (1.20–4.35)***	1.54 (0.74–3.20)	**0.043**	**0.92 (0.86–0.98)****	0.88 (0.43–1.80)	**0.36 (0.17–0.79)***	**0.021**
Adjusted 2[b]	1.00 (0.94–1.05)	1.57 (0.90–2.74)	0.73 (0.38–1.38)	0.501	1.05 (0.98–1.13)	**2.23 (1.07–4.67)***	1.12 (0.47–2.70)	0.070	0.92 (0.85–1.00)	0.88 (0.36–2.18)	0.37 (0.13–1.03)	0.121
Adjusted 3[b]	1.00 (0.94–1.06)	1.62 (0.91–2.90)	0.76 (0.38–1.54)	0.623	1.04 (0.96–1.13)	2.05 (0.96–4.38)	0.94 (0.36–2.45)	0.080	0.97 (0.99–1.00)	1.32 (0.48–3.66)	0.66 (0.20–2.19)	0.390
C3 models[a]												
Adjusted 1	1.01 (0.97–1.05)	**1.77 (1.11–2.83)***	0.92 (0.56–1.51)	0.947	1.05 (0.99–1.11)	**2.32 (1.24–4.34)****	1.30 (0.65–2.62)	**0.028**	0.97 (0.91–1.03)	1.22 (0.60–2.48)	0.61 (0.30–1.26)	0.121
Adjusted 2[b]	0.99 (0.94–1.04)	1.78 (0.99–3.18)	0.62 (0.33–1.18)	0.286	1.02 (0.95–1.10)	**2.47 (1.16–5.27)***	0.85 (0.35–2.04)	**0.018**	0.94 (0.86–1.03)	0.88 (0.32–2.41)	0.37 (0.13–1.07)	0.130
Adjusted 3[b]	1.00 (0.94–1.07)	1.84 (1.00–3.37)	0.66 (0.32–1.36)	0.435	1.06 (0.97–1.16)	**2.85 (1.26–6.43)***	1.08 (0.40–2.95)	**0.015**	0.92 (0.82–1.03)	0.72 (0.25–2.09)	**0.24 (0.06–0.87)***	0.068
C4 models[a]												
Adjusted 1	1.00 (0.96–1.05)	1.41 (0.89–2.25)	0.85 (0.52–1.40)	0.660	0.99 (0.93–1.05)	1.41 (0.76–2.61)	0.60 (0.29–1.22)	0.065	1.02 (0.96–1.08)	1.47 (0.72–2.99)	1.17 (0.57–2.39)	0.562
Adjusted 2[b]	1.00 (0.95–1.05)	1.32 (0.77–2.25)	0.76 (0.42–1.36)	0.452	0.95 (0.89–1.03)	0.95 (0.47–1.94)	0.43 (0.18–1.01)	0.104	1.05 (0.97–1.13)	1.96 (0.80–4.79)	1.43 (0.58–3.57)	0.340
Adjusted 3[b]	1.02 (0.93–1.09)	1.50 (0.85–2.64)	0.94 (0.48–1.82)	0.967	0.98 (0.90–1.06)	1.04 (0.50–2.18)	0.50 (0.20–1.27)	0.210	1.08 (0.99–1.19)	2.34 (0.90–6.07)	1.95 (0.68–5.63)	0.216
Overall inflammatory biomarker score models[a, c]												
Adjusted 1	0.98 (0.94–1.02)	1.50 (0.93–2.41)	0.65 (0.39–1.06)	0.140	1.00 (0.95–1.06)	1.59 (0.85–2.97)	0.76 (0.38–1.52)	0.107	0.95 (0.89–1.01)	1.37 (0.66–2.82)	0.54 (0.27–1.11)	**0.025**
Adjusted 2[b]	0.96 (0.91–1.01)	1.52 (0.86–2.70)	**0.47 (0.25–0.87)***	**0.044**	0.98 (0.91–1.06)	1.52 (0.72–3.21)	0.52 (0.22–1.25)	0.050	0.93 (0.85–1.01)	1.42 (0.54–3.72)	0.38 (0.14–1.02)	**0.023**
Adjusted 3[b]	0.99 (0.93–1.05)	1.76 (0.96–3.23)	0.61 (0.30–1.22)	0.272	1.00 (0.92–1.09)	1.64 (0.76–3.56)	0.60 (0.23–1.55)	0.070	0.97 (0.87–1.07)	1.84 (0.64–5.26)	0.59 (0.18–1.88)	0.078

Bold values mean that odds ratios or *p* for trend are statistically significant

OR odds ratio, *CI* confidence interval, *CRP* C-reactive protein, *IL-6* Interleukin-6, *C3* Complement component 3, *C4* Complement component 4

* $p < 0.05$; ** $p < 0.01$, *** $p < 0.001$

[a] Models adjustment were: (1) for sex in all sample and crude for girls and boys; (2) for sex (for all sample), age, pubertal stage (tanner A and B), body mass index, energy intake, socioeconomic status, sedentary time, moderate-to-vigorous physical activity, and smoking habits; (3) for the same variables of model 2 plus vegetable quantity

[b] These models were performed with $n = 329$ (55.9% girls) because there is some missing values in sedentary time and moderate-to-vigorous physical activity variables

[c] Overall inflammatory biomarker score were designed summing the inflammatory biomarkers (CRP, IL-6, C3 and C4) categories, wherein for each category was assigned one point if the biomarker was above the median adjusted by age and sex or zero if below the median

association between vegetable variety and CRP, continuously and by tertile: increasing the consumption of vegetable variety reduced the probability of having an higher CRP (OR 0.93; 95% CI 0.88–0.99; $p < 0.05$), and adolescents with higher vegetable variety intake (3rd tertile) had a lower prevalence of a higher level of CRP (OR 0.31; 95% CI 0.15–0.64; $p_{trend} = 0.004$) when compared to adolescents with lower variety (1st tertile), in the fully adjusted model (including vegetable quantity intake). The same trend was observed in both sexes separately, but only in boys we found an inverse association between continuous vegetable variety and CRP. In addition, adolescents with higher vegetable variety intake (3rd tertile) had a lower prevalence of higher overall inflammatory score (OR 0.47; 95% CI 0.25–0.87; $p_{trend} = 0.044$) when compared to adolescents with lower variety (1st tertile) in the model adjusted for biological and lifestyle variables. However, this association was lost when we included vegetable quantity intake. Furthermore, only girls presented a positive statistically significant trend to have a higher level of C3, but the third tertile was not statistically significant (OR 1.08; 95% CI 0.40–2.95; $p_{trend} = 0.015$) when compared to adolescents with lower variety (1st tertile) in the fully adjusted model, including vegetable quantity intake. However, girls with higher vegetable quantity intake (3rd tertile) had a lower prevalence of a higher level of C3 (OR 0.17; 95% CI 0.05–0.62; $p_{trend} = 0.004$) when compared to girls with lower quantity (1st tertile) in the fully adjusted model, including vegetable variety intake (Table 5 in supplementary material). In addition, boys and not girls with higher vegetable quantity intake (3rd tertile) had a lower prevalence of higher IL-6 (OR 0.24; 95% CI 0.08–0.71; $p_{trend} = 0.036$) and overall inflammatory score (OR 0.24; 95% CI 0.08–0.72; $p_{trend} = 0.035$) when compared to boys with lower quantity (1st tertile) in the model adjusted for biological and lifestyle variables (excluding vegetable variety intake).

The magnitude of association between fruit variety and inflammatory biomarkers, adjusted for confounders, is shown in Table 4. Increasing the consumption of fruit variety increased the probability of having an higher C4 (OR 1.09; 95% CI 1.00–1.20; $p < 0.05$), and C4 presented a positive statistically significant trend in respect to fruit variety; however, the third tertile was not statistically significant (OR 1.72; 95% CI 0.91–3.23; $p_{trend} = 0.016$). In addition, statistically significant positive associations and trends were observed, only for girls, for IL-6, C3, and inflammatory score. However, girls and not boys with higher fruit quantity intake (3rd tertile) had a lower prevalence of a higher level of C4 (OR 0.27; 95% CI 0.10–0.74; $p_{trend} = 0.033$) when compared to girls with lower quantity (1st tertile) in the fully adjusted model, including fruit variety intake (Table 6 in supplementary material).

Discussion

The main finding of the present study emphasizes the importance of consuming a variety of vegetables to reduce low-grade inflammation, considering that high vegetable variety was inversely associated with CRP (p for trend <0.05, in all models, for overall sample and by sex). This relationship remains independent of vegetable quantity intake (p for trend <0.05 in the fully adjusted model, including vegetable quantity). These results support the current dietary guidelines regarding the importance of vegetable variety for a healthy eating pattern [20].

The consumption of vegetables and fruits has been reported to be an important factor for the prevention of low-grade inflammation, but the focus of the discussion has especially been on the quantity of fruit and vegetable intake, while little has been discussed regarding variety, particularly for each of these two food groups [1]. Consuming a diet characterized by a large variety of vegetables, rather than consuming a monotonous diet, may favor reduced exposure to any undesirable, harmful components [52] and enables individuals to achieve intake of a larger number of nutrients and bioactive components [19, 53] including vitamins, minerals, and phytochemicals [54]. In fact, plant-based foods are recognized as rich in bioactive phytochemicals [55], including those that have been widely studied such as flavonoids and carotenoids, and other unknown bioactive components that could be beneficial, either alone or in combination [54]. Those bioactive compounds are recognized as having an anti-inflammatory effect, although their mechanisms remain poorly understood [56]; therefore, the exact components and their dosages for supplementation purposes to reduce inflammation have not yet been identified [57]. Unlike supplementation, the food matrix is accompanied by a variety of substances that can exert additive and synergistic functions [57], so the beneficial effects of those bioactive components and their diversity can also be attributed to additive and synergistic effects responsible for their potent antioxidant activities [58]. Despite our cross-sectional design, our results seem to reflect the additive and synergistic effects of the combination of different bioactive compounds, in a variety of vegetables as whole foods as an import factor in reducing low-grade inflammation, in this study assessed by the inflammatory biomarker CRP.

It is interesting to note that this inverse relationship between vegetable variety intake and low-grade inflammation was found only for CRP, though a positive trend was found for C3 model in girls and the overall inflammatory score models were inverse associated with vegetable variety intake, but this association was lost when adjusted for vegetable quantity intake. The evidence indicates that certain bioactive compounds can be helpful in decreasing

Table 4 Association between fruit variety and inflammatory biomarkers categories

	All sample				Girls				Boys			
	Fruit variety: OR (95% CI)				Fruit variety: OR (95% CI)				Fruit variety: OR (95% CI)			
	Continuous	Tertiles (1st tertile ≤9: OR = 1.00)			Continuous	Tertiles (1st tertile ≤9: OR = 1.00)			Continuous	Tertiles (1st tertile ≤9: OR = 1.00)		
		2nd tertile 10–11	3rd tertile =12	p_{trend}		2nd tertile 10–11	3rd tertile =12	p_{trend}		2nd tertile 10–11	3rd tertile =12	p_{trend}
CRP models[a]												
Adjusted 1	0.95 (0.89–1.02)	0.87 (0.56–1.35)	0.71 (0.42–1.20)	0.239	1.04 (0.94–1.16)	1.23 (0.68–2.22)	1.10 (0.50–2.41)	0.791	**0.86 (0.78–0.96)****	0.55 (0.28–1.08)	**0.47 (0.23–0.96)***	0.076
Adjusted 2[b]	0.95 (0.88–1.04)	0.97 (0.57–1.64)	0.62 (0.33–1.17)	0.315	1.05 (0.93–1.19)	1.18 (0.59–2.38)	1.03 (0.41–2.63)	0.893	**0.84 (0.74–0.97)***	0.73 (0.30–1.76)	**0.37 (0.15–0.94)***	0.103
Adjusted 3[b]	0.99 (0.90–1.08)	1.12 (0.65–1.93)	0.74 (0.39–1.42)	0.729	1.08 (0.95–1.24)	1.29 (0.63–2.63)	1.15 (0.44–2.98)	0.787	0.88 (0.76–1.02)	0.92 (0.36–2.32)	0.48 (0.18–1.28)	0.273
IL-6 models[a]												
Adjusted 1	1.04 (0.97–1.12)	1.01 (0.64–1.60)	1.17 (0.69–1.99)	0.807	**1.13 (1.02–1.26)***	1.37 (0.74–2.53)	**2.69 (1.22–5.94)***	0.050	0.96 (0.87–1.06)	0.67 (0.34–1.36)	0.56 (0.26–1.18)	0.266
Adjusted 2[b]	1.04 (0.95–1.13)	1.04 (0.61–1.79)	1.74 (0.92–3.30)	0.253	1.12 (0.98–1.27)	1.23 (0.61–2.47)	**3.67 (1.42–9.45)****	**0.024**	0.98 (0.87–1.12)	0.83 (0.34–2.07)	0.90 (0.34–2.37)	0.925
Adjusted 3[b]	1.09 (0.99–1.20)	1.10 (0.63–1.93)	**2.16 (1.11–4.20)***	0.066	**1.18 (1.03–1.35)***	1.52 (0.73–3.16)	**4.41 (1.67–11.71)****	**0.012**	1.02 (0.88–1.17)	0.95 (0.37–2.49)	1.06 (0.38–2.84)	0.977
C3 models[a]												
Adjusted 1	1.01 (0.94–1.08)	1.04 (0.67–1.62)	1.16 (0.70–1.94)	0.635	**1.12 (1.01–1.24)***	1.51 (0.84–2.72)	**2.56 (1.14–5.72)***	0.059	0.92 (0.84–1.01)	0.65 (0.33–1.26)	0.60 (0.30–1.21)	0.274
Adjusted 2[b]	1.05 (0.96–1.15)	1.08 (0.63–1.86)	1.36 (0.71–2.60)	0.451	**1.16 (1.02–1.32)***	1.69 (0.84–3.40)	**3.14 (1.19–8.28)***	0.055	0.93 (0.81–1.06)	0.63 (0.24–1.66)	0.57 (0.21–1.59)	0.500
Adjusted 3[b]	1.07 (0.97–1.17)	1.15 (0.66–2.00)	1.48 (0.76–2.88)	0.320	**1.18 (1.03–1.34)***	1.74 (0.86–3.55)	**3.30 (1.23–8.86)***	**0.047**	0.96 (0.82–1.11)	0.72 (0.27–1.96)	0.68 (0.23–1.98)	0.738
C4 models[a]												
Adjusted 1	1.04 (0.97–1.12)	**1.64 (1.06–2.56)***	1.17 (0.69–1.96)	0.110	**1.13 (1.02–1.26)***	**1.88 (1.04–3.41)***	2.02 (0.86–4.76)	0.063	0.97 (0.89–1.07)	1.38 (0.71–2.67)	0.76 (0.38–1.53)	0.277
Adjusted 2[b]	1.06 (0.97–1.15)	**1.71 (1.02–2.85)***	1.46 (0.79–2.68)	0.057	**1.17 (1.03–1.32)***	1.82 (0.93–3.55)	2.32 (0.93–5.78)	0.095	0.95 (0.84–1.07)	1.61 (0.68–3.80)	0.82 (0.33–2.01)	0.308
Adjusted 3[b]	**1.09 (1.00–1.20)***	**1.96 (1.15–3.33)***	1.72 (0.91–3.23)	**0.016**	**1.19 (1.05–1.36)****	1.96 (0.99–3.87)	2.52 (1.00–6.36)	0.064	1.00 (0.87–1.14)	2.14 (0.86–5.33)	1.17 (0.45–3.05)	0.214
Overall inflammatory biomarker score models[a, c]												
Adjusted 1	1.01 (0.94–1.08)	1.09 (0.70–1.70)	0.99 (0.59–1.65)	0.852	**1.14 (1.03–1.26)***	1.48 (0.82–2.67)	**2.54 (1.11–5.85)***	0.072	0.91 (0.82–1.00)	0.73 (0.72–1.43)	**0.47 (0.23–0.95)***	0.107
Adjusted 2[b]	1.02 (0.93–1.11)	1.10 (0.65–1.89)	1.22 (0.65–2.32)	0.545	**1.17 (1.03–1.33)***	1.47 (0.74–2.92)	**4.11 (1.43–11.87)****	**0.031**	**0.85 (0.73–0.99)***	0.77 (0.30–1.93)	**0.37 (0.14–0.98)***	0.124
Adjusted 3[b]	1.05 (0.96–1.15)	1.24 (0.72–2.15)	1.44 (0.74–2.78)	0.268	**1.21 (1.06–1.38)****	1.63 (0.81–3.27)	**4.90 (1.62–14.86)***	**0.017**	0.87 (0.75–1.02)	0.87 (0.34–2.26)	0.45 (0.16–1.24)	0.251

Bold values mean that odds ratios or *p* values for trend are statistically significant

OR odds ratio, *CI* confidence interval, *CRP* C-reactive protein, *IL-6* Interleukin-6, *C3* Complement component 3, *C4* Complement component 4

* $p < 0.05$; ** $p < 0.01$, *** $p < 0.001$

[a] Models adjustment were: (1) for sex in all sample and crude for girls and boys; (2) for sex (for all sample), age, pubertal stage (tanner A and B), body mass index, energy intake, socioeconomic status, sedentary time, moderate-to-vigorous physical activity, and smoking habits; (3) for the same variables of model 2 plus fruit quantity

[b] These models were performed with $n = 329$ (55.9% girls) because there is some missing values in sedentary time and moderate-to-vigorous physical activity variables

[c] Overall inflammatory biomarker score were designed summing the inflammatory biomarkers (CRP, IL-6, C3 and C4) categories, wherein for each category was assigned one point if the biomarker was above the median adjusted by age and sex or zero if below the median

cardiovascular disease risk factors [59], and CRP is recognized as an established inflammatory biomarker for the risk of cardiovascular events [60]. Thus, our findings are in accordance with a review showing that a number of dietary intervention studies have provided evidence that dietary flavonoids can modulate CRP production [3]. In addition, studies have indicated that total flavonoid intake [61] or serum level of β-carotene [62] are inversely associated with serum CRP.

Our results show a significant association (p for trend <0.05) between low-grade inflammation and vegetable variety but not for fruit variety, contrary to what we expected. Furthermore, fruit variety was positively and significantly associated with C4 and IL-6 for overall sample, and with IL-6, C3, C4, and inflammatory score only for girls; and which remains to be explained. Possibly, these results may be due to the fruit quantity was inversely associated with some inflammatory biomarkers in models 3 (Table 6 in supplementary material), including IL-6 (continuously), C4 and biomarker score (continuously and in tertiles). Then, fruit quantity appears to be more important in reducing the inflammation than the fruit variety.

Furthermore, an important factor to consider is a possible influence of variety intake on quantity intake, and we included these variables in models 3 as covariate to control the possible effect of quantity intake. In fact, Raynor and Osterholt demonstrated in an experimental study that wide fruit variety (different fruit snacks) increases the amount of fruit consumed compared to fruit monotony (same fruit snack) [63]. Moreover, we found a higher mean consumption of fruit quantity (230.0 ± 178.2 g) and variety (9.9 ± 2.9 categories in a maximum of 12) compared to vegetable quantity (143.9 ± 150.8 g) and variety (9.1 ± 4.6 categories in a maximum of 15). We also observed that fruit variety is more homogeneous (lower standard deviation) than vegetable variety, and therefore, vegetable variety was more discriminant than fruit variety on showing low-grade inflammation.

In addition, several studies have found an inverse association between fruit quantity and inflammatory biomarkers, especially CRP [64–67], and IL-6 [68], both biomarkers considered indicator of cardiovascular disease [69, 70], but Mendelian randomization analyses showed that IL-6 [71] but not CRP [72] is a causal factor in the development of coronary heart disease. However, the role of C3 and C4 remains unknown. According to our knowledge, no studies have been published about fruit variety and low-grade inflammation; when fruit and vegetable variety are measured together, the negative association with CRP may be described [73]. However, considering that the composition of fruits and vegetables may be different among them, particularly for sugar content (fructose) [52], to consider their separate effects seems to be relevant. One factor that could be addressed in future research is the focus on the fructose content of fruit. A direct association between fructose intake and insulin resistance may exist [74, 75], and it has been found that beverages sweetened with fructose can potentially increase CRP [76]. In fact, high fructose intake may be an inductor form of visceral adipose increase, which may stimulate inflammatory responses that further promote liver lipid accumulation and impair hepatic insulin signaling [77]. Furthermore, a positive relation between C4 and impaired glucose metabolism in adolescents were already observed [78]. The findings about IL-6 are controversial, while some authors have shown a positive relationship with impaired glucose metabolism in adolescents [79], other authors have demonstrated no association [78].

Several limitations should be acknowledged. First, variety intake has been recognized as a factor for increased quantity intake [80]. However, in model adjusted 3, we included the quantity intake, and in fact, the results changed in overall inflammatory score model. Second, we used a food-frequency questionnaire that combines several fruits and vegetables into single items, making it impossible to distinguish one from another, and thus the variety may have possibly been underestimated. Furthermore, several studies used food-frequency questionnaire to measure fruit and vegetable variety intake [21, 23, 25, 26, 73], which may be a positive factor for comparison studies. Third, food-frequency questionnaire may overestimate the dietary intake [81], particularly for healthy foods, such as fruit and vegetables, which are perceived as socially acceptable foods [82]. Our questionnaire considers 27 items for fruits and vegetables of 91 items in total, so it is expected that there is an overestimation of these foods. Forth, our variety criteria were considered an item of food-frequency questionnaire consumed monthly which can be a very long time to consider a variety. However, this cut-off point was used for several authors [25, 73, 83, 84]. Fifth, because of the lack of established cut-off points for inflammatory biomarkers for adolescents, and because the increase of inflammatory biomarkers in low-grade inflammation may be very low or even absent [2], we used sex–age-adjusted median values to create two categories of inflammatory states, permitting us to rank the sample and classify it according to lowest and highest inflammatory state. Nevertheless, our cut-off points for CRP (varying from 0.11 to 0.79 mg/L) are close to that reported by Visser et al. (0.22 mg/L) [12], reporting a positive association with overweight in children and adolescents. Furthermore, using the CRP cut-off point for

increased risk of cardiovascular events for adults [85], considering CRP categories of low <1 mg/L and average/high ≥1 mg/L, excluding adolescents with CRP >10 mg/L, our results are similar for vegetable variety in model 3 (OR 0.26; 95% CI 0.10–0.67; $p_{trend} = 0.007$). Sixth, in addition to food consumption, also confounding factors were based on self-reports, namely pubertal stage, which always gives a chance of bias.

The strengths of our work include, beyond the novelty of its aim, the use of objectively measured physical activity and sedentary time as covariates, once sedentary time is considered a risk factor for cardiovascular health independent of physical activity levels [86], and physical activity has been reported as an important inductor of an anti-inflammatory environment [87]. Moreover, we used only accurate food-frequency questionnaires, according to Goldberg's method [43], which is useful for evaluating the mean population bias in reports of energy intake. It recommends the use of information on physical activity rather than theoretical values available, which we followed. Furthermore, our models considered other important potential confounders such as age, body mass index, sex, and smoking habits that have been shown to be associated with inflammatory biomarker concentration [2, 3]. Another strength is the use of a set of inflammatory biomarkers and an overall inflammatory score because inflammatory biomarkers, in general and in healthy people, are non-specific pro-inflammatory response markers [3].

In summary, vegetable variety intake, independent of vegetable quantity intake, was inversely associated with CRP after adjustments for several biological and lifestyle confounders. These findings support the recommendation for choosing a variety of vegetables to ensure a healthy eating pattern. Relationship between low-grade inflammation and variety related to fruit intake remained unclear and studies considering other cut-off points for fruit and vegetable variety and other dietary intake assessment methodologies such as food record are desired. Future studies using longitudinal methodologies are also necessary to confirm or rule out our findings.

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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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