The Journal of Nutrition
Nutritional Immunology

Total Polyphenol Intake Is Inversely Associated with a Pro/Anti-Inflammatory Biomarker Ratio in European Adolescents of the HELENA Study

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ABSTRACT

Background: Although high dietary polyphenol intake is negatively associated with risk of certain inflammation-associated chronic diseases, the underlying mechanisms are not fully understood and few studies have explored this in adolescents.

Objective: This study aimed to evaluate the association between intakes of total polyphenols, polyphenol classes, and the 10 most commonly consumed individual polyphenols with inflammatory biomarkers in the blood of European adolescents.

Methods: In the Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) Study, 526 adolescents (54% girls; 12.5–17.5 y) had data on inflammatory biomarkers and polyphenol intake from 2 nonconsecutive 24-h recalls via matching with the Phenol-Explorer database. Inflammatory biomarkers in serum were IL-1, IL-2, IL-4, IL-5, IL-6, IL-10, transforming growth factor β1 (TGF-β1), TNF-α, IFN-γ, soluble vascular adhesion molecule 1 (sVCAM-1), soluble intercellular adhesion molecule 1 (sICAM-1), soluble E-selectin (sE-selectin), white blood cells, lymphocytes, T cells, and C-reactive protein. Multilevel linear models were used to test associations of polyphenol intake with a pro/anti-inflammatory biomarker ratio [(zTNF-α + zIL-6 + zIL-1)/3/zIL-10] as well as with separate inflammatory biomarkers, adjusted for sociodemographic variables, diet inflammation index, BMI z score, and serum triglycerides.

Results: The pro/anti-inflammatory biomarker ratio was linearly inversely associated with the intake of total polyphenols ($\beta = -0.11$, $P = 0.040$). When other inflammation biomarkers were considered, the serum IL-10 concentration was inversely associated with total polyphenol ($\beta = -0.12$, $P = 0.017$) and flavonoid ($\beta = -0.12$, $P = 0.013$) intakes, findings that were inconsistent with the biomarker ratio results. However, the anti-inflammatory capacity of polyphenols was confirmed by positive associations of IL-4 with phenolic acid ($\beta = 0.09$ $P = 0.049$) and stilbene ($\beta = 0.13$, $P = 0.019$) intakes and the negative association of IL-1, IL-2, and IFN-γ with lignan intake ($\beta = -0.10$, $P = 0.034$; $\beta = -0.09$, $P = 0.049$; $\beta = -0.11$, $P = 0.023$).

Conclusions: The negative relation with the overall pro/anti-inflammatory biomarker ratio suggests a potential anti-inflammatory role of high polyphenol intakes among European adolescents. Nevertheless, associations are dependent on polyphenol type and the inflammatory biomarker measured. *J Nutr* 2020;150:1610–1618.

Keywords: polyphenol, flavonoid, youth, adolescent, proanthocyanidin, inflammation, cytokines

Manuscript received October 15, 2019. Initial review completed January 3, 2020. Revision accepted February 25, 2020.
First published online March 28, 2020; doi: https://doi.org/10.1093/jn/nxaa064.

Introduction

Polyphenols are bioactive compounds that can be divided into 4 groups: flavonoids, phenolic acids, stilbenes, and lignans (1). In recent years, many studies have underlined the potential health benefit of dietary polyphenols as anti-inflammatory effects on atherosclerosis, type 2 diabetes, cancer, and mortality (2–6). Further research is needed since 1 meta-analysis showed mostly nonlinear associations in the prevention of type 2 diabetes (7) and a systematic review detected inconsistent effects of flavonoid consumption towards inflammation depending on polyphenol source and type of high-risk populations (8). Indeed, only certain polyphenol classes and individual polyphenols abundant in specific foods showed anti-inflammatory effects: for example, cocoa flavonoids showed anti-inflammatory effects in type 2 diabetics and olive oil phenolic compounds in mildly hypertensive women (8). An anti-inflammatory effect was also found for higher intakes of anthocyanins and flavonols among US adults (9). Thus, individual polyphenol classes and compounds should be considered when investigating their anti-inflammatory power.

Very few studies have focused on young populations such as adolescents. Existing evidence suggests that flavonoid consumption from fruit and vegetables during adolescence was inversely associated with a proinflammatory score in early adulthood (10), whereas no relation existed between total flavonoid intake and C-reactive protein (CRP), TNF-α, and IL-6 among adolescents (11). Nevertheless, adolescence is a vulnerable period during which the individuals start making their own food choices and often have unhealthy habits, while diseases and their risk factors may track into adulthood (e.g., tracking of obesity). It is notable that, in adolescents, polyphenol intake seems to be low (12) and signs of low-grade inflammation were shown to be already present (13).

Hence, the aim of the study was to evaluate the association of polyphenol intake with inflammatory biomarkers in European adolescents participating in the Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) cross-sectional study. In view of the aforementioned conflicts in the literature regarding specific subtypes of polyphenols and inflammation biomarkers, several subanalyses were undertaken. As a predictor, polyphenol intake was considered as total polyphenols, polyphenol classes, and the 10 most consumed individual polyphenols. The main outcome was the inflammatory summary variable of pro-inflammatory to anti-inflammatory cytokine ratio. Second, all separate inflammatory biomarkers were considered: serum cytokines [IL-1, IL-2, IL-4, IL-5, IL-6, IL-10, TNF-α, transforming growth factor β1 (TGF-β1), and IFN-γ)] (14), soluble vascular adhesion molecule 1 (sVCAM-1), soluble intercellular adhesion molecule 1 (sICAM1), soluble E-selectin (sE-selectin), immune cells [white blood cell count, lymphocyte count, and T-cell count by cluster of differentiation (CD3) recognition], and the acute-phase protein CRP.

Methods

Study population

A detailed description of the HELENA study has been published previously (15). A total of 3528 European adolescents aged 12.5–17.5 y from 10 European cities were recruited: Athens and Heraklion (Greece), Dortmund (Germany), Ghent (Belgium), Lille (France), Pecs (Hungary), Rome (Italy), Stockholm (Sweden), Vienna (Austria), and Zaragoza (Spain) (16). The study protocol was approved by the ethics committee of each city involved and conducted according to the guidelines of the Declaration of Helsinki. Written parental and participants' informed consent was obtained for all examinations (17).

For this study, only data from the 24-h dietary recalls, anthropometry, and a particular set of blood biomarkers were used to perform the cross-sectional analysis. Data on nutritional intake (two 24-h dietary recalls) from Heraklion and Pecs (n = 678) could not be included because of incomplete data. The blood samples were only collected in a randomly selected subset of HELENA participants (n = 1089, of whom 211 were from Heraklion and Pecs). Other exclusion criteria were as follows: adolescents who took cardiovascular or nonsteroid anti-inflammatory drugs during the last month (n = 5), without valid data on all inflammatory biomarkers (n = 322), with inflammatory markers below the detection limit (value <0.12 pg/mL, n = 4), with CRP blood concentrations >10 mg/L (n = 16; indicative of currently ongoing infection), and with extreme polyphenol intakes (n = 5; >1000 mg · 1000 kcal^{-1} · d^{-1}). Only adolescents healthy enough to attend school participated, and none had fever in the last 24 h before blood withdrawal. Finally, 526 participants were included in the present analysis (**Supplemental Figure 1**). Included and excluded participants did not differ according to sex, age, parental education, alcohol consumption, and smoking status. More of the included participants were from non-Mediterranean countries, had a higher pubertal stage (more Tanner stage 3), had a higher material condition in the family [high Family Affluence Scale (FAS) score (5–8), which was based on adolescents' report on Internet availability at home (0, no; 1, yes), family car ownership (0–3, depending on amount), computer ownership (0–3, depending on amount), and having one's own bedroom (0, no; 1, yes)], and more often had an optimal BMI.

Dietary assessment

Dietary data were collected using a self-administered, computerized, validated 24-h recall from the HELENA-Dietary Assessment Tool (DIAT) on 2 nonconsecutive days, within a time span of 2 wk, but not on Friday and Saturday (18). The nutrient composition of the diet was linked to the German Food Code and Nutrient Database (Bundeslebensmittelschlüssel, BLS, version II.3.1) (19).

Dietary polyphenol intake was estimated after assignment of polyphenol contents from the Phenol-Explorer database (20), accounting for cooking and processing of foods, as previously described (12). Individual polyphenol intakes were estimated by multiplying the polyphenol content in a food by the amount of this food item eaten per day (grams per day) and then taking the sum over the day per individual. For proanthocyanidin oligomers, the degree of polymerization was indicated (e.g., proanthocyanidin 4–6 oligomers for tetra- to hexamers).

The Diet Inflammatory Index (DII) was calculated as proposed by Shivappa et al. (21) from the 24-h dietary recalls including 25 nutrients.

The HELENA (Healthy Lifestyle in Europe by Nutrition in Adolescence) study was carried out with the financial support of the European Community Sixth RTD Framework Program (contract FOODCT-2005-007034). RWW was sponsored as a PhD student by the Indonesia Endowment Fund for Education (LPDP, Indonesia).

Author disclosures: The authors report no conflicts of interest. Where authors are identified as personnel of the International Agency for Research on Cancer/WHO, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/WHO. The European Community is not liable for any use that may be made of the information contained herein.

Supplemental Tables 1 and 2 and Supplemental Figures 1 and 2 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/jn/.

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Abbreviations used: CD3, cluster of differentiation 3; CRP, C-reactive protein; DII, Diet Inflammatory Index; FAS, Family Affluence Scale; HELENA, Healthy Lifestyle in Europe by Nutrition in Adolescence; MAPK, mitogen-activated protein kinase; sE-selectin, soluble E selectin; sICAM1, soluble intercellular adhesion molecule 1; sVCAM-1, soluble vascular adhesion molecule 1; TGF-β1, transforming growth factor β1; Th, T helper.

Higher DII scores were associated with increased concentrations of serum TNF-α, IL-1, IL-2, IFN-γ, and sVCAM in the HELENA study (21).

Inflammation biomarkers

Blood samples were collected after overnight fasting via venipuncture from the antecubital vein by a qualified nurse. A detailed description of the blood analysis has been reported elsewhere (22). The following inflammatory biomarkers were measured: serum cytokines (IL-1, IL-2, IL-4, IL-5, IL-6, IL-10, TGF-β1, TNF-α), serum adhesion markers (sVCAM-1, sICAM-1, sE-selectin), immune cells in EDTA blood (white blood cell count, lymphocyte count, and T-cell count by CD3 recognition), and serum acute-phase protein CRP. Serum cytokines were measured using the High-Sensitivity Human Cytokine MILLIPLEXTM MAP kit (Millipore Corporation). CRP was determined in serum using an in-house sandwich ELISA. The serum adhesion molecules were analyzed using a commercial ELISA kit (Diaclone).

The pro/anti-inflammatory biomarker ratio was calculated after standardization of the serum cytokines by calculating z scores to give them equal weight, using the following equation: [(TNF-α + IL-6 + IL-1)/3/IL-10]. The ratio was built based on the most frequent literature stating IL-10 as a potent anti-inflammatory cytokine (23, 24). IL-10 inhibits proinflammatory cytokines, especially TNF-α, IL-1, and IL-6, produced by activated macrophages (25). IL-10 has been suggested as a potential protective factor for atherosclerosis (26) and unstable angina or acute myocardial infarction (27). In several studies, the IL-6 to IL-10 ratio was an important predictor of new inflammation-related coronary events (28–30). After all, IL-6, IL-1, and TNF-α are proinflammatory cytokines. Moreover, the T helper (Th) 1 to T helper 2 ratio (Th1:Th2) was determined by dividing the z score of Th1-produced cytokines by the z score of Th2-produced cytokines with the following equation: [(TNF-α + IFN-γ + IL-2)/3]/[(IL-4 + IL-5 + IL-6 + IL-10)/4].

Demographic and lifestyle measurements

Socioeconomic status was assessed by parental education and the FAS indicating material conditions in the family (31). Based on questionnaire data, smoking status, alcohol status, and moderate-to-vigorous physical activity were computed. BMI was calculated from measured weight and height (kg/m^2) using child-specific references from Cole and Lobstein (32) and pubertal status was based on the Tanner and Whitehouse classification (33). Moreover, serum triglycerides were obtained from blood samples collected after a 10-h overnight fast by following established blood collection and analysis protocols (22). The cities Athens in Greece, Rome in Italy, and Zaragoza in Spain were considered as Mediterranean.

Statistical analysis

ANOVA or Kruskal-Wallis test was used for continuous variables and the chi-square test for categorical variables to evaluate demographic/lifestyle differences in quartiles of energy-adjusted polyphenol intake. Bonferroni's or Dunn-Bonferroni's post hoc test was used for further comparisons.

The multilevel method enables a 2-level model to adjust for the clustered design (adolescents within countries) by using country as a random factor. Multilevel linear regression models of the inflammatory biomarkers (a pro/anti-inflammatory biomarker ratio as main hypothesis and separate inflammatory measures as subhypotheses) were used to examine their associations with energy-adjusted polyphenol intake (total, classes of, and individual polyphenols). Multilevel model 1 was adjusted for age, sex, European region, education of the mother, education of the father, and puberty status. Multilevel model 2 was additionally adjusted for DII, BMI z score, and serum triglycerides. This choice of included confounders was mainly based on significant associations with either polyphenol intake or inflammation biomarkers. For the latter, all inflammation biomarkers were tested together as one outcome using multivariate regression analyses.

To illustrate general patterns, the LOESS curve fitting (local polynomial regression) was applied for total polyphenol intake (**Supplemental Figure 2**). To illustrate the detected significant associations, we used the scatterplot of the significant linear association for total polyphenols and polyphenol classes in **Figure 1** and individual polyphenols in **Figure 2** (only the linear fitting line is illustrated based on predicted values). As an effect size for significant findings, R^2 and standardized regression coefficients (β) are shown. All inflammatory biomarkers (except for lymphocytes and CD3) were log-transformed to obtain a normal distribution, and the estimated means were back-transformed for interpretation. Reported P values <0.05 (2-tailed) were considered significant, and the analyses were processed using Statistical Package for Social Science (SPSS, version 25).

Results

Characteristics of study participants

The median (IQR) of total polyphenol intake was 349 mg/d (179, 576) and 168 mg · 1000 kcal^{-1} · d^{-1} (92.7, 265). Flavonoids, on average, contributed most to total polyphenol intake, whereas stilbene intake had the lowest contribution to total polyphenol intake (**Table 1**). Participants with higher total polyphenol intakes were more often girls, older, from non-Mediterranean countries, had higher puberty status, and a lower DII (Table 1). Based on BMI, 14% of adolescents (36 males, 38 females) were overweight, while 3.6% (12 males, 7 females) were obese. Inflammation biomarkers (**Supplemental Table 1**) were significantly associated with sex, country, alcohol use, BMI z score, and serum triglycerides.

In the following paragraphs, only the results for model 2 (fully adjusted, independent from other inflammation-related dietary components) will be discussed. For a few polyphenol–inflammation associations, a significant association in model 1 generally became borderline nonsignificant in model 2 ($P = 0.050$–0.059).

Inflammation and total polyphenol intake

Higher polyphenol consumption was related to a lower serum pro/anti-inflammatory biomarker ratio (Figure 1, **Supplemental Table 2**). With regard to separate inflammatory parameters, only a significant linear negative relation for serum IL-10 was found. Nevertheless, the LOESS best-fitting curves in Supplemental Figure 2 confirmed that most inflammatory serum parameters showed negative trends with polyphenol intake, while only IL-4, lymphocytes, IFN-γ, white blood cells, TGF-β1, and Th1:Th2 showed a positive association trend in the upper extreme intakes.

Inflammation and polyphenol classes

Inflammatory biomarkers according to energy-adjusted intake of polyphenol classes are shown in Figure 1 and Supplemental Table 2. Negative linear associations were found between flavonoid intake and serum IL-10; stilbene intake and Th1:Th2 ratio; and lignan consumption and serum IL-1, serum IL-2, and serum IFN-γ. However, positive linear associations were found for phenolic acid intake with serum IL-4, and for stilbene intake with serum IL-4, serum IL-5, serum sVCAM-1, and serum IFN-γ.

Inflammation and individual polyphenols

For the 10 most consumed individual polyphenols, the best-fitting line for the significant linear trend can be seen in. The serum pro/anti-inflammatory biomarker ratio was negatively associated with consumption of proanthocyanidin polymers, proanthocyanidin 4–6 oligomers, and proanthocyanidin 7–10 oligomers.

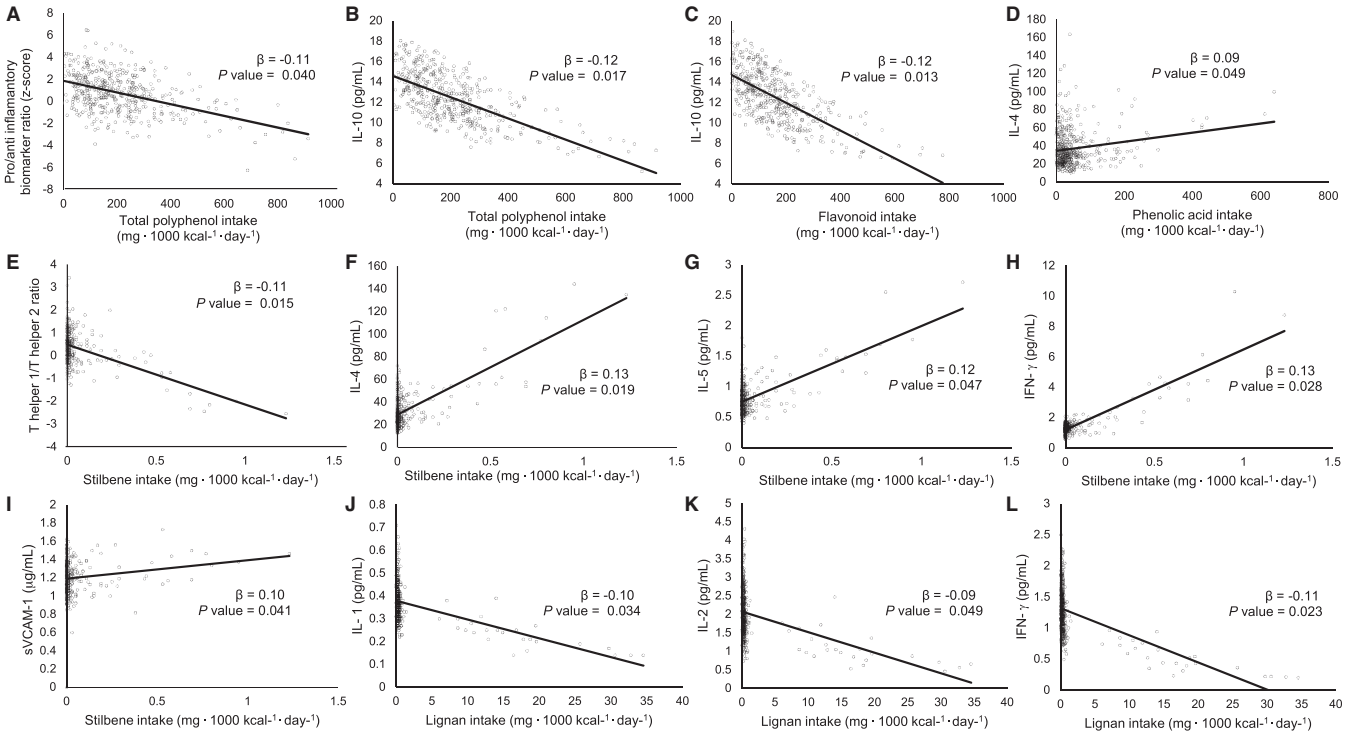

FIGURE 1 (A–L) Significant associations between the intake of total polyphenols and polyphenol classes with inflammatory biomarkers in European adolescents ($n = 526$). The model was adjusted for age, sex, European region, education of mother, education of father, puberty status, DII, BMI *z* score, and triglycerides. DII, Diet Inflammatory Index; sVCAM-1, soluble vascular adhesion molecule 1; Pro/anti-inflammatory biomarker ratio, [(TNF-α + IL-6 + IL1)/3/IL-10]; T helper 1/T helper 2 ratio, type 1 T helper and type 2 T helper ratio [(TNF-α + IFN-γ + IL-2)/3]/[(IL-4 + IL-5 + IL-6 + IL-10)/4].

Sensitivity analysis

Excluding dietary underreporters (when the individual ratio of energy intake divided by the estimated basic metabolic rate was <0.96) resulted in a 20% sample size reduction with consequently several significant values becoming borderline significant (e.g., *P* value of 0.04 becoming 0.05) but with no drastic changes.

Discussion

To our knowledge, this is the first study to evaluate the relation between dietary intake of total polyphenols and individual classes and compounds with a large set of inflammatory biomarkers in European adolescents. We confirmed some anti-inflammatory capacity as the pro/anti-inflammatory biomarker ratio was negatively related to the intake of total polyphenols, flavonoids, proanthocyanidin polymers, proanthocyanidin 4–6 oligomers, proanthocyanidin 7–10 oligomers, (−)-epicatechin, and (+)-catechin. Similarly, subanalyses confirmed higher anti-inflammatory IL-4 and lower IL-2, but no consistent direction in Th1 to Th2 ratio or cell-types were found. Contradictory findings were the negative associations with IL-10 (when considering it an anti-inflammatory cytokine) and rather proinflammatory associations for ferulic acids.

Inflammation and total polyphenols

In our study, a higher total polyphenol intake was associated with a lower serum pro/anti-inflammatory biomarker ratio. Indeed, polyphenols have shown regulatory activity on reducing proinflammatory cytokines by attenuating oxidative stress–mediated inflammatory signaling events and by suppressing TNF-α–induced mitogen-activated protein kinase (MAPK) and NF-κB–controlled signaling cascades (4, 34).

A contradictory finding is the observed negative polyphenol association with IL-10. The hypothesis was that polyphenol intake could increase anti-inflammatory cytokines. For example, chocolate, as the main polyphenol food source in this HELENA study (12), exerts anti-inflammatory effects, among others, by increasing mRNA expression of the anti-inflammatory cytokine IL-10 (35). Still, some studies have also found contradictory results for IL-10. IL-10 was decreased by consumption of polyphenol-rich cocoa products in a randomized controlled trial among Spanish adults (36), and IL-10 did not show its anti-inflammatory activities on stimulated human polymorphonuclear leukocytes (37). A potential explanation is that IL-10 might need cofactors to act as an anti-inflammatory mediator (37) and it has different signaling mechanism pathways in each subset of immune cells (38). More recently, the proinflammatory potential of IL-10 has been described; for example, it can be proinflammatory when administrated during cancer treatment (39), although this effect might not be relevant in our population, since our population was healthy and thus did not use IL-10 treatment. Moreover, the effects of polyphenols depend on the original plant compounds, the host's microbial metabolite production, and host-derived conjugate production (40).

Inflammation and polyphenol classes

Similarly to total polyphenols, flavonoid intake (as the most consumed polyphenol class) was negatively associated with the pro/anti-inflammatory biomarker ratio and IL-10. There were no linear associations with other inflammation biomarkers. In support of this finding, a previous study in adolescents

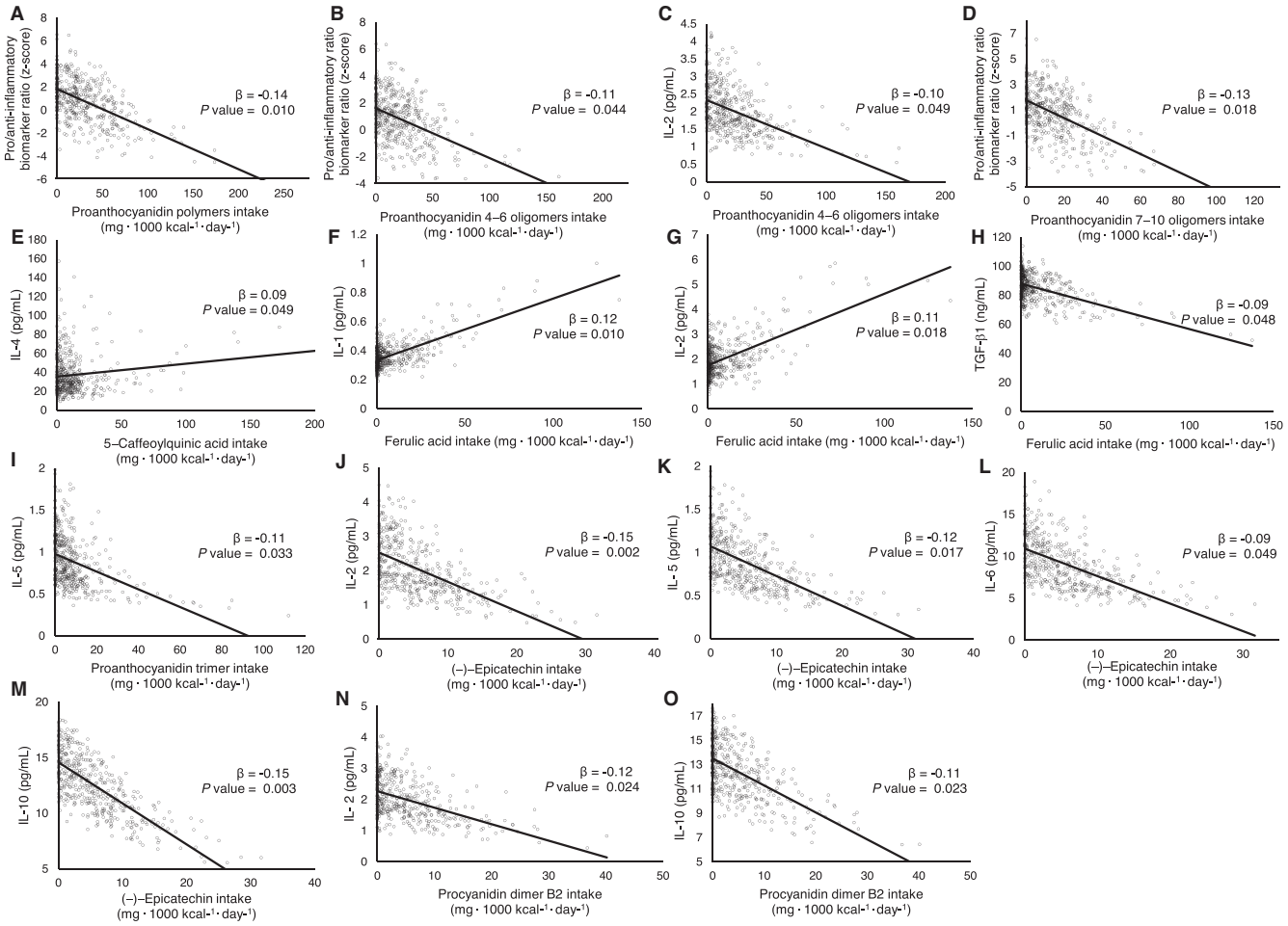

FIGURE 2 (A–O) Significant associations between the intake of the top 10 most consumed individual polyphenols with inflammatory biomarkers in European adolescents (n = 526). The model was adjusted for age, sex, European region, education of mother, education of father, puberty status, DII, BMI z score, and triglycerides. DII, Diet Inflammatory Index; Pro/anti-inflammatory biomarker ratio, [(TNF-α + IL-6 + IL1)/3/IL-10]; TGF-β1, transforming growth factor β1.

found no association between flavonoid intake and CRP, TNF-α, or IL-6 (11). Although flavonoid intake from fruit and vegetables during adolescence was negatively associated with a proinflammatory score in adulthood (calculated from high-sensitivity CRP, IL-6, IL-18, chemerin, leptin, and adiponectin) (10), this was not the case in our sample. It should be noted that the consumption of fruit and vegetables in this population is only half the recommended amount (41), making the advantageous effects of high intakes less easy to detect. The fact that the beneficial effect was only visible in the extremes suggests the importance of developing Recommended Dietary Intakes for polyphenols (42).

Phenolic acid intake was associated only with higher anti-inflammatory IL-4. As coffee was the main food contributor of phenolic acids in the HELENA study (12), this corroborates previous findings: IL-4 was positively associated with coffee consumption in rats (43) and tended to be increased by moderate soluble green/roasted (35:65) coffee intake in hypercholesterolemic adults (44).

A higher intake of stilbenes was associated with a lower Th1 to Th2 ratio but higher IL-4, IL-5, and sVCAM-1. The findings on IL-4 and IL-5 corroborate the Th1 to Th2 ratio findings as they are major effector cytokines secreted by Th2 (45). The anti-inflammatory activity of resveratrol [which was the most abundant stilbene in the HELENA study (12)] has previously been reflected by increased IL-4 in a retrospective study (46) and decreased TNF-α in an in vitro study (47), making the positive association with sVCAM-1 rather contradictory.

Finally, the same anti-inflammatory capacity was shown for lignans. Lignan consumption was inversely associated with proinflammatory IL-1 and IL-2. In 11,913 Italian adults of the Moli-sani study, lignan consumption was also associated with an overall low-grade inflammation index but was not significantly associated with CRP (48). Again, it should be considered that the mean intake of lignans in the Moli-sani study (79.5 mg/d) was higher than in the HELENA study (1 mg/d). The huge differences of lignan intake might be due to the different methodology (FFQ vs 24-h recall, different polyphenol database), population (older population than ours), and food source of lignans (seasonal fruit in the Moli-sani study and bread in the HELENA study). Indeed, a previous study found that polyphenol intakes estimated via various databases might differ substantially (49).

Inflammation and individual polyphenols

All 10 tested individual compounds showed some associations with inflammatory parameters but none stood out. Interestingly, a lower pro/anti-inflammatory biomarker ratio was found for higher consumers of proanthocyanidin polymers,

TABLE 1 Baseline characteristics, polyphenol intake, and clinical biomarkers according to energy-adjusted quartiles of polyphenol intake in the HELENA study[1]

	Polyphenol intake				
Characteristic	Q1 ($n = 132$)	Q2 ($n = 132$)	Q3 ($n = 132$)	Q4 ($n = 130$)	*P*
Polyphenol intake, mg · 1000 kcal^{-1} · d^{-1}					
Total polyphenols	52.9 (36, 73)[d]	120 (100, 143)[c]	212 (187, 246)[b]	364 (299, 461)[a]	<0.001
Flavonoids	43.9 (17, 69)[d]	97.5 (76, 116)[c]	172 (147, 200)[b]	290 (228, 390)[a]	<0.001
Phenolic acids	11 (4, 22)[d]	23 (14, 41)[c]	35 (22, 61)[b]	61 (35, 131)[a]	<0.001
Stilbenes	0.0001 (0.0, 0.01)[b]	0.005 (0.0, 0.02)[a,b]	0.01 (0.0, 0.02)[a]	0.02 (0.0, 0.05)[a]	0.004
Lignans	0.2 (0.1, 0.3)	0.2 (0.2, 0.4)	0.3 (0.2, 0.4)	0.3 (0.2, 0.4)	0.46
Other polyphenols	5 (2, 12)[c]	8 (4, 15)[b]	10 (4, 19)[a,b]	10 (6, 20)[a]	<0.001
Background variables					
Girls, %	46	49	56	64	0.021
Age, y	14.6 ± 1.1[b]	14.7 ± 1.3[b]	14.8 ± 1.1[a,b]	15 ± 1.1[a]	0.043
European region, %					<0.001
Mediterranean countries	25	30	20	8	
Non-Mediterranean countries	75	70	80	92	
Education of mother,[2] %					0.23
Primary or lower secondary	42	31	26	31	
Higher secondary	27	33	38	35	
University degree	31	36	36	34	
Education of father,[2] %					0.9
Primary or lower secondary	41	41	27	31	
Higher secondary	26	25	39	29	
University degree	33	34	34	40	
Low FAS score, %	40	43	38	38	0.83
Smoking status, %					0.28
Never	59	62	70	57	
Former smoker	26	19	15	22	
Current smoker	16	19	15	21	
Alcohol user, %	20	26	25	33	0.14
Diet quality (≥median), %	55	48	58	52	0.36
Diet Inflammatory Index	2.3 ± 1.4[a]	2.3 ± 1.3[a]	2 ± 1.4[a,b]	1.7 ± 1.5[b]	0.001
Energy intake, kcal/d	2264 ± 1154	2388 ± 1115	2195 ± 851	2154 ± 1038	0.30
Physical activity					0.54
<60 min/d	35	32	29	28	
≥60 min/d	65	68	71	72	
BMI *z* score	0.4 ± 1.1	0.5 ± 1.1	0.2 ± 1	0.2 ± 1	0.06
Tanner stage, %					0.006
Stage 1	11	14	12	4	
Stage 2	26	32	25	18	
Stage 3	48	33	43	48	
Stage 4	15	21	20	30	
Clinical biomarkers					
Systolic blood pressure, mmHg	117 ± 12.4	118 ± 12.5	115 ± 12.5	116 ± 14.3	0.51
Diastolic blood pressure, mmHg	64.1 ± 9.1[a,b]	65.8 ± 8.8[a]	62.7 ± 9.2[b]	65 ± 8.5[a]	0.036
Serum fasting glucose, mg/dL	90.3 ± 6.8	91 ± 6.6	89.4 ± 6.5	89.7 ± 6.5	0.19
Serum total cholesterol, mg/dL	161 ± 27.4	161 ± 27.7	162 ± 26.2	162 ± 29	0.98
Serum HDL cholesterol, mg/dL	57.9 ± 10.8	54.9 ± 9.9	56.3 ± 10.1	55.6 ± 10.5	0.11
Serum LDL cholesterol, mg/dL	90.5 ± 24	94.5 ± 25.1	94.8 ± 93.5	94.3 ± 25.1	0.46
Serum triglycerides, mg/dL	70.8 ± 39.8	70.1 ± 32.3	65.8 ± 30.3	69.9 ± 32.6	0.63
Inflammatory parameters[3]					
IL-1, pg/mL after inflammatory parameters	0.2 (0.1, 0.9)	0.3 (0.1, 1.2)	0.3 (0.1, 0.8)	0.2 (0.1, 0.6)	0.22
IL-2, pg/mL	2.6 (0.4, 6.4)	3.1 (0.7, 10)	2.5 (0.7, 6.3)	1.9 (0.4, 4.3)	0.06
IL-4, pg/mL	39.1 (3.5, 201)	64.5 (5.1, 263)	22.5 (3.1, 135)	23.9 (3.1, 160)	0.07
IL-5, pg/mL	1.0 (0.4, 2.4)[a,b]	1.3 (0.3, 3.6)[a]	0.8 (0.2, 1.9)[b]	0.7 (0.2, 2)[b]	0.015
IL-6, pg/mL	11.5 (4.2, 31)[a]	18.7 (4.3, 40.6)[a]	6.2 (2.7, 21.3)[b]	7.4 (2.5, 23.8)[b]	0.001
IL-10, pg/mL	10.9 (6.8, 20.9)	11.1 (5.5, 23.4)	12 (6.1, 24.2)	8.9 (6, 17)	0.22
TNF-α, pg/mL	5.8 (4.1, 8.1)	6.1 (4, 7.8)	5.3 (4.2, 8.1)	5.2 (4.1, 6.9)	0.42
TGF-β1, ng/mL	102 (64.2, 151)	95 (46.8, 144)	97.8 (63.6, 124)	78.6 (51.4, 123)	0.20
IFN-γ, pg/mL	0.2 (0.1, 7.4)	1.6 (0.1, 10)	1.8 (0.1, 8)	0.1 (0.1, 5.7)	0.21

(*Continued*)

TABLE 1 (*Continued*)

Characteristic	Polyphenol intake				
	Q1 ($n = 132$)	Q2 ($n = 132$)	Q3 ($n = 132$)	Q4 ($n = 130$)	*P*
CRP, mg/L	0.4 (0.2, 0.9)	0.5 (0.2, 1)	0.4 (0.2, 0.9)	0.3 (0.1, 0.9)	0.11
WBCs, $10^3/\mu$L	6.2 (5.3, 7.1)	5.9 (5.3, 7.1)	6 (5.1, 6.9)	6.1 (5.3, 6.9)	0.33
Lymphocytes, $10^3/\mu$L	2.1 (1.8, 2.6)	2.1 (1.8, 2.5)	2.1 (1.8, 2.3)	2.1 (1.8, 2.4)	0.27
CD3, %	69.1 (64.1, 73.3)	68.7 (63.4, 73.3)	69.2 (64.1, 72.8)	70.6 (64.5, 73.9)	0.50
sVCAM-1, μg/mL	1.3 (1, 1.5)	1.2 (1, 1.5)	1.2 (1, 1.5)	1.2 (1, 1.4)	0.66
sICAM-1, ng/mL	153 (116, 191)	141 (108, 189)	138 (105, 188)	135 (103, 183)	0.66
sE-selectin, ng/mL	33.3 (25, 47.6)	33.5 (25, 47.4)	33 (23.2, 45.9)	33.5 (23, 45.5)	0.69

[1]Values are medians (IQRs) for polyphenol intakes and inflammatory biomarkers, means ± SDs for clinical biomarkers, and percentages for categorical variables as specified in row titles. *P* values are based on 1-factor ANOVA test or Kruskal-Wallis test for continuous variables or chi-square test for categorical variables. Labeled means or medians without a common letter differ, $P \leq 0.05$ [post hoc test for multiple comparisons (Bonferroni test or Dunn-Bonferroni post hoc) was used for the comparison between quartiles]. CD3, cluster of differentiation 3; CRP, C-reactive protein; FAS, Family Affluence Scale; HELENA, Healthy Lifestyle in Europe by Nutrition in Adolescence; Q, quartile; sE-selectin, soluble E selectin; sICAM-1, soluble intercellular adhesion molecule 1; sVCAM-1, soluble vascular adhesion molecule 1; TGF-β1, transforming growth factor β1; WBC, white blood cell.

[2]Defined as "lower education" for primary education (until age 12 y) and "lower secondary education" (until age 14–15 y), "higher secondary education" (until age 18–20), and "university education" (often until age 23 y).

[3]IL Interleukin, IL-1, IL-2, IL-4, IL-5, IL-6, IL-10; TNF-α, tumor necrosis factor alpha; TGFβ-1, transforming growth factor beta; IFN-γ, interferon-gamma; CRP, C-reactive protein; WBCs, white blood cells; lymphocytes, CD3, cluster of differentiation; sVCAM-1, soluble vascular adhesion molecule; sICAM-1, soluble intercellular adhesion molecule; and sE-selectin, soluble cell adhesion molecule

proanthocyanidin 4–6 oligomers, and proanthocyanidin 7–10 oligomers, which are the top 3 most consumed individual flavanols. Indeed, proanthocyanidins have been found to prevent DNA damage or lipid peroxidation and suppress many pathways (e.g., NF-κB) in cytokine production (50). The anti-inflammatory mechanisms of procyanidins include the modulation of eicosanoid-generating enzymes, the production and secretion of inflammatory mediators (e.g., cytokines or nitric oxide), and the modulation of MAPKs and NF-κB pathways (51). Proanthocyanidins also decrease the inflammatory and pro-oxidant processes occurring in the gastric and colonic mucosa, contributing to the gastrointestinal mucosa integrity (52). As chocolate was a major food contributor to proanthocyanidins in our population (12), cocoa flavanols might be responsible for the effect: cocoa flavanols decrease proinflammatory cytokines and prevent the production of the inflammatory mediators NF-κB, cyclooxygenase-2 (COX-2), and inducible NO synthase (iNOS) (53). Nevertheless, the flavanol and (−)-epicatechin doses in our HELENA study were lower than the 900 mg flavanols and 100 mg (−)-epicatechin for which beneficial health effects have been claimed (54).

Strengths and limitations

To our knowledge, this is the first study to investigate detailed associations between intakes of polyphenols (total polyphenols, polyphenol classes, and individual polyphenols) and inflammation biomarkers in adolescents. Herein, the differential effects of the most consumed polyphenols or classes were tested and a diverse spectrum of inflammatory markers was studied. Second, this study has a multicountry design, which reflects the diversity in dietary intake across Europe. Third, intake was estimated based on a validated computerized 2-d 24-h dietary recall (HELENA-DIAT) linked to the most comprehensive polyphenol database (Phenol-Explorer). Fourth, inflammation was sufficiently high to detect associations; our inflammatory biomarker concentrations often were higher than those found in another adolescent population (e.g., TNF-α: 6.4 ± 4.6 vs. 4.2 ± 2 pg/mL) (11).

Nevertheless, some limitations do exist in the present study. The adolescents in the HELENA study were from 1 urban city of each country (15) and the sample size was low, especially in Mediterranean countries, so the dietary polyphenol estimates are not representative of the entire European population, which does not allow cross-country comparisons. As another limitation, the use of 24-h recalls has the disadvantage of relying on the respondents' memory and their capability to estimate consumption. Furthermore, dietary reports can miss details in certain polyphenol-rich items like herbs and oils and the Phenol-Explorer did not include some food items such as palm oil. Use of databases on polyphenol content in foods would have inevitably led to some misclassification of polyphenol intake as polyphenol content in a given food can vary widely according to plant species, time of year, year of harvest, and extent of processing and because there is a lack of accurate data on the consumption of polyphenols from dietary supplements (55). Regarding the estimation of health risks, this cross-sectional study does not permit causality statements and the analyses are rather exploratory without adjustment for multiple testing (by testing separate inflammatory parameters as a subhypothesis next to the main hypothesis on pro/anti-inflammatory biomarker ratio). Moreover, distinguishing effects of single polyphenols or classes might be difficult due to the interaction of different polyphenols, since most studies suggested that the combination of phytochemicals rather than any single polyphenol is important for health benefit (56). Finally, the requirement of having a blood sample resulted in a smaller sample size.

Conclusions

In conclusion, high polyphenol intake may contribute to the prevention of inflammation-related chronic diseases as it is related to a reduced pro/anti-inflammatory biomarker ratio and to certain individual inflammatory parameters (e.g., higher anti-inflammatory IL-4 and lower proinflammatory IL-2). However, negative associations with IL-10 were found, which is often presumed to be an anti-inflammatory cytokine. The molecular mechanisms of food polyphenol actions remain poorly understood and each polyphenol (class) might show a unique pattern. Longitudinal studies and polyphenol intake biomarkers are needed to explore the health benefits in more detail.

Acknowledgments

We acknowledge the work of Mieke De Maeyer and the Phenol-Explorer team for the support in polyphenol estimation. The authors' responsibilities were as follows—NM, SDH, and LAM: designed the research; SDH, LAM, M Ferrari, M Forsner, FG, IH, AGK, MK, YM, AM, DM, AIR, and KW: conducted the research; IH, VK, JAR, and AS: provided essential materials; RWW: analyzed the data; RWW and NM: wrote the manuscript and had primary responsibility for final content; and all authors: read and approved the final manuscript.

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