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Plasma Concentration of 36 (Poly)phenols and Prospective Body Weight Change in Participants from the EPIC Cohort

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Abstract
Introduction: Dietary intake of (poly)phenols has been linked to reduced adiposity and body weight (BW) in several epidemiological studies. However, epidemiological evidence on (poly)phenol biomarkers, particularly plasma concentrations, is scarce. We aimed to investigate the associations between plasma (poly)phenols and prospective BW change in participants from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. ***Methods:*** This study included 761 participants with data on BW at baseline and after 5 years of follow-up. Plasma concentrations of 36 (poly)phenols were measured at baseline using liquid chromatography-tandem mass spectrometry. Associations were assessed through general linear mixed models and multinomial logistic regression models, using change in BW as a continuous or as a categorical variable (BW loss, maintenance, gain), respectively. Plasma (poly)phenols were assessed as log2-transformed continuous variables. The false discovery rate (FDR) was used to control for multiple comparisons. ***Results:*** Doubling plasma (poly)phenol concentrations showed a borderline trend towards a positive association with BW loss. Plasma vanillic acid showed the strongest association (−0.53 kg/5 years; 95% confidence interval [CI]: −0.99, −0.07). Similar results were observed for plasma naringenin comparing BW loss versus BW maintenance (odds ratio: 1.1; 95% CI: 1.0, 1.2). These results did not remain significant after FDR correction. ***Conclusion:*** Higher concentrations of plasma (poly)phenols suggested a tendency towards 5-year BW maintenance or loss. While certain associations seemed promising, they did not withstand FDR correction, indicating the need for caution in interpreting these results. Further studies using (poly)phenol biomarkers are needed to confirm these suggestive protective trends.

Introduction

Phenols and polyphenols, referred to as (poly)phenols hereafter, are secondary metabolites from plants with bioactive properties [1]. More than 500 individual (poly)phenols have been identified from different plant foods in the human diet, with flavonoids and phenolic acids representing the major classes [1]. Fruits, vegetables, wholegrain cereals, olive oil, cocoa, tea, and coffee are some of the main dietary sources of (poly)phenols [2].

Several epidemiological studies estimating intakes through dietary questionnaires or urine biomarkers have reported associations between dietary (poly)phenols and body weight (BW) change [3–6]. A French cohort study observed an association between higher intake of different (poly)phenols and a smaller increase in body mass index (BMI) and waist circumference [3]. An Italian cohort study concluded that higher flavonoid intake was associated with a lower BW [4]. Despite not assessing specifically anthropometric outcomes, three recent cohort studies have reported data on dietary (poly)phenols and central obesity as marker of metabolic syndrome (MetS). In a Danish cohort, dietary intake of total (poly)phenols, flavonoids, and phenolic acid was associated with lower odds of MetS, defined as the presence of at least three markers including high WC, high plasma triglycerides or HDL-cholesterol, high systolic or diastolic blood pressure, and/or high HbA1c [7]. Likewise, higher flavonoid consumption in Chinese adults [8] and dietary intake of the subclass flavonol in a Polish cohort [9] were found to be potentially protective against MetS, probably mainly impacting central obesity.

We recently investigated the associations between dietary intake of (poly)phenols (i.e., total, classes, subclasses, and individually) and 5-year BW change in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort [5, 6]. In general, intakes of most of the individual (poly)phenols and total flavonoids were inversely associated with 5-year BW change, except for (poly)phenols from coffee (i.e., hydroxycinnamic acids).

Our motivation to investigate the hypothesis of an inverse association between plasma (poly)phenols and BW gain is multifaceted. Previous research has suggested that dietary (poly)phenols may possess anti-obesity properties [3–6, 8, 9], but reliance on self-reported dietary data can introduce bias [10]. To mitigate this and obtain a more objective measure of dietary intake, we turned to plasma biomarkers. These nutritional biomarkers offer a reliable quantification of (poly)phenol exposure, allowing for a more accurate assessment of their impact on BW changes. Notably, limited research has explored the relationship between plasma (poly)phenols and obesity markers, underscoring the need for a more comprehensive investigation. Utilizing data from approximately 800 participants with information on 36 well-characterized plasma (poly)phenols and BW change, our study aimed to elucidate the potential role of these (poly)phenol biomarkers in BW management.

Methods

Population and Data Collection

The EPIC study is a multicentre prospective cohort that includes over half a million participants from 10 Western European countries [11]. It primarily aimed to evaluate the association between dietary and lifestyle factors and the risk of cancer and cancer-related diseases. Details on recruitment and study design have been published previously [11]. For the present study, a convenient sample of cancer-free controls was selected from two EPIC-nested case-control studies (colon and thyroid cancer studies) (n = 1,321) [12, 13]. Participants with no plasma (poly)phenol measurement (n = 430) and with no follow-up BW were excluded (n = 73). Data from Greece were not available at the time of this study, and therefore, Greek participants were excluded (n = 57). The final sample included 761 participants (online suppl. Fig. S1; for all online suppl. material, see https://doi.org/10.1159/000535803).

The majority of lifestyle factors were collected at recruitment through standardized questionnaires, and medical history was self-reported at baseline [11]. For this study, we included data on baseline age, sex, physical activity, education level, menopausal status, and alcohol consumption. We also included data on changes in smoking status at follow-up. Dietary data were collected at baseline through validated country-specific dietary questionnaires [14]. To estimate nutrient and total energy intake, the standardized EPIC Nutrient Database was used [15]. Baseline BW and height were collected by trained staff using standardized methods, except for centres from in France, Oxford, and Norway, where they were self-reported [11]. At follow-up, BW was self-reported in all centres, with the exception of Doetinchem and Cambridge, where it was measured [16]. The accuracy of self-reported BW was improved with prediction equations derived from EPIC-Oxford participants, in which BW at baseline was both measured and self-reported [17]. To calculate the 5-year BW change, baseline BW was subtracted from follow-up BW for each participant. The result was then divided by the number of follow-up years to obtain the annual BW change and multiplied by 5 to finally obtain the BW change over 5 years.

Plasma (poly)phenol measurements were available to participants from 19 EPIC centres (from Denmark, Germany, Italy, Norway, Spain, Sweden, the Netherlands, and the UK). Blood samples were collected at baseline following standardized procedures [18]. Plasma concentrations of (poly)phenols (nmol/L) were measured by a highly sensitive method based on differential isotope labelling with 12 and 13 C-dansyl chloride and an ultra-performance liquid chromatography-tandem mass spectrometry system (UPLC-MS/MS) with prior enzymatic hydrolysis. This method allowed the quantification with high accuracy and reproducibility of a large selection of compounds representative of the main classes of dietary (poly)phenols in low volumes of plasma [18]. Limits of quantification (LOQ) for the individual (poly)phenols varied between 0.11 nmol/L for apigenin and 44.4 nmol/L for quercetin. Intra-batch coefficients of variability (CV) varied between 2.3 and 9.0%, and inter-batch CV was <20% for the majority of (poly)phenols, except for quercetin (23.4%) and enterodiol (20.3%). Details about the laboratory methodology have been published elsewhere [18].

Statistical Analysis

Baseline characteristics were calculated according to categories of BW change over 5 years. BW change was categorized into three groups: loss (<−1.5 kg/5 years), maintenance (from −1.5 to 1.5 kg/5 years), and gain (>1.5 kg/5 years). Data on 36 plasma (poly)phenols (nmol/L) spanning the majority of compounds found in the human diet were available for this study and were analysed as continuous variables. Right-skewed distributions were standardized using log2-transformations with zero values imputed with half the LOQ for each (poly)phenol. Therefore, results were expressed as doubling plasma (poly)phenol concentrations. Spearman rank coefficients were calculated to assess correlations between individual plasma (poly)phenol concentrations. Correlations were also evaluated between plasma (poly)phenol levels and the intake of the following 12 (poly)phenol-rich food groups: potatoes and other tubers, vegetables, legumes, cereals, fats and oils, condiments, fruits, nuts and seeds, olives, coffee, tea, and herbal teas.

Two general linear mixed models (GLMM) were fitted to evaluate the association between plasma (poly)phenols (nmol/L) and continuous BW change (kg/5 years). In addition, we fitted multinomial logistic regression models using BW change over 5 years as a categorical variable with three categories: BW maintenance (from −1.5 to 1.5 kg/5 years) as the reference category, BW loss (<−1.5 kg/5 years), and BW gain (>1.5 kg/5 years).

For model adjustment, we selected variables a priori [19–23]: age (continuous, years), sex, baseline BMI (continuous, kg/m^2), follow-up years (continuous), energy intake (continuous, kcal/day), fibre intake (continuous, g/day), vitamin C intake (continuous, mg/day),

physical activity using the Cambridge index [24] (categories: inactive, moderately inactive, moderately active, active), menopausal status (categories: pre, post and peri-menopausal), change in smoking status at follow-up (categories: stable never smoker, stable current smoker, starter, quitter, former at follow-up), laboratory batch, plausibility of energy intake reporting (categories according to the ratio of reported energy intake (EI) to predicted basal metabolic rate (BMR): under (EI:BMR <1.14), plausible (1.14–2.1) and over reporters (>2.1), with the use of cut-off points proposed by Goldberg et al. [25]), education level (categories: none, primary, technical, secondary, longer), alcohol consumption (continuous, g/day), EPIC centres, and type of cancer project (thyroid/colon). Some of these variables were excluded after stepwise regression screening (i.e., menopausal status, education level, and alcohol consumption). Participants with missing values in categorical adjustment variables were placed in a separate category, while continuous adjustment variables presented no missing values. Aikaike Information Criterion was used to compare and select the best-fitting models. Restricted cubic splines were used to evaluate the non-linearity of the associations for continuous covariates. BMI, follow-up years, and energy intake showed a non-linear relationship with BW change. Thus, splines with 3 knots (percentile 10, 50, and 90) were included as covariates for these three variables. Knot positions were determined using the Harrell criteria [26].

For GLMM, in Model 1, age, sex, and baseline BMI were used as covariates. EPIC centres and type of cancer project (thyroid or colon cancer control groups) were included as random effects to control for potential confounding due to differences in follow-up procedures, questionnaire design, and blood sample collection and analysis. Model 2 was additionally adjusted for years of follow-up, physical activity level, change in smoking status at follow-up, laboratory batch, energy intake, and plausibility of energy intake reporting. To account for certain dietary variables that may be related to both exposure and outcome, we fitted a third model, adding intake of fibre (g/day) and intake of vitamin C (mg/day) as further confounding variables. A sensitivity analysis was performed for each model to exclude participants with chronic diseases at baseline (diabetes, stroke, or myocardial infarction, $n = 92$, leaving $n = 669$ included). We further fitted interactions between (poly)phenol concentrations and sex, baseline age, and smoking status at follow-up [27, 28]. p values for interactions were calculated using the likelihood ratio test. The adjustment variables for multinomial logistic regression models were the same as the GLMMs, except for EPIC centres and type of cancer project that was included here as fixed effects.

For all models, p values were adjusted by computing the false discovery rate (FDR) to control for multiple comparisons and considered statistically significant at an FDR q value <0.05. All statistical analyses were performed with *R* Statistical Software version 4.2.2 [29].

Results

Descriptive Data Analysis

Table 1 shows characteristics of the 761 participants included in this study according to categories of BW change over 5 years. Overall, mean (SD) 5-year BW change was 0.6 (4.5) kg and ranged from − 18.2 to 21.8 kg. A total of 293 participants (38.6%) gained >1.5 kg of weight over 5 years, whereas 194 (25.5%) lost >1.5 kg/5 years. Baseline BW and BMI were higher in participants in the BW loss category. More than 50% of participants in the BW loss category had lower levels of education, whereas more than 50% of participants in the BW gain category presented higher educational levels. According to change in smoking status at follow-up, a high proportion of participants were classified as never smokers (48%), followed by former smokers (including never at baseline and former at follow-up, 23%). The majority of participants were females (77%), as the thyroid cancer control group included only female participants and represented 40% of the study population, while also 60% of the colon cancer group were females. Table 2 shows the median and 5th and 95th percentiles of plasma concentrations of (poly)phenols among participants. The highest plasma concentration values were observed for caffeic acid (median 367.0 nmol/L) and 4-hydroxyphenylacetic acid (287.0 nmol/L), whereas the lowest concentrations were observed for equol (0.4 nmol/L) and enterodiol (1.0 nmol/L). Figure 1 illustrates the statistically significant ($p \leq 0.05$) correlations between each of the plasma (poly)phenols and between plasma (poly)phenols and (poly)phenol-rich food groups. The strongest correlation was observed between 3,5-dihydroxybenzoic acid and 3,5-dihydroxy-phenylpropionic acid ($r = 0.90$). Correlation coefficients between plasma (poly)phenols and food groups were mostly low ($r < 0.40$), only highlighting correlations for tea (epicatechin $r = 0.46$; 3,5-dihydroxy-benzoic acid $r = 0.45$) and coffee (ferulic acid $r = 0.51$). The strongest inverse correlations were identified between protocatechuic acid and caffeic acid ($r = -0.52$), while isoharmentin displayed notable inverse correlations with three compounds: 3,4-dihydroxy-phenilacetic acid ($r = -0.52$), gallic acid ($r = -0.55$), and 3,4-dihydroxy-phenilpropionic acid ($r = -0.56$).

Plasma Concentration of (Poly)phenols and BW Change

We obtained nearly identical results for models 2 and 3. Consequently, we present the more extensively adjusted model, namely, model 3. Figure 2 shows results after modelling continuous 5-year BW change against log2-transformed plasma concentrations of (poly)phenols and adjusting for relevant confounders. Only plasma vanillic acid concentration appeared to be inversely associated with BW change in model 3 (*beta* per doubling concentration: −0.53 kg/5 years; 95% confidence interval [CI]: −0.99, −0.07), and a borderline association was

Table 1. Characteristics of 761 participants from the EPIC study according to categories of BW change over 5 years

Characteristic	BW loss (<−1.5 kg/5 years)	BW maintenance (−1.5 to 1.5 kg/5 years)	BW gain (>1.5 kg/5 years)	*p* value[a]
Participants, *n* (%)	194 (25.5)	274 (36.0)	293 (38.5)	0.001
Follow-up time, years	5.1 (2.7)	7.1 (3.2)	6.3 (2.9)	<0.001
BW change, kg/5 years	−4.7 (3.2)	0.1 (0.8)	4.5 (3.2)	<0.001
Age, years	54.8 (8.5)	53.5 (7.9)	52.9 (8.5)	0.059
Energy intake, kcal/day, median (IQR)	1,905 (745)	2,045 (855)	1,935 (790)	0.349
Alcohol consumption, g/day, median (IQR)	5.7 (14.0)	4.3 (15.1)	5.3 (15.0)	0.668
Fibre intake, g/day, median (IQR)	22.4 (9.1)	22.5 (9.9)	21.6 (9.5)	0.491
Vitamin C intake, mg/day, median (IQR)	123.8 (75.0)	118.8 (72.8)	110.3 (75.7)	0.026
BW, kg	73.6 (12.7)	67.1 (11.2)	68.7 (12.0)	<0.001
BMI, kg/m^2	28.2 (4.5)	25.4 (3.6)	25.3 (3.8)	<0.001
Sex, *n* (%)				0.358
Female	157 (80.9)	207 (75.5)	224 (76.5)	
Male	37 (19.1)	67 (24.5)	69 (23.5)	
Project, *n* (%)				0.436
Colon cancer control	117 (60.3)	155 (56.5)	181 (61.7)	
Thyroid cancer control	77 (39.7)	119 (43.5)	112 (38.3)	
Plausibility of energy intake reporting[b], *n* (%)				0.127
Under reporters	33 (17.0)	28 (10.2)	46 (15.7)	
Plausible reporters	148 (76.3)	216 (78.8)	219 (74.7)	
Over reporters	13 (6.7)	30 (11.0)	28 (9.6)	
Physical activity level, *n* (%)				0.001
Inactive	50 (25.8)	74 (27.0)	27 (19.5)	
Moderately inactive	76 (39.1)	103 (37.6)	123 (41.9)	
Moderately active	30 (15.5)	51 (18.6)	55 (18.8)	
Active	38 (19.6)	46 (16.8)	57 (19.5)	
Change in smoking status at follow-up, *n* (%)				<0.001
Stable never smoker	105 (54.0)	122 (44.0)	138 (47.0)	
Stable current smoker	33 (17.0)	30 (11.0)	34 (12.0)	
Starter	5 (2.5)	2 (0.8)	5 (1.5)	
Quitter	5 (2.5)	3 (1.2)	12 (4.0)	
Former at follow-up[c]	35 (18.0)	66 (24.0)	75 (25.5)	
Prevalent disease[d], *n* (%)				0.104
No	172 (88.6)	245 (89.4)	252 (86.0)	
Yes	12 (5.7)	14 (5.1)	11 (3.7)	
Education level, *n* (%)				0.004
None	37 (19.1)	25 (9.1)	23 (7.8)	
Primary school	73 (37.6)	103 (37.6)	111 (37.8)	
Technical school	21 (10.8)	35 (12.8)	39 (13.3)	
Secondary school	35 (18.0)	59 (21.5)	78 (26.6)	
Longer education	25 (12.9)	51 (18.6)	39 (13.3)	
Menopausal status[e], *n* (%)				0.001
Pre-menopausal	91 (46.9)	94 (34.3)	94 (32.1)	
Post-menopausal	97 (50.0)	177 (64.6)	186 (63.5)	
Peri-menopausal	6 (3.1)	3 (1.1)	13 (4.4)	

Data are expressed as mean (SD) and collected at recruitment if not stated otherwise. BMI, body mass index; EPIC, European Prospective Investigation into Cancer and Nutrition; IQR, interquartile range (P25–P75). Percentages may not add up to 100 due to missing values. [a]*p* values by ANOVA, χ^2 or Kruskal-Wallis test among BW change categories for each variable. [b]Categories according to the ratio of reported energy intake (EI) to predicted basal metabolic rate (BRM): under (EI: BMR <1.14), plausible (1.14–2.1), and over reporters (>2.1), with the use of cut-off points proposed by Goldberg et al. [26]. [c]Includes never at baseline but former at follow-up. [d]Diabetes, stroke, or myocardial infarction at baseline. [e]Only for female participants (*n* = 588).

Table 2. Median and 5th and 95th percentiles of plasma concentration (nmol/L) of (poly)phenols among 761 participants from the EPIC study

(Poly)phenol	Median	P5th	P95th
(−)-Epicatechin	14.3	5.5	82.5
(−)-Epigallocatechin	11.1	11.1	48.3
(−)-Gallocatechin	11.1	11.1	15.6
(+)-Catechin	15.5	5.5	58.0
3,4-dihydroxy-phenylacetic acid	31.6	13.9	65.9
3,4-dihydroxy-phenylpropionic acid	146.5	12.5	321.8
3,5-dihydroxy-benzoic acid	23.2	6.6	158.8
3,5-dihydroxy-phenylpropionic acid	31.6	9.2	162.0
3-hydroxy-benzoic acid	19.7	6.8	62.4
3-hydroxy-phenylacetic acid	58.8	2.2	238.9
4-hydroxy-benzoic acid	272.0	160.1	518.8
4-hydroxy-phenylacetic acid	287.0	156.3	888.0
Apigenin	13.5	9.2	18.7
Caffeic acid	367.0	106.0	558.0
Daidzein	10.7	2.9	135.9
Enterodiol	1.0	0.2	8.9
Enterolactone	9.4	1.0	55.9
Equol	0.4	0.1	2.5
Ferulic acid	102.5	52.0	423.5
Gallic acid	28.0	12.2	82.6
Gallic acid ethyl ester	1.1	1.1	7.1
Genistein	5.4	1.3	59.7
Hesperetin	2.2	0.5	122.4
Homovanillic acid	80.5	51.0	162.5
Isorhamnetin	63.0	48.3	94.0
Kaempferol	87.0	59.1	126.9
m-Coumaric acid	8.10	0.5	76.4
Naringenin	3.70	1.1	77.9
Hydroxy-tyrosol	20.2	5.5	50.9
p-Coumaric acid	21.2	12.8	45.2
Phloretin	1.1	1.1	8.8
Protocatechuic acid	178.0	126.0	279.4
Quercetin	250.0	107.0	524.4
Resveratrol	2.6	1.1	13.6
Tyrosol	3.2	1.6	9.7
Vanillic acid	189.0	114.0	367.3

EPIC, European Prospective Investigation into Cancer and Nutrition.

observed for tyrosol (*beta*: −0.29 kg/5 years; 95% CI: −0.62, 0.00). It is worth mentioning that the majority of (poly)phenols displayed a suggestive trend towards inverse associations with BW gain. However, it is important to emphasize that, following the application of FDR adjustment, none of these associations reached statistical significance. Furthermore, similar trends were observed in the sensitivity analysis, which excluded participants with chronic diseases at recruitment (online suppl. Table S1). No statistically significant interactions were observed with respect to sex, age, or changes in smoking status at follow-up.

Table 3 shows the results from multinomial logistic regression analyses comparing BW loss versus BW maintenance (reference category). Most of the (poly) phenols showed a tendency towards BW loss. Plasma naringenin concentration was associated with BW loss in model 3 (odds ratio [OR]: 1.1; 95% CI: 1.0, 1.2). Additionally, plasma levels of ferulic acid (OR: 1.3; 95% CI: 1.0, 1.7), caffeic acid (OR: 1.7; 95% CI: 1.0, 3.0), and kaempferol (OR: 1.7; 95% CI: 1.0, 2.9) exhibited borderline associations. Table 4 presents results comparing BW gain with BW maintenance. We observed a pattern consistent with our previous analysis. Specifically, there were no statistically significant associations for BW gain, either before or after the application of the FDR correction, except for a suggestive inverse association for 3,5-dihydroxybenzoic acid (OR: 0.9; 95% CI: 0.8, 1.0).

Discussion

The current study suggested a tendency towards BW maintenance or reduction over 5 years at higher concentrations of plasma (poly)phenols. We would like to draw attention to the potential protective associations observed between plasma concentrations of vanillic acid and naringenin and BW loss. It is important to note that while the results related to vanillic acid are derived from GLMMs, those concerning naringenin are derived from multinomial models. It is noteworthy that both vanillic acid and naringenin have been proposed as metabolites of dietary flavonoids, as discussed below. Given their shared potential dietary sources, it is plausible that they may exhibit similar behaviours. However, we must approach these associations with caution due to the complexity of the relationships involved.

Even though both GLMMs and multinomial models included the same covariates and followed the same tendency, results were different. One possible explanation for these differences might be that plasma concentrations do not necessarily represent the same compounds present in foods. Natural vanillic acid is a phenolic compound widely present in vanilla beans and in different fruits and grains [30], but it can also be a derivative metabolite from different precursors. For example, as a result of the host metabolism, intake of caffeic acid from coffee has been shown to generate a high increase in urine levels of vanillic acid in vivo [31]. Likewise, one study using animal models observed that after red wine consumption, which is naturally rich in flavonoids and phenolic acids, vanillic acid was found in animal urine

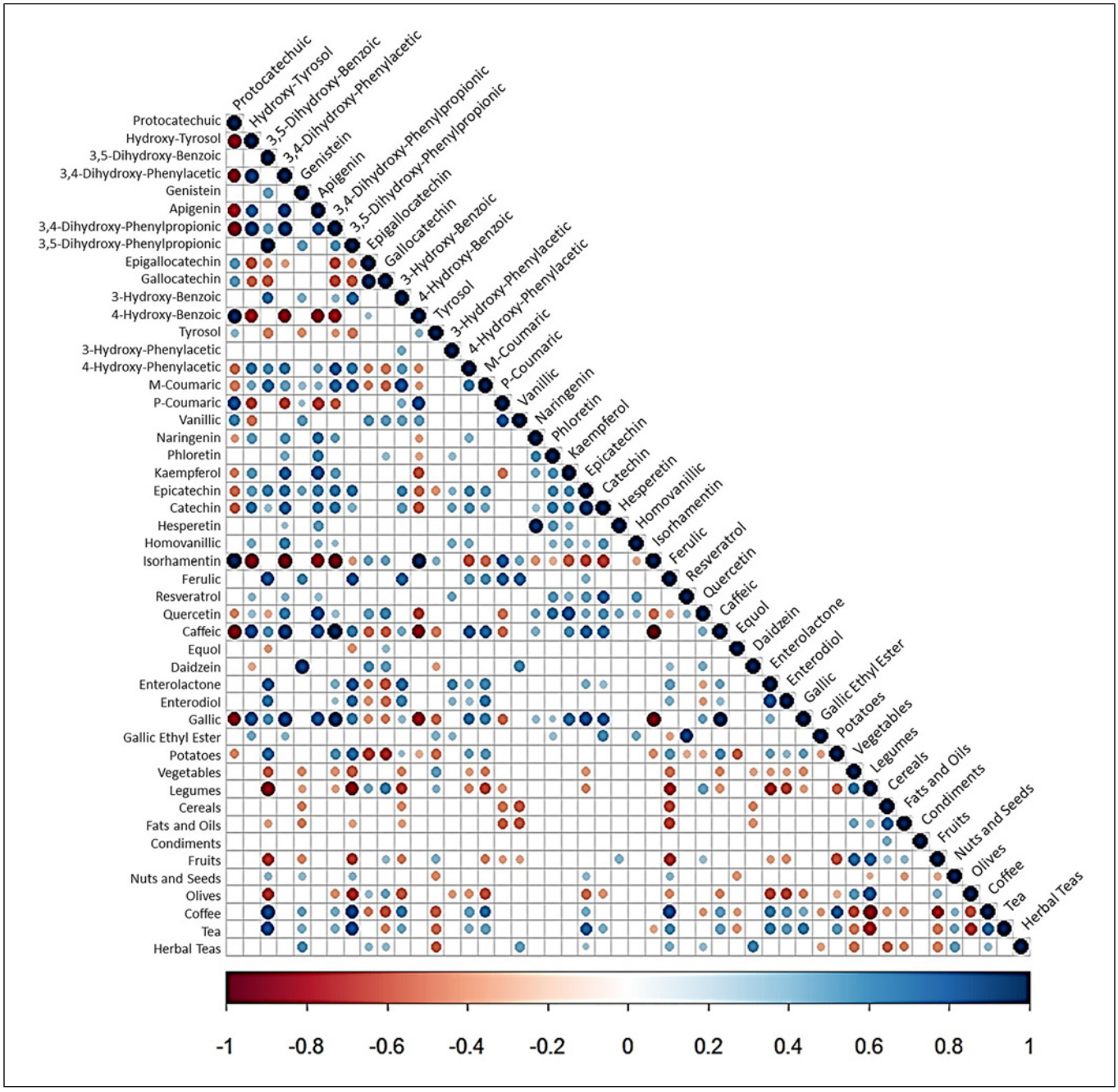

Fig. 1. Heat map showing Spearman rank correlations between plasma (poly)phenols and habitual intakes of selected food groups among participants from the EPIC study. Only significant correlations are shown ($p \leq 0.05$). Colour of the circles indicates the strength and direction of the correlations, and the size indicates the strength of the p value (the bigger, the stronger).

together with other microbial metabolites [32]. One study in vivo showed that after intake of an oral dose of cyanidin 3-glucoside (an anthocyanin widely found in fruits, particularly berries), vanillic acid was present in both human urine and serum [33].

Naringenin occurs naturally in an inactive form as naringin (the glycoside form) and is converted into its active form (aglycone) by bacteria belonging to the gut microbiome [34]. Naringin is a component of the everyday human diet, mainly present in citrus fruits. The

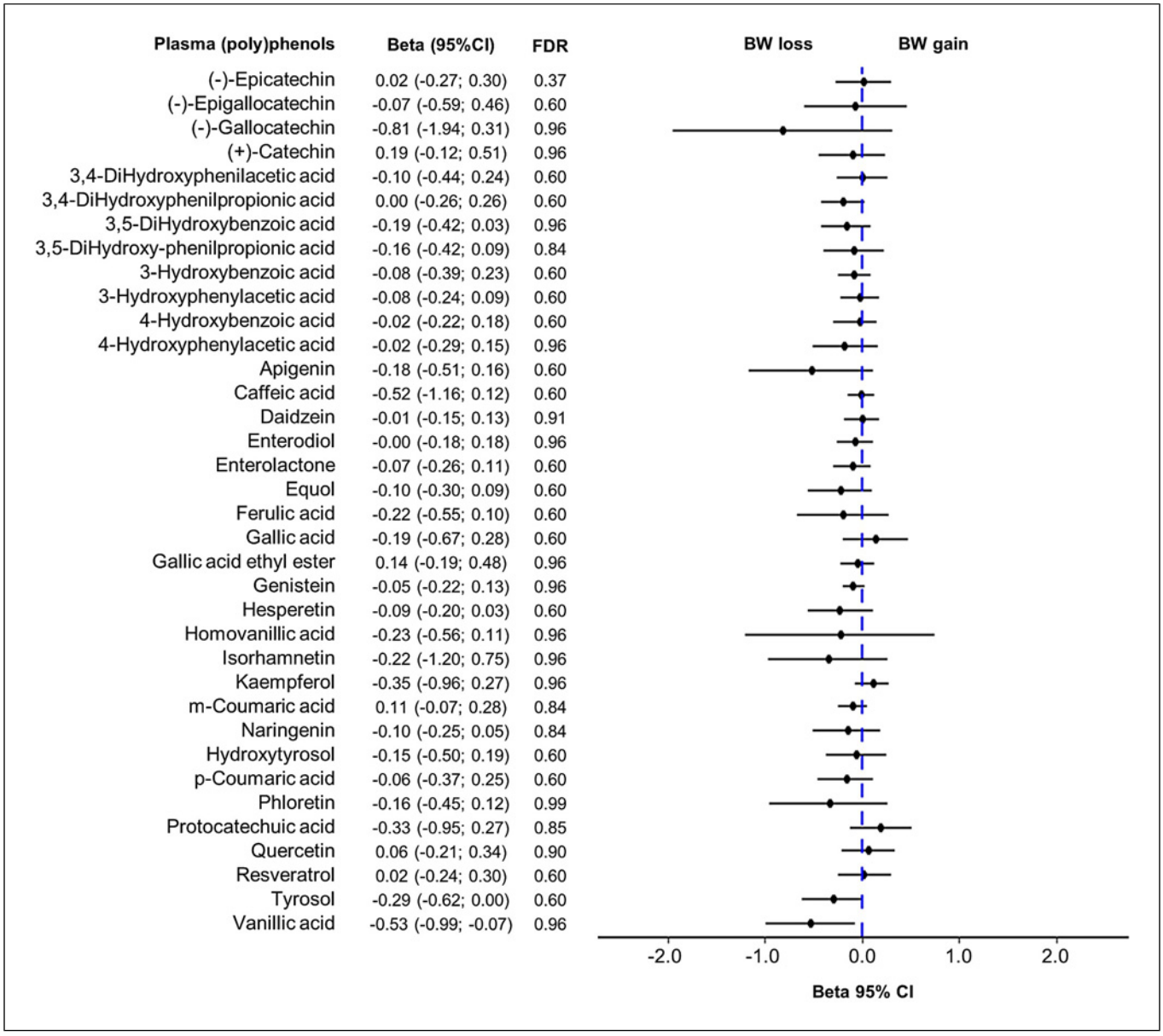

Fig. 2. *Beta* coefficients of BW changes associated with baseline log2-transformed plasma (poly)phenol concentrations for 761 participants from the EPIC study. General linear mixed models with the cancer project and EPIC centre as random effects. *Beta* values indicate 5-year BW change (kg) based on log2-transformed (poly)phenol plasma concentrations and, therefore, correspond to a doubling in plasma concentration of (poly)phenols. Model 3: Adjusted for age, sex, BMI (3-knot restricted cubic spline), follow-up time in years (3-knot restricted cubic spline), physical activity level, change in smoking status at follow-up, (poly)phenols laboratory batch, total energy intake (3-knot restricted cubic spline), plausibility of dietary energy reporting, intake of fibre (g/day), and intake of vitamin C (mg/day). BW, body weight; CI, confidence interval; FDR, false discovery rate.

gut microbiota metabolizes naringin and breaks it down to naringenin which is absorbed in the gut [35]. One study using animal models observed that the major components in plasma and urine after 18 h of gastric gavage of naringenin were glucuronides as well as the colonic metabolite 3-(4-hydroxyphenyl) propionic acid [36]. Thus, compounds present in plasma are not necessarily classified as those precursors present in diet – while naringenin is classified as a flavonoid in diet, one of its major human gut microbial metabolites is 3-(4-hydroxyphenyl) propionic acid, classified as phenolic acid [37].

Table 3. ORs for BW loss[a] (n = 194) versus BW maintenance (reference category[b], n = 274) for log2-transformed plasma (poly)phenol concentrations in participants from the EPIC study

Plasma (poly)phenols	Model 1[c]			Model 3[d]		
	OR (95% CI)	p value	FDR	OR (95% CI)	p value	FDR
(−)-Epicatechin	1.0 (0.8; 1.3)	0.80	0.92	1.0 (0.8; 1.3)	0.20	0.68
(−)-Epigallocatechin	1.0 (0.7; 1.5)	0.95	0.97	1.0 (0.7; 1.5)	0.97	0.99
(−)-Gallocatechin	1.3 (0.6; 2.8)	0.52	0.89	1.3 (0.6; 2.8)	0.54	0.82
(+)-Catechin	0.9 (0.7; 1.1)	0.21	0.74	0.9 (0.7; 1.1)	0.21	0.68
3,4-dihydroxy-phenylacetic acid	1.0 (0.8; 1.3)	0.88	0.96	1.0 (0.8; 1.3)	0.83	0.93
3,4-dihydroxy-phenylpropionic acid	1.0 (0.9; 1.2)	0.69	0.91	1.0 (0.9; 1.3)	0.64	0.82
3,5-dihydroxy-benzoic acid	1.0 (0.8; 1.2)	0.97	0.97	1.0 (0.9; 1.2)	0.90	0.95
3,5-dihydroxy-phenylpropionic acid	1.0 (0.9; 1.3)	0.71	0.91	1.1 (0.9; 1.3)	0.61	0.82
3-hydroxy-benzoic acid	1.1 (0.9; 1.3)	0.41	0.84	1.1 (0.-9; 1.3)	0.52	0.80
3-hydroxy-phenylacetic acid	1.0 (0.9; 1.2)	0.56	0.91	1.1 (0.9; 1.2)	0.36	0.76
4-hydroxy-benzoic acid	1.0 (0.9; 1.1)	0.81	0.92	1.0 (0.9; 1.1)	0.87	0.95
4-hydroxy-phenylacetic acid	1.0 (0.8; 1.2)	0.82	0.92	1.0 (0.8; 1.2)	0.80	0.93
Apigenin	1.1 (0.8; 1.6)	0.43	0.84	1.2 (0.8; 1.6)	0.39	0.77
Caffeic acid	1.8 (1.0; 3.1)	0.05	0.47	1.7 (1.0; 3.0)	0.05	0.51
Daidzein	0.9 (0.8; 1.0)	0.05	0.47	0.9 (0.8; 1.0)	0.07	0.51
Enterodiol	1.0 (0.9; 1.1)	0.59	0.91	1.0 (0.9; 1.1)	0.60	0.82
Enterolactone	0.9 (0.9; 1.1)	0.91	0.96	1.0 (0.9; 1.1)	0.99	0.99
Equol	1.0 (0.8; 1.1)	0.65	0.91	1.0 (0.8; 1.1)	0.68	0.84
Ferulic acid	1.3 (1.0; 1.7)	0.04	0.47	1.3 (1.0; 1.7)	0.15	0.51
Gallic acid	1.2 (0.8; 1.6)	0.39	0.84	1.2 (0.8; 1.7)	0.30	0.72
Gallic acid ethyl ester	0.9 (0.7; 1.2)	0.44	0.84	0.9 (0.7; 1.2)	0.51	0.82
Genistein	1.0 (0.9; 1.1)	0.75	0.92	1.0 (0.9; 1.2)	0.80	0.93
Hesperetin	1.0 (1.0; 1.1)	0.43	0.84	1.0 (1.0; 1.1)	0.43	0.78
Homovanillic acid	1.2 (0.8; 1.4)	0.66	0.91	1.1 (0.8; 1.4)	0.63	0.82
Isorhamnetin	0.7 (0.4; 1.4)	0.35	0.84	0.7 (0.3; 1.4)	0.30	0.72
Kaempferol	1.6 (0.9; 2.7)	0.09	0.59	1.7 (1.0; 2.9)	0.06	0.51
m-Coumaric acid	1.1 (1.0; 1.2)	0.28	0.84	1.1 (1.0; 1.2)	0.39	0.68
Naringenin	1.1 (1.0; 1.2)	0.05	0.47	1.1 (1.0; 1.2)	0.04	0.51
Hydroxy-tyrosol	1.1 (0.9; 1.4)	0.47	0.84	1.1 (0.9; 1.4)	0.43	0.78
p-Coumaric acid	1.2 (0.9; 1.5)	0.20	0.74	1.2 (0.9; 1.5)	0.21	0.68
Phloretin	1.1 (0.9; 1.3)	0.36	0.84	1.1 (0.9; 1.4)	0.23	0.68
Protocatechuic acid	1.3 (0.7; 2.6)	0.39	0.84	1.4 (0.7; 2.8)	0.35	0.76
Quercetin	0.8 (0.7; 1.0)	0.10	0.59	0.8 (0.7; 1.0)	0.12	0.66
Resveratrol	1.0 (0.9; 1.2)	0.67	0.91	1.0 (0.9; 1.3)	0.64	0.82
Tyrosol	1.2 (0.9; 1.4)	0.18	0.74	1.2 (0.9; 1.4)	0.20	0.68
Vanillic acid	1.3 (0.9; 1.8)	0.14	0.72	1.3 (0.9; 1.9)	0.15	0.66

CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; FDR, false discovery rate; OR, odds ratio. ORs correspond to a doubling in (poly)phenol concentration. [a]BW loss: weight change < −1.5 kg/5 years. [b]Reference category: BW maintenance from −1.5 to 1.5 kg/5 years. [c]Adjusted for age, sex, BMI (3-knot restricted cubic spline), cancer project, and EPIC centre. [d]Further adjusted for follow-up time in years (3-knot restricted cubic spline), physical activity level, change in smoking status at follow-up, (poly)phenols laboratory batch, total energy intake (3-knot restricted cubic spline), plausibility of dietary energy reporting, intake of fibre (g/day), and intake of vitamin C (mg/day).

As far as we know, there is a lack of evidence on plasma (poly)phenols and obesity-related parameters. Previous cohort studies have investigated similar relationships but with dietary or urinary (poly)phenols. The SU.VI.MAX study [3] concluded that higher dietary (poly)phenol intake, particularly flavonoids and their subclasses, may help reduce BW gain. The MEAL study observed that higher flavonoid intake was associated with a lower BW [4]. In line with this, the large randomized PREDIMED study concluded that higher (poly)phenol intakes, objectively measured through total urinary (poly)phenol excretion, were inversely correlated with BW and obesity [38]. Bertoia et al.

Table 4. ORs for BW gain[a] (n = 293) versus BW maintenance (reference category[b], n = 274) for log2-transformed (poly)phenol concentrations in participants from the EPIC study

Plasma (poly)phenols	Model 1[c]			Model 3[d]		
	OR (95% CI)	p value	FDR	OR (95% CI)	p value	FDR
(−)-Epicatechin	1.0 (0.8; 1.1)	0.61	0.98	1.0 (0.8; 1.1)	0.57	0.94
(−)-Epigallocatechin	0.9 (0.6; 1.2)	0.33	0.93	0.9 (0.6; 1.2)	0.33	0.93
(−)-Gallocatechin	0.9 (0.5; 1.8)	0.82	0.98	0.9 (0.5; 1.8)	0.74	1.00
(+)-Catechin	0.9 (0.8; 1.1)	0.56	0.97	0.9 (0.8; 1.1)	0.55	0.94
3,4-dihydroxy-phenylacetic acid	0.9 (0.8; 1.1)	0.51	0.96	0.9 (0.8; 1.1)	0.54	0.94
3,4-dihydroxy-phenylpropionic acid	1.0 (0.8; 1.1)	0.50	0.96	1.0 (0.8; 1.1)	0.52	0.94
3,5-dihydroxy-benzoic acid	0.9 (0.8; 1.0)	0.07	0.93	0.9 (0.8; 1.0)	0.07	0.93
3,5-dihydroxy-phenylpropionic acid	0.9 (0.8; 1.1)	0.29	0.93	0.9 (0.8; 1.1)	0.31	0.93
3-hydroxy-benzoic acid	1.0 (0.9; 1.2)	0.64	0.98	1.0 (0.9; 1.2)	0.64	0.96
3-hydroxy-phenylacetic acid	1.0 (0.9; 1.1)	0.42	0.96	1.0 (0.9; 1.1)	0.55	0.94
4-hydroxy-benzoic acid	0.9 (0.8; 1.1)	0.24	0.93	0.9 (0.8; 1.0)	0.24	0.93
4-hydroxy-phenylacetic acid	0.9 (0.8; 1.1)	0.23	0.93	0.9 (0.8; 1.1)	0.24	0.93
Apigenin	0.9 (0.8; 1.1)	0.46	0.96	0.9 (0.8; 1.1)	0.47	0.94
Caffeic acid	1.0 (0.7; 1.5)	0.80	0.98	1.1 (0.7; 1.5)	0.78	1.00
Daidzein	0.9 (0.9; 1.0)	0.12	0.93	0.9 (0.9; 1.0)	0.14	0.93
Enterodiol	1.0 (0.9; 1.1)	0.81	0.98	1.0 (0.9; 1.1)	0.84	1.00
Enterolactone	1.0 (0.8; 1.0)	0.11	0.93	0.9 (0.8; 1.0)	0.12	0.93
Equol	1.0 (0.9; 1.1)	0.86	0.98	1.0 (0.9; 1.1)	0.86	1.00
Ferulic acid	1.0 (0.8; 1.2)	0.90	0.98	1.0 (0.8; 1.2)	1.00	1.00
Gallic acid	1.0 (0.7; 1.3)	0.93	0.99	1.0 (0.7; 1.3)	0.97	1.00
Gallic acid ethyl ester	1.0 (0.8; 1.2)	0.98	0.99	1.0 (0.8; 1.2)	0.99	1.00
Genistein	1.0 (0.9; 1.1)	0.78	0.98	1.0 (0.9; 1.1)	0.77	1.00
Hesperetin	1.0 (0.9; 1.0)	0.33	0.93	1.0 (0.9; 1.0)	0.38	0.94
Homovanillic acid	0.9 (0.8; 1.1)	0.30	0.93	0.9 (0.7; 1.1)	0.31	0.93
Isorhamnetin	0.8 (0.5; 1.3)	0.37	0.94	0.8 (0.5; 1.3)	0.34	0.93
Kaempferol	1.1 (0.8; 1.6)	0.54	0.97	1.1 (0.8; 1.6)	0.53	0.94
m-Coumaric acid	1.0 (0.9; 1.2)	0.43	0.96	1.0 (0.9; 1.2)	0.41	0.94
Naringenin	1.0 (0.9; 1.1)	0.76	0.98	1.0 (0.9; 1.1)	0.87	1.00
Hydroxy-tyrosol	1.0 (0.8; 1.2)	0.90	0.98	1.0 (0.8; 1.2)	0.90	1.00
p-Coumaric acid	1.0 (0.8; 1.1)	0.67	0.98	1.0 (0.8; 1.1)	0.64	0.96
Phloretin	0.9 (0.7; 1.0)	0.11	0.93	0.9 (0.7; 1.0)	0.14	0.93
Protocatechuic acid	0.8 (0.6; 1.2)	0.28	0.93	0.8 (0.6; 1.1)	0.25	0.93
Quercetin	0.9 (0.8; 1.1)	0.24	0.93	0.9 (0.7; 1.1)	0.26	0.93
Resveratrol	1.0 (0.9; 1.2)	0.99	0.99	1.0 (0.9; 1.2)	1.00	1.00
Tyrosol	0.9 (0.7; 1.1)	0.34	0.93	1.0 (0.7; 1.1)	0.31	0.93
Vanillic acid	1.0 (0.8; 1.3)	0.84	0.98	1.0 (0.8; 1.3)	0.82	1.00

CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; FDR, false discovery rate; OR, odds ratio. ORs correspond to a doubling in (poly)phenol concentration. [a]BW gain: weight change >1.5 kg/5 years. [b]Reference category: BW maintenance from −1.5 to 1.5 kg/5 years. [c]Adjusted for age, sex, BMI (3-knot restricted cubic spline), cancer project, and EPIC centre. [d]Further adjusted for follow-up time in years (3-knot restricted cubic spline), physical activity level, change in smoking status at follow-up, (poly) phenols laboratory batch, total energy intake (3-knot restricted cubic spline), plausibility of dietary energy reporting, intake of fibre (g/day), and intake of vitamin C (mg/day).

[39] observed, in three prospective cohorts, that higher intake of foods rich in flavonoids may contribute to BW maintenance and prevention of obesity. A longitudinal study from the Netherlands found that a higher intake of flavonols and flavones was associated with lower increase in BMI over 14 years in the general female population [40].

In comparing our current study to our previous work utilizing dietary (poly)phenol data from the EPIC-PANACEA cohort [5, 6], we observed few distinct differences in the findings. Our previous dietary-based research found a strong, statistically significant inverse link between (poly)phenol intake and BW gain. However, in this study

using plasma (poly)phenol concentrations, associations were less pronounced and borderline statistically significant. Two key factors contribute to these disparities. Firstly, we had dietary data for a much larger subgroup (around 350,000) of the EPIC cohort, while plasma (poly)phenol analysis was limited to under 800 participants due to logistical constraints. This variation in sample size could affect our ability to detect associations. Secondly, using biomarkers like plasma (poly)phenols offers a more objective measure of diet but may not capture its full complexity due to individual differences in bioavailability and metabolism [41]. In contrast, dietary data provide a comprehensive view of dietary patterns [42]. In spite of these differences, both measurements (dietary data and nutritional biomarkers) provide evidence that (poly)phenols may have a protective impact in BW maintenance.

In addition, the discrepancies in explaining these associations can be attributed to differences in (poly) phenol bioavailability. In general, (poly)phenols show low bioavailability (<20%) which can be affected by several factors, including chemical structure (including sugar moiety), food matrix, interaction with other compounds, and individual conditions like intestinal activity, gut microbiota composition, sex, or age [41]. According to pharmacokinetic studies, (poly)phenols that are most absorbed in humans are isoflavones and phenolic acids, followed by catechins, flavanones, and quercetin glucosides. Low-molecular-weight (poly) phenols are easily absorbed through the gut barrier [43, 44]. When they reach the basal membrane of the enterocytes and when they enter the liver, they are conjugated to glucuronic acid, sulphate, and methyl groups to facilitate their transport and excretion and limit their potential toxicity [43, 44]. Conversely, large molecular weight (poly)phenols such as proanthocyanidins are poorly absorbed in the small intestine, and they reach the colon to be metabolized by the gut microbiota into lower molecular weight compounds, generally phenolic acids, which can be partially absorbed in the colon [45].

Increasing evidence supports the idea that the gut microbiome plays a key role in the relationship between (poly)phenols and metabolism, body fat, and obesity. It has been shown, for example, that diets high in (poly) phenol-rich whole plant-based foods improve gut microbiota profiles when compared to diets high in animal-based products [46]. Interactions between (poly)phenols and the gut microbiome have also been shown to decrease obesity-related conditions such as development of adipose tissue and obesity-induced inflammatory genes [47]. Plasma concentrations of different (poly)phenols may be a reflection of these metabolites resulting from dietary (poly)phenols-microbiome interactions [48].

The robust positive correlations observed between certain plasma (poly)phenols, such as the noteworthy correlation between 3,5-dihydroxy-benzoic acid and 3,5-dihydroxy-phenylpropionic acid, can be attributed to a complex interplay of dietary factors, metabolic processes, and individual variability. In a previous study assessing the pharmacokinetics of novel metabolites in urine, it was observed that these two compounds were new candidate biomarkers for whole-grain wheat and rye intake [49]. Therefore, both 3,5-dihydroxy-benzoic acid and 3,5-dihydroxy-phenylpropionic acid were proposed as potential biomarkers to increase the accuracy of whole-grain wheat and rye intake in epidemiology studies. These findings underscore the multifaceted nature of (poly)phenol metabolism and its dependence on dietary patterns, metabolic pathways, and individual characteristics, offering valuable insights for future research in (poly) phenol metabolism and its potential health implications. The strong correlations observed between certain compounds and tea and coffee may reflect some characteristics of dietary patterns in our population. Tea and coffee are frequently consumed by individuals as part of their daily routines [11]. Consistent and habitual consumption of these beverages may result in a continuous supply of (poly)phenols to the body, potentially leading to higher and steadier plasma levels over time [50].

As previously mentioned, one limitation of our investigation is the interpretation of human study data when working with these compounds. For example, as the occurrence of these metabolites in circulating blood is the result of digestive and hepatic activity, the complex interaction between (poly)phenols, individual gut microbiota, and host metabolism cannot be disregarded [1]. Another limitation is the relatively small sample size with available measurements of plasma (poly)phenols, particularly for subgroup analyses. The EPIC sampling characteristics do not allow the total generalizability of these findings to other populations. In addition, the fact that female participants constituted the vast majority of the study population means males were underrepresented. Concentrations of (poly)phenols were measured in single plasma samples at baseline; thus, intra-individual variations in circulating levels of these compounds were not available, which could also lead

to attenuation of the observed associations [51]. Because of the observational nature of the study design, although we were able to adjust our models for relevant lifestyle and dietary covariates, the possibility of residual confounding cannot be ruled out.

A major strength of this study is its prospective and multicentre design, including participants from different European countries with wide variation in diet. In addition, we had data on a relatively large number of (poly)phenols ($n = 36$), spanning all major classes found in the human diet. While plasma (poly)phenols in this study may indicate a plant-based diet, it is important to consider a broader context. While we incorporated fibre and vitamin C intake into our model, we recognize a lack of detailed knowledge regarding the potential biological mechanisms connecting plasma (poly)phenols to BW loss. Consequently, attributing our findings solely to a healthier diet may be overly simplistic. Nevertheless, further research is needed to explore how (poly)phenols and plant-based compounds influence BW regulation. In epidemiological studies, prediction of (poly)phenol intake mainly relies on food records and composition tables, often failing to assess total intake accurately [52]. Thus, assessing the relationship between diet-related compounds and health outcomes can be challenging. The measurement of plasma concentrations of (poly)phenols represents an objective measurement of a snapshot of internal exposure to these compounds that could come directly from different dietary sources or their precursors [51]. This has been a way of reducing the potential bias from dietary questionnaire-based data. While the evidence on the determination of plasma (poly)phenols is not extensive, a recent review described the common analytical technique utilizing LC-MS/MS [53]. However, the use of differential isotope labelling in our methodology is an extra advantage. This methodology reinforces the robustness, sensitivity, and specificity of our analytical approach and its applicability to quantifying low plasma (poly)phenol concentrations [54].

In conclusion, this prospective investigation suggested a tendency towards 5-year BW loss or maintenance at higher plasma (poly)phenol concentrations at baseline. Among specific (poly)phenols, vanillic acid and naringenin can be highlighted, which may act as biomarkers of flavonoid intake. While these specific associations seemed promising, they did not withstand FDR correction, indicating the need for caution in interpreting these results. These findings are preliminary, and further studies using (poly)phenol biomarkers are needed to better understand the potential observed trends. This study may contribute to the identification of specific (poly)phenols for future mechanistic studies or clinical trials on obesity-related pathways in humans.

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Statement of Ethics

The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and has obtained ethical approval from participating centres and the IARC Ethics Committee (reference number 20-02). Written informed consent was obtained from all study participants.

Conflict of Interest Statement

The authors have no conflicts of interest to declare. Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article, and they do not necessarily represent the decisions, policies, or views of the International Agency for Research on Cancer/World Health Organization.

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Author Contributions

R.Z.-R. designed research and wrote paper – reviewed and edited; M.G.-L. conducted research and wrote paper – prepared original draft; A.K.E., A.T., J.A.R., S.S., C.C., V.K., T.J., M.B.S., A.O., F.P., R.T., L.M., G.M., G.S., M.W.L., M.B., C.L., M.C.-B., E.M.-M., S.C.-Y., M.G., P.A., I.J., J.H., N.G.F., H.F., M.M., C.D., A.K.H., E.K.A., and D.A. provided essential material; M.G.-L. and D.G.-F. performed statistical analysis; and E.A.-A., J.C., and M.G.-L. had primary responsibility for final content. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

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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