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Plasma polyphenols associated with lower high-sensitivity C-reactive protein concentrations: a cross-sectional study within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort

Laura M. Harms1, Augustin Scalbert2, Raul Zamora-Ros3, Sabina Rinaldi2, Mazda Jenab2, Neil Murphy2, David Achatinre2, Anne Tjonneland4,5, Anja Olsen4, Kim Overvad6,7, Francesca Romana Mancini8,9, Yahya Mahamat-Saleh8,9, Marie-Christine Boutron-Ruault8,9, Tilman Kühn10, Verena Katzke10, Antonia Trichopoulou11,12, Georgia Martimianaki11, Anna Karakatsani11,13, Domenico Palli14, Salvatore Panico15, Sabina Sieri16, Rosario Tumino17, Carlotta Sacerdote18, Bas Bueno-de-Mesquita19,20,21,22, Roel C. H. Vermeulen19,23,24, Elisabete Weiderpass2, Therese Haugdahl Nøst25, Cristina Lasheras26, Miguel Rodriguez-Barranco27,28, José María Huerta29, Aurelio Barricarte28,30,31, Miren Dorrnoro32, Johan Hultdin33, Julie A. Schmidt34, Marc Gunter2, Elio Riboli19 and Krasimira Aleksandrova1,35*

1Nutrition, Immunity and Metabolism Senior Scientist Group, Department of Nutrition and Gerontology, German Institute of Human Nutrition Potsdam-Rehbruecke (DIfE), 14558 Nuthetal, Germany
2International Agency for Research on Cancer, World Health Organization, 69008 Lyon, France
3Unit of Nutrition and Cancer, Cancer Epidemiology Research Programme, Catalan Institute of Oncology, Bellvitge Biomedical Research Institute (IDIBELL), 08908 Barcelona, Spain
4Danish Cancer Society Research Center, 2100 Copenhagen, Denmark
5Department of Public Health, University of Copenhagen, 2200 Copenhagen, Denmark
6Department of Public Health, Aarhus University, DK-8000 Aarhus C, Denmark
7Department of Cardiology, Aalborg University Hospital, 9100 Aalborg, Denmark
8CESP, faculté de médecine, université Paris-Sud, 75006 Paris, France
9UVSQ, INSERM, Université Paris-Saclay, 94805 Villejuif, France
10Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), 69120 Heidelberg, Germany
11Hellenic Health Foundation, 11527 Athens, Greece
12WHO Collaborating Center for Nutrition and Health, Unit of Nutritional Epidemiology and Nutrition in Public Health, Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National and Kapodistrian University of Athens, 15772 Athens, Greece
132nd Pulmonary Medicine Department, School of Medicine, National and Kapodistrian University of Athens, “ATTIKON” University Hospital, 12462 Chaidari, Greece
14Molecular and Nutritional Epidemiology Unit, Cancer Research and Prevention Institute– ISPO, 50139 Firenze, Italy
15EPIC Centre of Naples, Dipartimento di Medicina Clinica e Chirurgia Federico II University, 80131 Napoli, Italy
16Epidemiology and Prevention Unit Fondazione Istituto Nazionale dei Tumori di Milano, 20133 Milano, Italy
17Cancer Registry and Histopathology Unit, “Civic–M. P. Arezzo” Hospital, 97100 Ragusa, Italy
18Unit of Cancer Epidemiology, Città della Salute e della Scienza University-Hospital and Center for Cancer Prevention (CPO), 10126 Turin, Italy
19Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London SW7 2AZ, UK
20National Institute for Public Health and the Environment (RIVM), 3720 BA Bilthoven, The Netherlands
21Department of Gastroenterology and Hepatology, University Medical Centre, 3584 CX Utrecht, The Netherlands
22Department of Social and Preventative Medicine, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia
23Division of Environmental Epidemiology, Institute for Risk Assessment Sciences, Utrecht University, 3584 CX Utrecht, The Netherlands
24Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, 3584 CG Utrecht, The Netherlands
25Department of Community Medicine, University of Tromsø, The Arctic University of Norway, 9019 Tromsø, Norway
26Department of Functional Biology, Faculty of Medicine, University of Oviedo, 33006 Oviedo, Spain
27Andalusian School of Public Health (EASP), Instituto de Investigación Biosanitaria de Granada (lbs GRANADA), Universidad de Granada, 18011 Granada, Spain
28CIBER de Epidemiología y Salud Pública (CIBERESP), 28029 Madrid, Spain
Experimental studies have reported on the anti-inflammatory properties of polyphenols. However, results from epidemiological investigations have been inconsistent and especially studies using biomarkers for assessment of polyphenol intake have been scant. We aimed to characterise the association between plasma concentrations of thirty-five polyphenol compounds and low-grade systemic inflammation state as measured by high-sensitivity C-reactive protein (hsCRP). A cross-sectional data analysis was performed based on 315 participants in the European Prospective Investigation into Cancer and Nutrition cohort with available measurements of plasma polyphenols and hsCRP. In logistic regression analysis, the OR and 95% CI of elevated serum hsCRP (>3 mg/l) were calculated within quartiles and per standard deviation higher level of plasma polyphenol concentrations. In a multivariable-adjusted model, the sum of plasma concentrations of all polyphenols measured (per standard deviation) was associated with 29 (95% CI 50, 1) % lower odds of elevated hsCRP. In the class of flavonoids, daidzein was inversely associated with elevated hsCRP (OR 0.66, 95% CI 0.46, 0.96). Among phenolic acids, statistically significant associations were observed for 3,5-dihydroxyphenylpropionic acid (OR 0.58, 95% CI 0.39, 0.86), 3,4-dihydroxyphenylpropionic acid (OR 0.63, 95% CI 0.46, 0.87), ferulic acid (OR 0.65, 95% CI 0.44, 0.96) and caffeic acid (OR 0.69, 95% CI 0.51, 0.93). The odds of elevated hsCRP were significantly reduced for hydroxytyrosol (OR 0.67, 95% CI 0.48, 0.93). The present study showed that polyphenol biomarkers are associated with lower odds of elevated hsCRP. Whether diet rich in bioactive polyphenol compounds could be an effective strategy to prevent or modulate deleterious health effects of inflammation should be addressed by further well-powered longitudinal studies.

Key words: Polyphenols: Plasma measurements: C-reactive protein: Inflammation: Chronic diseases

The aetiological role of chronic low-grade inflammation in the development of a plethora of chronic diseases including CVD and cancer has been long recognised1–3. Targeting inflammation could therefore represent an effective approach for preventing onset of chronic diseases. Recent evidence has suggested that inflammatory biomarkers such as high-sensitivity C-reactive protein (hsCRP) could be successfully modulated following consumption of plant-originated foods such as whole grains, fruits, vegetables, nuts and olive oil (Mediterranean-style diet)5,6. Plant-based foods contain high quantities of polyphenols, a large group of plant secondary metabolites with a growing body of evidence indicating beneficial effects on overall health7. Studies exploring the link between polyphenols and inflammation in vitro or in animal models have suggested antioxidative and anti-inflammatory properties for specific polyphenol compounds8–10. However, to what extent these results could be translated to free-living humans remains unclear11. Several epidemiological studies have evaluated the association between intake of selected dietary polyphenols and inflammatory biomarkers providing inconsistent evidence12–16. Interpretation of data from these studies is challenged by measurement inaccuracies and inter-individual variability of self-reported polyphenol intakes. Many ingested polyphenols are absorbed in the gut and eventually transformed by the gut microbiota and/or host tissues into metabolites that have been used as biomarkers of intake11. Measurements of polyphenols and their metabolites in plasma could provide more reliable estimates of exposure, yet studies employing biomarkers of polyphenol intake have been scant and limited to evaluation of specific polyphenol compounds12–16.

The aim of the present analysis was to characterise the association between plasma concentrations of thirty-five polyphenol compounds and state of low-grade inflammation as measured by hsCRP taking into account various factors of potential influence in a well-phenotyped cross-sectional sample from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.

Methods

Study population and collection of blood samples and data

EPIC is a multicentre prospective cohort of 521 330 participants, aged ≥35 years, who were recruited in 1992–2000, predominantly
from the general population of ten European countries, including France, Italy, Spain, the UK, The Netherlands, Greece, Germany, Sweden, Denmark and Norway\(^{17}\).

The flow chart of study population selection for the present analysis is described in online Supplementary Fig. S1. Among all EPIC participants, 387,889 provided blood samples. Among these, 5,235 participants who were alive and free of major chronic diseases, that is, cancer, served as healthy controls in previous analyses where concentrations of hsCRP\(^{18}\) and polyphenols\(^{19}\) have been measured. Among these, 4,061 participants were excluded due to missing hsCRP measurements, leaving a sample of 1174 participants. Of them, further 859 participants were excluded due to lack of available polyphenol measurements, providing a final analytical study sample of 315 participants.

As previously reported, blood samples were collected according to standardised procedures and stored at the International Agency for Research on Cancer (−196°C, liquid N\(_2\)) for all countries except Denmark (−150°C, nitrogen-vapour) and Sweden (−80°C, freezers\(^{17}\)). Participants completed standardised questionnaires on socio-demographic and lifestyle characteristics and personal history at recruitment, and most participants also had anthropometric measurements and blood samples taken at recruitment before disease onset or diagnosis. Dietary intakes over the previous 12 months were assessed at recruitment using validated country or centre-specific dietary questionnaires\(^{20}\). All participants provided a written informed consent. Ethical approval for the EPIC study was obtained from the review boards of the International Agency for Research on Cancer (Lyon, France) and local participating centres.

**Laboratory methods and reporting**

Plasma hsCRP concentrations were measured using a high-sensitivity assay (Beckman-Coulter) on a Synchron LX-20 Pro autoanalyser (Beckman-Coulter)\(^{18}\). The interassay CV were 6.0 and 6.5 % at hsCRP concentrations of 1-16 mg/l and 189 mg/l, respectively. Plasma polyphenol measurements for thirty-five compounds were performed using a highly sensitive method based on differential isotope labelling with (13)C- and (12)C-dansyl chloride by tandem MS\(^{21}\). Limits of quantification for the polyphenols varied between 0·11 mmol/l for apiigenin and 44·4 mmol/l for quercetin. Intra-batch CV varied between 2·3 and 9·0 %. Intra-batch CV were <20 % for all except for quercetin, gallic acid, hydroxytyrosol and enterodiol.

**Statistical analysis**

Differences in medians of hsCRP and polyphenol concentrations according to participant characteristics were assessed using Wilcoxon–Mann–Whitney test for dichotomous variables and Kruskal–Wallis test for variables with more than two categories. Participants with missing values in any of the polyphenol subclasses or hsCRP were excluded, while missing values in categorical adjustment variables were placed in a separate category.

Right-skewed data distributions were standardised using box-cox transformations. Values of plasmatic polyphenol concentrations were z-transformed for analysis according to standard deviations and back-transformed to natural units for presentation in text and tables. Several compounds, including gallicatechin, epigallocatechin, phloretin and gallic acid ethyl ester, were excluded from statistical analysis because of a too limited number of values above the limit of detection (<5 %).

A variable ‘combined polyphenols’ was created based on the sum of plasma concentrations of all polyphenols measured in the study sample.

Geometric means and 95 % CI of hsCRP by plasma polyphenol concentrations were estimated using ANCOVA. Statistical tests for trend for a given polyphenol were calculated using the ordinal quartile entered into the models as a continuous variable. Covariates for the multivariable-adjusted analyses were chosen a priori based on reported associations with circulating hsCRP in the literature. The variable list included age, sex, country, education, smoking status, alcohol intake, red and processed meat consumption, fibre consumption, fish and shellfish intake, physical activity, BMI, waist circumference, prevalent diabetes and cardiovascular problems\(^{22–26}\). In logistic regression analysis, ‘elevated hsCRP’ was defined as response variable dichotomised based on established cut point of hsCRP ≥ 3 mg/l. A hsCRP <3 mg/l denoting individual chronic inflammatory status\(^{4}\). The OR and 95 % CI of elevated hsCRP were calculated within quartiles of polyphenols distribution and per SD increase of polyphenol concentrations. To test for non-linearity, we fitted restricted cubic splines, at the 10th, 50th and 90th percentiles of polyphenol concentrations, to the fully adjusted logistic regression models and used the Wald \(\chi^2\) test.

To identify major dietary predictors of circulating polyphenol concentrations in our study sample, we applied a variable selection using adaptive least absolute shrinkage and selection operator (LASSO) regression model with ‘combined polyphenols’ as dependent variable and reported individual food intakes (n 212) as independent variables. Least absolute shrinkage and selection operator is a penalised regression method proven to outperform traditional regression methods (i.e. stepwise and forward selection) when there are correlated predictors or when the number of predictors is large as in our study. SBC was used as a tuning method to build a model using adaptive least absolute shrinkage and selection operator regression. As a next step, \(\beta\)-coefficients and 95 % CI between the variable ‘combined polyphenols’ and the identified best set of dietary predictors were calculated in linear regression analysis.

In sensitivity analyses, main associations were evaluated excluding participants with polyphenol concentrations in the highest and lowest percentile, women using hormone replacement therapy (n 22) and individuals whose waist circumference was imputed (n 11). Analyses were also repeated excluding participants with hsCRP ≥ 10 mg/l (n 18) potentially indicating acute inflammatory response. Statistical tests were considered to be significant when \(P<0.05\). All statistical analyses were performed in SAS (Version 9.4, Enterprise Guide 6.1, SAS Institute Inc.).

**Results**

In the present study, sample hsCRP ranged from 0·20 to 23·16 mg/l. In total, 113 participants (36 % of the sample) had
hsCRP ≥ 3 mg/l. Median hsCRP concentrations were higher in women as well as in participants with reported CVD and type 2 diabetes and higher BMI and waist circumference at study baseline compared with their counterparts (Table 1). hsCRP concentrations were lower in participants with medium to high fibre intake and high fish and shellfish intake (see Table 1). The relative proportion of polyphenol subclasses and individual compounds to the combined polyphenol variable is presented in online Supplementary Fig. S2A and S2B, respectively. Phenolic acids (75%) and flavonoids (25%) represented the largest share of polyphenol subclasses, whereas caffeic acid (16%), 4-hydroxyphenylacetic acid (13%) and quercetin (15%) had greatest share among individual polyphenols.

Median values of combined polyphenols were higher in women and in participants free of CVD at study baseline (online Supplementary Table S1). No substantial differences were observed according to levels of physical activity, BMI and waist circumference categories, fish and shellfish intake and country of origin of EPIC participants (see online Supplementary Tables S1 and S2).

In multivariable-adjusted model, higher plasma concentrations of combined polyphenols (modelled continuously per SD higher concentrations) were associated with 29 (95% CI 50, 1) % lower odds of elevated hsCRP (Table 2). Per so higher concentration, the OR of elevated hsCRP were 0.71 (95% CI 0.44, 1.15) for flavonoids, 0.74 (95% CI 0.54, 1.02) for phenolic acids, 0.71 (95% CI 0.52, 0.98) for lignans, 1.07 (0.78, 1.45) for stilbenes (resveratrol only) and 0.88 (95% CI 0.66, 1.17) for tyrosols (Fig. 1). For the majority of polyphenol concentrations summed according to subclasses, the associations proved to be linear, with the exception of resveratrol (P for non-linearity > 0.05) (see Fig. 2). A more detailed inspection of analyses by quartiles of resveratrol showed that the OR for elevated hsCRP were 0.38 (95% CI 0.15, 0.94), 0.86 (95% CI 0.41, 1.82) and 0.79 (95% CI 0.34, 1.83) in the second, third and fourth quartiles compared with the first quartile, respectively (Table 2). Several specific polyphenol compounds were statistically significantly associated with lower odds for elevated CRP (Fig. 2). Such associations were revealed for daidzein (flavonoid); ferulic acid, caffeic acid, 3,4-dihydroxyphenylpropionic acid and 3,5 dihydroxybenzoic acid (phenolic acids); enterolactone and enterodiol (lignans) and hydroxytyrosol (phenolic alcohol) (online Supplementary Table S3). In spline regression analysis, no pronounced deviation from linearity could be seen for associations with majority of individual polyphenol compounds (online Supplementary Fig. S3). Exceptions were the associations with enterolactone (P non-linearity = 0.028), 3,4-dihydroxyphenylpropionic acid (P non-linearity < 0.001) and m-coumaric acid (P non-linearity = 0.03).

The best subset of dietary predictors of combined plasma polyphenol concentrations estimated based on adapted least absolute shrinkage and selection operator regression model is shown in Table 3. The model explained overall 23±4 % of the variation in combined plasma polyphenol concentrations. In a linear regression model, based on the best subset in which each predictor was mutually adjusted for each other, significant positive associations were observed between plasma polyphenol concentrations and the following dietary intake variables: ‘Pasta-like cereal-based products (not 100 % cereal); ‘Sauces (not specified); ‘Tomato sauces; ‘Kiwi; ‘Tea’ and ‘Coffee’ (Table 3).

In sensitivity analysis, excluding participants with polyphenol concentrations in the highest and lowest percentile, women using hormone replacement therapy (n 22) and individuals whose waist circumference was imputed (n 11) did not substantially affect main results (data not shown).

Discussion
In this cross-sectional analysis embedded within the EPIC cohort, we characterised plasma concentrations of thirty-five polyphenols in relation to hsCRP taking into account various factors of potential influence. These analyses showed that high plasma polyphenol concentrations were associated with lower odds of elevated hsCRP. Among specific polyphenol compounds, the associations have been most pronounced for daidzein (flavonoid); ferulic acid, caffeic acid, 3,4-dihydroxyphenylpropionic acid and 3,5 dihydroxybenzoic acid (phenolic acids); enterolactone and enterodiol (lignans) and hydroxytyrosol (phenolic alcohol).

To the best of our knowledge, this is the first epidemiological study to characterise potential anti-inflammatory properties of multiple polyphenol compounds measured in human plasma in a population-based sample of diverse European populations characterised by high variation in food intakes. Previously, only two small cross-sectional studies explored correlations between CRP concentrations and individual polyphenols in blood mostly focusing on compounds associated with coffee and tea intakes. The first study conducted among Japanese healthy females (n 57) showed that plasma chlorogenic acid was inversely correlated with circulating CRP, whereas plasma total coffee polyphenol and plasma caffeic acid were weakly inversely associated with CRP14,15. The second study also conducted in generally healthy Japanese females (n 57) suggested that plasma total and individual catechins associated with green tea intake were weakly to moderately associated with C-reactive protein16. Comparison of our findings with data from these studies is hampered by the lower number of target compounds and differing analytical techniques.

So far, several randomised control trials explored effects of dietary interventions based on polyphenol-rich foods on CRP levels, thereby conducting measurements of plasma polyphenol concentrations at pre- and post-intervention period. Results from two randomised control trials conducted in German16 and Finnish15 study participants showed no evidence of correlation between relative changes in plasma flavonoids (i.e. quercetin and kaempferol) and changes in CRP. In contrast, a randomised control trial that evaluated intervention with soya supplements showed a strong inverse correlation between changes in specific flavonoids (i.e. daidzein) and changes in CRP12. However, when polyphenol compounds such as hydroxytyrosol29 and daidzein30 were administered as dietary supplements in randomised control trial studies, no effect on CRP could be observed. The discrepancy between observational and experimental epidemiological studies may be explained by the fact that...
Table 1. Serum high-sensitivity C-reactive protein (hsCRP) concentrations by participant characteristics (n=315) (Numbers and percentages; medians and 25th and 75th percentiles)

| Variable                        | n   | %     | Median | 25th percentile | 75th percentile | P*   |
|---------------------------------|-----|-------|--------|-----------------|-----------------|------|
| Sex                             |     |       |        |                 |                 |      |
| All                             | 315 | 100.0 | 2.15   | 1.06            | 4.05            | 0.001|
| Male                            | 116 | 36.8  | 1.65   | 0.76            | 3.19            |      |
| Female                          | 199 | 63.2  | 2.56   | 1.17            | 4.43            |      |
| Age (years)                     |     |       |        |                 |                 |      |
| <40                             | 5   | 1.6   | 2.33   | 1.73            | 2.81            | 0.21 |
| 40–49                           | 41  | 13.0  | 1.65   | 0.56            | 2.61            |      |
| 50–59                           | 143 | 45.4  | 2.25   | 0.97            | 4.33            |      |
| 60–69                           | 120 | 45.4  | 2.15   | 1.14            | 4.27            |      |
| ≥70                             | 6   | 1.9   | 2.72   | 2.15            | 7.02            |      |
| Highest school level            |     |       |        |                 |                 |      |
| Not specified                   | 7   | 2.2   | 4.11   | 1.37            | 5.39            | 0.012|
| None                            | 19  | 6.0   | 1.64   | 1.08            | 4.43            |      |
| Primary school completed        | 123 | 39.0  | 2.62   | 1.44            | 5.16            |      |
| Technical/professional school   | 69  | 21.9  | 1.77   | 0.76            | 3.17            |      |
| Secondary school                | 47  | 14.9  | 2.42   | 1.09            | 3.84            |      |
| Longer education                | 50  | 15.9  | 1.58   | 0.74            | 2.91            |      |
| Diabetes mellitus               |     |       |        |                 |                 |      |
| Not specified                   | 25  | 7.9   | 1.83   | 1.16            | 3.63            | 0.67 |
| No                              | 276 | 87.6  | 2.21   | 1.07            | 4.05            |      |
| Yes                             | 14  | 4.4   | 2.47   | 0.88            | 6.49            |      |
| CVD                             |     |       |        |                 |                 |      |
| Not specified                   | 39  | 12.4  | 2.69   | 1.09            | 5.16            | 0.028|
| No                              | 178 | 56.6  | 1.91   | 0.85            | 3.69            |      |
| Yes                             | 98  | 31.1  | 2.57   | 1.25            | 4.40            |      |
| Smoking status                  |     |       |        |                 |                 |      |
| Not specified                   | 1   | 0.3   | 3.76   | 3.76            | 3.76            | 0.87 |
| Never                           | 150 | 47.6  | 2.15   | 0.97            | 3.85            |      |
| Former                          | 96  | 30.5  | 1.98   | 1.10            | 4.08            |      |
| Current                         | 68  | 21.6  | 2.24   | 1.14            | 4.07            |      |
| Alcohol consumption (g/d)       |     |       |        |                 |                 |      |
| Non-drinkers                    | 16  | 5.1   | 4.14   | 0.93            | 7.02            | 0.35 |
| ≤10                             | 164 | 52.1  | 2.33   | 1.11            | 4.02            |      |
| >10                             | 112 | 35.6  | 1.87   | 0.91            | 3.81            |      |
| Physical activity               |     |       |        |                 |                 |      |
| Not specified                   | 13  | 4.1   | 2.85   | 1.09            | 3.85            | 0.78 |
| Inactive                        | 31  | 9.8   | 1.62   | 0.97            | 3.90            |      |
| Moderately inactive             | 91  | 28.9  | 2.48   | 0.90            | 4.65            |      |
| Moderately active               | 148 | 47.1  | 2.17   | 1.12            | 3.79            |      |
| Active                          | 32  | 10.2  | 1.89   | 0.81            | 4.41            |      |
| BMI (kg/m²)                     |     |       |        |                 |                 |      |
| <20                             | 6   | 1.9   | 1.26   | 0.47            | 3.99            | <0.001|
| 20–24.9                         | 112 | 35.6  | 1.77   | 0.66            | 2.90            |      |
| 25–29.9                         | 151 | 47.9  | 2.31   | 1.11            | 4.24            |      |
| ≥30                             | 46  | 14.6  | 3.14   | 1.83            | 5.65            |      |
| Waist circumference (cm)        |     |       |        |                 |                 |      |
| Men                             |     |       |        |                 |                 |      |
| <80                             | 50  | 43.1  | 1.26   | 0.55            | 2.60            | 0.025|
| ≥80                             | 66  | 56.9  | 1.83   | 1.09            | 3.90            |      |
| Women                           |     |       |        |                 |                 |      |
| <80                             | 87  | 43.7  | 1.79   | 0.85            | 3.54            | <0.001|
| ≥80                             | 112 | 56.3  | 3.17   | 1.81            | 4.72            |      |
| Total energy intake (kJ/d)      |     |       |        |                 |                 |      |
| Men                             |     |       |        |                 |                 |      |
| ≤10 460                         | 72  | 62.1  | 1.83   | 0.83            | 3.69            | 0.43 |
| >10 460                         | 44  | 37.9  | 1.52   | 0.76            | 2.63            |      |
| Women                           |     |       |        |                 |                 |      |
| ≤8368                          | 123 | 61.8  | 2.78   | 1.42            | 4.70            | 0.11 |
| >8368                          | 76  | 38.2  | 2.13   | 1.04            | 4.21            |      |
| Total dietary fibre (g/d)       |     |       |        |                 |                 |      |
| ≤20                            | 119 | 37.8  | 2.66   | 1.62            | 5.00            | <0.001|
| 20–30                          | 151 | 47.9  | 1.91   | 0.89            | 3.87            |      |
| >30                            | 45  | 14.3  | 1.50   | 0.73            | 2.56            |      |
Polyphenol extracts used in supplementation and fortification may lack the synergistic effects and health benefits of a diet naturally rich in polyphenols. Our data specifically pointed to polyphenol compounds that could be particularly bioactive exerting anti-inflammatory properties. Among these, daidzein has been known as one of the most common compounds within the subclass of isoflavones. The chemical structure of isoflavones resembles the structure of oestrogens, and main food sources include soya and its processed products. In our data, a strong anti-inflammatory link was further suggested for the cinnamic acid derivatives of phenolic acids, including 3,4-dihydroxyphenylpropionic acid, 3,5-dihydroxyphenylpropionic acid, caffeic acid and ferulic acid. Caffeic acid has been described as the most abundant phenolic acid which main source is coffee. Coffee contains an ester known as chlorogenic acid that is largely hydrolysed into caffeic acid in the gut. However, caffeic acid

### Table 1. (Continued)

| Variable                                | n  | %   | Serum hsCRP (mg/l) | P*  |
|------------------------------------------|----|-----|--------------------|-----|
| Processed and red meat intake (g/d)     |    |     | Median             | 25th percentile | 75th percentile |     |
| ≤50                                      | 80 | 25.4| 1.90               | 1.21           | 3.13           | 0.17 |
| 50–150                                   | 210| 66.7| 2.39               | 1.01           | 4.72           |     |
| >150                                     | 25 | 7.9 | 1.54               | 0.82           | 2.62           |     |
| Fish and shellfish intake (g/d)         |    |     |                    |                |                |     |
| Non-consumers                           | 13 | 4.1 | 2.15               | 1.50           | 3.77           | 0.78 |
| ≤50                                      | 236| 74.9| 2.22               | 1.07           | 4.02           |     |
| >50                                      | 66 | 21.0| 1.96               | 1.02           | 4.05           |     |

* P values by Wilcoxon–Mann–Whitney test or Kruskal–Wallis test among subgroups for each variable.

Fig. 1. Risk for high-sensitivity C-reactive protein ≥3 mg/l per standard deviation increase of polyphenol concentrations. Models were adjusted for age, sex, country, diabetes, cardiovascular problems, education, smoking status, alcohol intake, red and processed meat consumption, total fibre consumption, fish and shellfish intake, total physical activity and BMI-adjusted waist circumference. Values are adjusted odds ratios, with 95% confidence intervals represented by horizontal bars.
Table 2. High-sensitivity C-reactive protein (hsCRP) concentrations and estimated risk for elevated hsCRP (>3 mg/l) according to quartiles (Q) of polyphenol concentrations and per standard deviation increase (Geometric mean values and 95 % confidence intervals; odds ratios and 95 % confidence intervals)

| Polyphenol subclasses | Q1 (n 78) | Q2 (n 79) | Q3 (n 79) | Q4 (n 79) | \( P \) \(_{\text{linear trend}} \) | OR for hsCRP \( \geq 3 \) mg/l | OR for hsCRP \( \geq 3 \) mg/l | OR for hsCRP \( \geq 3 \) mg/l | OR for hsCRP \( \geq 3 \) mg/l |
|----------------------|----------|----------|----------|----------|-----------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Combined polyphenols |          |          |          |          |                 |                       |                       |                       |                       |
| hsCRP (mg/l)         |          |          |          |          |                 |                       |                       |                       |                       |
| Geometric mean       | 2.34     | 1.76     | 2.15     | 1.80     | –               |                       |                       |                       |                       |
| Model 1†             | 2.32     | 1.81, 2.97 | 1.77     | 1.39, 2.27 | 1.99           | 1.58, 2.52           | 1.50           | 1.14, 1.97           | 0.12                   |
| Model 2‡             | 2.23     | 1.70, 2.91 | 1.68     | 1.28, 2.20 | 1.75           | 1.34, 2.28           | 1.34           | 1.00, 1.79           | 0.069                  |
| OR for hsCRP \( \geq 3 \) mg/l | 1.00 | 1.16 | 0.52, 2.60 | 0.57 | 0.25, 1.29 | 0.42 | 0.16, 1.11 | 0.038 | 0.71 | 0.50, 0.99 | 0.045 |
| Phenolic acids       |          |          |          |          |                 |                       |                       |                       |                       |
| hsCRP (mg/l)         |          |          |          |          |                 |                       |                       |                       |                       |
| Geometric mean       | 2.12     | 2.23     | 1.77     | 1.91     | –               |                       |                       |                       |                       |
| Model 1†             | 2.02     | 1.40, 2.89 | 2.10     | 1.63, 2.71 | 1.85           | 1.43, 2.39           | 1.62           | 1.23, 2.15           | 0.51                   |
| Model 2‡             | 1.88     | 1.29, 2.73 | 1.99     | 1.52, 2.61 | 1.71           | 1.29, 2.25           | 1.41           | 1.04, 1.91           | 0.24                   |
| OR for hsCRP \( \geq 3 \) mg/l | 1.00 | 0.86 | 0.26, 2.87 | 0.74 | 0.22, 2.53 | 0.43 | 0.12, 1.59 | 0.10 | 0.71 | 0.44, 1.15 | 0.17 |
| Stilbenes (resveratrol only) |          |          |          |          |                 |                       |                       |                       |                       |
| hsCRP (mg/l)         |          |          |          |          |                 |                       |                       |                       |                       |
| Geometric mean       | 2.59     | 2.14     | 1.84     | 1.92     | –               |                       |                       |                       |                       |
| Model 1†             | 2.18     | 1.69, 2.81 | 2.10     | 1.65, 2.68 | 1.72           | 1.36, 2.17           | 1.65           | 1.27, 2.15           | 0.30                   |
| Model 2‡             | 2.13     | 1.62, 2.79 | 1.91     | 1.47, 2.48 | 1.61           | 1.23, 2.09           | 1.40           | 1.06, 1.96           | 0.11                   |
| OR for hsCRP \( \geq 3 \) mg/l | 1.00 | 0.82 | 0.37, 1.85 | 0.63 | 0.28, 1.43 | 0.28 | 0.11, 0.72 | 0.008 | 0.74 | 0.54, 1.02 | 0.066 |
| Tyrosols             |          |          |          |          |                 |                       |                       |                       |                       |
| hsCRP (mg/l)         |          |          |          |          |                 |                       |                       |                       |                       |
| Geometric mean       | 2.32     | 1.63     | 1.97     | 1.9     | –               |                       |                       |                       |                       |
| Model 1†             | 2.22     | 1.81, 2.72 | 1.46     | 1.09, 1.96 | 1.81           | 1.42, 2.31           | 1.78           | 1.38, 2.29           | 0.13                   |
| Model 2‡             | 2.06     | 1.64, 2.60 | 1.35     | 0.99, 1.84 | 1.67           | 1.28, 2.19           | 1.61           | 1.20, 2.16           | 0.12                   |
| OR for hsCRP \( \geq 3 \) mg/l | 1.00 | 0.38 | 0.15, 0.94 | 0.86 | 0.41, 1.82 | 0.79 | 0.34, 1.83 | 0.95 | 1.07 | 0.78, 1.45 | 0.69 |

* Values are geometric means (n 315).
† Adjusted for age, sex, country and total energy intake
‡ Adjusted for age, sex, country, diabetes, cardiovascular problems, education, smoking status, alcohol intake, red and processed meat consumption, total fibre consumption, fish and shellfish intake, total physical activity and BMI-adjusted waist circumference.
also accounts for over 75% of the total hydroxycinnamic acid content of fruits(34). Major sources of caffeic acid include blueberries, kiwis, plums, cherries and apples, as well as specific herbs and spices(44). 3,4-Dihydroxyphenylpropionic acid also known as dihydrocaffeic acid is a metabolite identified in human plasma after ingestion of caffeic acid(36) but can also be formed from other polyphenols such as catechin present in foods and beverages such as tea, cocoa and wine. Ferulic acid is the most abundant phenolic acid found in cereal grains mostly present in their outer parts(34). Maize flour, whole-grain wheat, rice and oat flours are known as main dietary sources of ferulic acid. Coffee may represent another dietary source of ferulic acid concentration(33). 3,5-Dihydroxyphenylpropionic acid is a metabolite of alkylresorcinols, associated with whole-grain wheat intake(35). Tyrosol (4-hydroxyphenylethanol) and hydroxytyrosol (3,4-dihydroxyphenylethanol) are the main phenolic alcohols contained mainly in extra virgin olive oil but are also present in red and white wines and beer(36). In particular, hydroxytyrosol is found in red wine and is additionally produced in vivo after red wine ingestion(36). Finally, our analysis pointed to anti-inflammatory properties of enterolactone and enterodiol representing the class of lignans. They are formed from dietary lignans found in relatively low concentrations in various seeds, grains, fruits and vegetables and in higher concentrations in sesame and flax seeds(37). They have been widely studied for their oestrogenic properties and were defined for this reason as phyto-oestrogens. Interestingly, our analysis revealed a specific J-shaped association between resveratrol and inflammatory status such that moderate resveratrol levels were associated with lower odds for elevated hsCRP. In contrast, very low levels and very high levels of resveratrol have been found associated with elevated inflammation levels. This finding could provide a curious parallel with the known J-shaped association for wine consumption and health outcomes(38). Indeed, moderate wine consumption is a characteristic of the Mediterranean diet, and studies around the world have shown a beneficial effect of moderate wine on human health(39). Whether consuming moderate amounts of resveratrol could provide a key for achieving optimal inflammatory status and lower risk of chronic diseases should be further evaluated. Overall, our data add to the increasing line of evidence from basic research on anti-inflammatory properties of polyphenols. Potential mechanisms explaining this link include (a) acting as an antioxidant or increasing antioxidant gene or protein expression, (b) attenuating endoplasmic reticulum stress signalling, (c) blocking pro-inflammatory cytokines or endotoxin-mediated kinases and transcription factors involved in metabolic disease, (d) suppressing inflammatory or inducing metabolic-gene expression via increasing histone deacetylase

Fig. 2. Odds ratios and 95% confidence interval function for high-sensitivity C-reactive protein (hsCRP) ≥ 3 mg/l estimated by a restricted cubic spline function with three knots at the 10th, 50th and 90th percentile of concentrations of total polyphenols and polyphenol classes. Models were adjusted for age, sex, country, diabetes, cardiovascular problems, education, smoking status, alcohol intake, red and processed meat consumption, total fibre consumption, fish and shellfish intake, total physical activity and BMI-adjusted waist circumference. Nonlin., non-linear.
activity and (c) activating transcription factors that antagonise chronic inflammation(40). More specifically, polyphenols that manifested an inverse association with hsCRP in our data, that is, daidzein, caffeic acid and its derivatives, enterolactone and enterodiol were also shown to pass the intestinal barrier and directly modulate cytokine production(46), whereas hydroxytyrosol was further suggested to exacerbate improvement in the antioxidant potential of plasma(46).

It should also be noted that the metabolites present in blood circulation result from digestive and hepatic activity and supposedly differ from the native compounds, and the complex interaction with individual gut microbiota and metabolism should be taken into account when interpreting human study data(67). The bioavailability may differ greatly among the various polyphenol compounds, and the most abundant ones in human diet would not necessarily be those that have the best bioavailability profile. Nevertheless, high plasma concentrations of polyphenol metabolites could reflect regular and frequent consumption of plant products. Based on dietary data collected in the EPIC cohort, main foods that predicted concentrations of combined polyphenols included specific pasta-like cereal-based products and sauces (i.e. soya sauce and tomato sauce), coffee and tea. Among fruits, only kiwi was retained in the model. A polyphenol-rich dietary pattern with dense bioactive nutrient composition could have strong anti-inflammatory effect, and further methodological work would be warranted to develop and evaluate preventive potential of such a dietary approach.

A major strength of our study is the comparatively large number of polyphenols investigated spanning all major classes found in the diet. We were able to simultaneously quantify concentrations of thirty-five polyphenols by applying a newly developed analytical method(40). The measurement of plasma concentrations of polyphenols represents a snapshot of internal exposure to these compounds that could originate from several dietary sources directly or their precursors. Thus, any potential bias using exposure measurements from questionnaire-based data acquisition is circumvented. Another strength of our study is that, compared with previous studies, we considered a large variety of covariates in the association of plasma polyphenols and hsCRP. Further, we were able to explore associations across study subjects of different lifestyle and dietary habits in nine different countries. As compared with characteristics of the full EPIC cohort, no indication of selection bias could be seen(17). The key limitation of our study is its cross-sectional design, which precludes making inferences regarding causality. Furthermore, because of the observational nature of the study, the possibility of residual confounding cannot be avoided. Both polyphenols and hsCRP were measured in single plasma samples from baseline, meaning that intra-individual variations in circulating concentrations of these biomarkers were unaccounted for(46). hsCRP concentrations, on the other hand, have been shown to be relatively stable in previous studies of non-diseased people, with an intra-class correlation coefficient of 0.67 over a 4-year period(49). The variability in these measures could have biased the results towards the null. Our results are restricted to the measured polyphenol compounds and do not provide full picture on full polyphenol metabolome.

In summary, the present study revealed that high plasma polyphenol concentrations were associated with lower odds of elevated hsCRP. Among specific polyphenol compounds, the associations have been most pronounced for daidzein, ferulic acid, caffeic acid, 3,4-dihydroxyphenylpropionic acid and 3,5 dihydroxybenzoic acid, enterolactone, enterodiol and hydroxytyrosol. Whether diet rich in polyphenol compounds could be an effective strategy to prevent or modulate deleterious health effects of inflammation should be addressed by further well-powered longitudinal studies.

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There are no conflicts of interest for any co-author.

Availability of data and materials

For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at http://epic.iarc.fr/access/index.php

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Supplementary material

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