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ORIGINAL ARTICLE

Epidemiology/Genetics

Association between classes and subclasses of polyphenol intake and 5-year body weight changes in the EPIC-PANACEA study

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Abstract

Objective: The aim of this study was to evaluate the associations among the intake of total polyphenols, polyphenol classes, and polyphenol subclasses and body weight change over 5 years.

Methods: A total of 349,165 men and women aged 25 to 70 years were recruited in the Physical Activity, Nutrition, Alcohol, Cessation of Smoking, Eating Out of Home and Obesity (PANACEA) project of the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort from nine European countries. Body weight was measured at baseline and at follow-up after a median time of 5 years. Polyphenol intake, including four main polyphenol classes and eighteen subclasses, was estimated using validated dietary questionnaires and Phenol-Explorer. Multilevel mixed linear regression models were used to estimate the associations.

Results: Participants gained, on average, 2.6 kg (±5.0 kg) over 5 years. Total flavonoids intake was inversely associated with body weight change (−0.195 kg/5 years, 95% CI: −0.262 to −0.128). However, the intake of total polyphenols (0.205 kg/5 years, 95% CI: 0.138 to 0.272) and intake of hydroxycinnamic acids (0.324 kg/

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5 years, 95% CI: 0.267 to 0.381) were positively associated with body weight gain. In analyses stratified by coffee consumption, hydroxycinnamic acid intake was positively associated with body weight gain in coffee consumers (0.379 kg/5 years, 95% CI: 0.319 to 0.440), but not in coffee nonconsumers (−0.179 kg/5 years, 95% CI: −0.490 to 0.133).

Conclusions: Higher intakes of flavonoids and their subclasses are inversely associated with a modest body weight change. Results regarding hydroxycinnamic acids in coffee consumers require further investigation.

INTRODUCTION

Overweight and obesity are defined as abnormal or excessive body fat accumulation. Obesity is one of the principal contributors to the global burden of chronic diseases, particularly cardiovascular disease, type 2 diabetes, and certain types of cancers [1]. The prevalence has increased rapidly: the World Health Organization reports that more than 2 billion adults have overweight and obesity worldwide, whereas, in Europe, nearly 60% of adults are classified as having overweight or obesity [2, 3]. Obesity results from a complex interaction of several factors such as diet, lifestyle, socioeconomics, genetics, and environment [4].

Even a moderate weight loss of 5% to 10% has been shown to lead to the significant improvement of several cardiometabolic parameters (e.g., triglycerides, blood pressure, waist circumference, insulin sensitivity, β-cell function) [5] and a lower risk of comorbidities, including cardiovascular disease [6], diabetes mellitus [6], hypertension [7], dyslipidemia [8], and overall mortality [9].

Polyphenols are bioactive phytochemicals found in plant foods and beverages such as fruit, vegetables, seeds, herbs, spices, whole grains, tea, coffee, and wine [10]. They comprise a large variety of chemical structures and they are divided into four main classes: flavonoids, phenolic acids, stilbenes, and lignans [10, 11]. Increasing preclinical and clinical evidence has suggested a role of polyphenols as antiobesity compounds. Indeed, several *in vitro* and *in vivo* studies have shown that polyphenols may stimulate thermogenesis and energy expenditure, inhibit adipocyte differentiation and growth, increase lipolysis, induce β oxidation, and decrease appetite [12, 13]. The antiobesity effects of polyphenols, particularly flavonoids, have also been supported by numerous clinical trials [11, 14].

In contrast, few observational epidemiological studies have examined the role of polyphenol intake in body weight control. The Supplementation with Antioxidant Vitamins and Minerals (Supplementation en Vitamines et Mineraux Antioxydants [SU.VI.MAX]) study observed that a high intake of total polyphenols was associated with lower waist circumference and body mass index (BMI) after 6 years of follow-up [15]. Similarly, an inverse association among total flavonoid intake and body weight, BMI, and waist circumference was observed in the National Health and Nutrition Examination Survey (NHANES) [16]. Likewise, results from the Prevención con Dieta Mediterránea (REDIMED) study indicated that total urinary polyphenol excretion was inversely associated with changes in body weight, BMI, waist circumference, and waist to height ratio over 5 years [17]. Furthermore, the Health, Alcohol and Psychosocial factors in Eastern Europe (HAPPIEE) study reported an inverse association among high total polyphenol intake, particularly from stilbenes and lignans, and BMI and waist circumference [18]. However, these epidemiological studies have some limitations, including a limited number of classes

Study Importance

What is already known?

- Several experimental studies have reported that polyphenols can stimulate different mechanisms in body weight loss, such as thermogenesis, energy expenditure, and induced β oxidation, among others.
- Some clinical trials have described the antiobesity effects of pharmacological doses of some polyphenols.
- There is scarce epidemiological research investigating the associations between classes and subclasses of polyphenols and body weight change, especially with nonflavonoids.

What does this study add?

- This study provides evidence suggesting that the intake of flavonoids is associated with the maintenance of body weight in both men and women.
- Hydroxycinnamic acid intake from coffee is associated with an increase in body weight in coffee consumers, but not in coffee nonconsumers.

How might these results change the direction of research?

- For a better understanding on the influence of polyphenols on body weight loss, future randomized controlled trials using combinations of polyphenols or plant extracts mimicking polyphenol-rich diets are needed.
- Further research evaluating the effect of hydroxycinnamic acids in body weight change is also warranted.

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and/or subclasses of polyphenols investigated and a low variability of polyphenol intake due to small geographic variations. Therefore, the present study aimed to examine the associations among intakes of total polyphenols and all polyphenol classes and subclasses estimated using the Phenol-Explorer database and body weight change over 5 years in the large, multicountry European Prospective Investigation into Cancer and Nutrition-Physical Activity, Nutrition, Alcohol, Cessation of Smoking, Eating Out of Home and Obesity (EPIC-PANACEA) cohort.

METHODS

Study population

EPIC is a prospective cohort study with 521,448 participants, aged from 25 to 70 years, recruited between 1992 and 2000 in 23 centers from 10 Western European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the UK. The EPIC Study was approved by the local ethics committees from the participating centers and the ethical review board of the International Agency for Research on Cancer. All participants signed an informed consent. Further details on the study design and methods have been described previously [19].

The EPIC-PANACEA study is a subcohort of EPIC with follow-up data of anthropometric measurements, and it was originally designed to investigate the determinants of obesity and weight change in EPIC countries. In the present study, we excluded pregnant women and participants with missing diet or lifestyle questionnaires, missing data on weight and height, or unreliable anthropometric values at baseline ($n = 23{,}713$). In addition, we excluded participants with missing data on weight at follow-up ($n = 122{,}154$) and those with unrealistic body weight changes (<−5 or >5 kg/y over several years) or implausible/unusual anthropometry at follow-up (BMI at follow-up < 16 kg/m^2; $n = 2288$). More details regarding the EPIC-PANACEA study design have been described elsewhere [20]. Finally, participants from Greece ($n = 24{,}128$) did not provide data for the present study; therefore, they were also excluded. The final analysis included 93,435 men and 255,730 women.

Anthropometric measures and body weight change

Body weight in EPIC-PANACEA was measured at baseline and at follow-up. The time between the first and second measurements ranged from 2 years (Germany) to 11 years (Italy), with an overall median of 5 years. Standardized methods were used to take anthropometric measurements (body weight and height), except for the centers of France, Norway, and Oxford (UK), where participants self-reported their anthropometric values at baseline. In the follow-up, body weight was self-reported in all centers except in Cambridge (UK) and Doetinchem (the Netherlands), where weight was measured via standardized methods [20]. For the accuracy of self-reported anthropometric measurements (at baseline and follow-up), Oxford correction equations were used to predict measured weight and to calculate the corrected weight change [21]. Our primary outcome was weight change in kilograms per 5 years, calculated as weight at follow-up minus weight at baseline divided by the follow-up time in years to obtain the annual weight change and then multiplied by 5 years.

Dietary assessment and other covariates

Habitual diet was recorded at baseline by validated country- or center-specific dietary questionnaires that captured food and beverage intakes over the previous 12 months [19]. In most centers, these were self-administered food frequency questionnaires, except for Ragusa (Italy), Naples (Italy), and Spain, where face-to-face interviews were conducted and meal-structured questionnaires were used. A combined method of a semiquantitative food frequency questionnaire and a 7-day record was used in the UK and Malmö (Sweden) [19]. Nutrients and total energy intakes were estimated using the standardized EPIC Nutrient Database [22]. Dietary polyphenol intake was estimated using the Phenol-Explorer database, which contains content values for 502 polyphenols in 452 foods and beverages, together with retention factors for cooked and processed food [23]. Dietary polyphenols were divided into four major classes: total flavonoids, phenolic acids, stilbenes, and lignans, plus a minority class of polyphenols and 18 subclasses, specified in Table 2; all classes and subclasses were then summed to calculate total polyphenol intake.

Moreover, validated questionnaires were used at baseline to collect data on tobacco use, education level, menstrual history, physical activity (inactive, moderately inactive, moderately active, active), and clinical data. In addition, information on smoking status (never, former, current) was also collected at follow-up.

Statistical analyses

Polyphenol intake was assessed as a categorical variable based on quintiles distributed throughout the entire EPIC-PANACEA study. In addition, linear trend tests were calculated assigning the median of each quintile as scores. Polyphenol intake was also analyzed as a continuous variable after $\log_2$ transformation to reduce the skewness of intake distributions. Before $\log_2$ transformation, zero values were replaced with half of the nonzero minimum of the polyphenol class or subclass. One-unit increase corresponded to the absolute body weight change (kilograms per 5 years) associated with doubling in intake.

Multilevel mixed linear regression models were used to estimate the association among total, classes, and subclasses of polyphenol intake and body weight change over 5 years, using the EPIC center as a random effect and polyphenol intake and relevant confounders as fixed effects. Missing values (3.5% for educational level, 1.5% for physical activity, 2.1% for education, 4.7% for smoking status) were classified into a separate category (unknown) and included in the models. BMI at baseline and follow-up time in years had a nonlinear association with weight change. Consequently, they were included in the models as restricted cubic splines with three knots (10th, 50th,

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and 90th percentiles) according to Harrell [24]. We fitted multivariable models adjusting for potential confounders (as fixed effects) selected a priori. Model 1 was adjusted for sex (male and female), age at baseline (years), and BMI (kilograms per meters squared). In model 2, we also adjusted for lifestyle characteristics: follow-up time (years), alcohol consumption (grams per day), education level (none, primary education, technical or professional school, secondary school, higher education, and unknown), physical activity (inactive, moderately inactive, moderately active, active, and unknown), smoking status at follow-up (never, former, and current), and menopausal status (pre-, post-, and peri-surgically postmenopausal and unknown). Model 3 was further adjusted for variables related to energy: total energy intake (kilocalories per day) and plausibility of energy intake reporting (yes and no) [19]. In addition, for model 3, we replaced total energy (kilocalories per day) with the all-components model (adjusting for all individual components providing energy of the diet) [25]; however, the results remained similar to the previous model; therefore, we did not present them. Finally, model 4 was model 3 additionally adjusted for other dietary factors: vitamin C (milligrams per day) and fiber (grams per day) intake. Furthermore, polyphenol intake was included in the statistical models as energy density (2000 mg/kcal/d). Results from both methods were almost identical, and energy density results were not reported.

The main food source of phenolic acids is coffee, which plays a role in body weight change [26]. Therefore, we performed analyses separately for hydroxycinnamic acid (HCA) class intake in coffee consumers and nonconsumers. Also, because caffeine has been associated with body weight loss [26], we evaluated the associations between total coffee and the type of coffee (caffeinated vs. decaffeinated) and body weight in order to investigate the effect of caffeine in body weight and differentiate the relationships between HCAs and caffeine from coffee intake.

Interaction analyses were performed between classes and subclasses of polyphenol intake (continuous, milligrams per day) and sex, age (<50 and ≥50 years), menopause status (peri-, post-, and premenopause), physical activity (inactive, moderately inactive, moderately active, and active), smoking status at follow-up (never, former, and current smokers), and BMI at baseline (underweight, normal weight, overweight, and obesity) in relation to body weight change. *P* values for the interaction were calculated using the likelihood ratio test. Sex, menopause, smoking status, and BMI had a statistically significant interaction; therefore, models were further fitted separately for each category of the variables. Finally, to assess the robustness of the results, we conducted a sensitivity analysis excluding participants with chronic diseases at baseline (type 2 diabetes, cardiovascular disease, and/or cancer) and participants who either quit smoking or started smoking or had missing data on smoking during follow-up. All p values presented were considered statistically significant at $p < 0.05$. Statistical analyses were performed using SAS software version 9.3 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Participants in the highest quintile of polyphenol intake were more likely to be men and older and they had, on average, a lower BMI and a higher education, alcohol consumption, and total energy intake (Table 1). In addition, they were more likely to be more physically active and current smokers. Women with higher total polyphenol intakes were less likely to be premenopausal than those with lower intakes. In all quintiles of total polyphenol intake, phenolic acids were the main contributors, followed by flavonoids, whereas lignans and stilbenes were consumed in low amounts (between 1 and 3 mg/d).

On average, study participants gained 2.6 kg (±5.0 kg) per 5 years of body weight during the follow-up. Body weight changes over 5 years by quintile of total, classes, and subclasses of polyphenol intakes are shown in Table 2 and Supporting Information Table S1. Total polyphenol intakes were positively associated with body weight gain; participants in the highest intake quintile had a 0.205-kg (95% confidence interval [CI]: 0.138 to 0.272) greater 5-year weight gain compared with those in the lowest quintile after multivariable adjustments (model 4; Table 2). Analysis by polyphenol classes showed that higher intakes of flavonoids (β_{Q5} vs. $_{Q1}$ −0.195 kg/5 years, 95% CI: −0.262 to −0.128) and stilbenes (only when modeled continuously, β_{log2} −0.032 kg/5 years, 95% CI: −0.039 to −0.024) were inversely associated with body weight change. Similarly, intakes of individual subclasses of flavonoids, except for isoflavonoids, were statistically, significantly, and inversely associated with body weight change (Table 2). A body weight gain was observed comparing participants in the extreme quintiles of total phenolic acid intake (β_{Q5} vs. $_{Q1}$ 0.328 kg/5 years, 95% CI: 0.268 to 0.386) and its subclass HCAs (β_{Q5} vs. $_{Q1}$ 0.324 kg/5 years, 95% CI: 0.267 to 0.381). However, other subclasses of phenolic acids showed an inverse association with body weight change, such as hydroxybenzoic acid (β_{Q5} vs. $_{Q1}$= −0.244 kg/5 years, 95% CI: −0.317 to −0.170) and hydroxyphenylacetic acid (β_{Q5} vs. $_{Q1}$= −0.204 kg/5 years, 95% CI: −0.275 to −0.132). Minor polyphenol classes such as tyrosols and hydroxycoumarins showed an inverse association with body weight change. Analyses by quintiles of classes, subclasses, and total polyphenol intake were supported by the results using the continuous variable after the $\log_2$ transformation (Figure 1).

Women presented a slightly stronger positive association between total polyphenol intake and body weight gain compared with men (p value interaction < 0.001; Supporting Information Table S2). Total polyphenol and phenolic acid intakes were strongly associated with body weight gain among women in perimenopause (Supporting Information Table S3). For smoking status at follow-up, we found that total polyphenol and phenolic acid class intakes were more strongly associated with weight gain in former smokers, whereas the opposite occurred with total flavonoid intake (Supporting Information Table S4). For BMI, there was an inverse trend between total flavonoid intake and body weight change in participants with underweight, normal weight, and overweight, but a positive trend was detected among participants with obesity (Supporting Information Table S5).

Additional analyses for HCAs were performed by dividing the analysis by coffee consumption, in which we observed a positive association with weight gain in coffee consumers, but not in coffee nonconsumers (Supporting Information Table S6). Subsequently, we separately analyzed the association for total coffee and type of coffee

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TABLE 1 Baseline characteristics of the population according to quintiles of total polyphenol intake in the EPIC-PANACEA study ($n = 349,165$)

	Quintile of intake				
Category	**Quintile 1 ($n = 69,832$)**	**Quintile 2 ($n = 69,826$)**	**Quintile 3 ($n = 69,826$)**	**Quintile 4 ($n = 69,841$)**	**Quintile 5 ($n = 69,840$)**
Total polyphenol intake (mg/d)	558.2 (441.2-706.0)	854.8 (788.8-970.7)	1117.5 (1049.4-1248.4)	1427 (1342-1607.3)	1923.8 (1759.7-2856.3)
Follow-up time (y)	5.1 ± 2.4	5.5 ± 2.7	5.3 ± 2.4	4.9 ± 2.0	4.6 ± 1.5
Weight change (kg/5 years)[a]	2.4 ± 5.2	2.5 ± 4.9	2.6 ± 5.0	2.7 ± 4.9	2.8 ± 5.0
Age (y)	50.4 ± 8.9	50.8 ± 9.2	51.7 ± 9.3	52.6 ± 9.2	52.9 ± 8.6
BMI (kg/m^2)	25.6 ± 4.4	25.1 ± 4.1	25.0 ± 4.0	24.8 ± 3.9	24.7 ± 3.8
Alcohol use (g/d)	6.4 ± 12.2	9.5 ± 13.7	12.3 ± 15.6	14.3 ± 17.6	16.7 ± 20.8
Energy intake (kcal/d)	1777 ± 517	1964 ± 544	2092 ± 567	2182 ± 592	2366 ± 634
Women (%)	79.4	74.1	72.0	70.9	69.7
Education level (%)					
None	11.6	4.5	2.4	1.3	0.8
Primary school	28.4	26.9	22.8	19.6	18.3
Technical school	20.2	23.0	23.0	23.2	22.1
Secondary school	20.7	22.1	22.1	21.9	21.9
Higher education	17.5	26.2	26.2	28.3	31.0
Missing	1.4	3.2	3.2	5.4	5.7
Physical activity level (%)					
Inactive	23.6	19.3	17.3	16.8	16.0
Moderately inactive	32.6	35.0	34.9	34.6	33.6
Moderately active	29.5	27.7	26.1	26.1	26.9
Active	12.5	16.2	19.3	20.4	22.3
Missing	1.5	1.6	1.8	1.8	1.0
Smoking at follow-up (%)					
Never	54.1	47.8	47.6	47.8	44.2
Former	25.5	28.4	30.1	32.2	34.3
Current	15.7	17.2	16.8	16.7	20.0
Missing	4.5	6.4	5.3	3.1	1.3
Prevalent diseases at baseline (%)[b]					
No	85.6	86.7	85.3	81	78.7
Yes	8.0	7.5	7.7	7.5	7.2
Missing	6.3	5.6	6.9	11.3	14.0
Menopause (%)					
Premenopausal	29.1	26.3	23.1	21.0	19.9
Postmenopausal	30.6	30.1	32.4	33.8	32.9
Perimenopausal	17.4	15.6	14.1	13.5	14.5
Surgery	2.1	2.0	2.3	2.4	2.3
Classes of polyphenol intake (mg/d)					
Phenolic acids	249.7 (142.4-500.7)	462.0 (328.0-704.5)	585.6 (430.3-917.6)	708.0 (525.7-1215.6)	1025.7 (675.9-1918.3)
Flavonoids	224.8 (150.6-449.6)	340.7 (234.7-649.6)	468.2 (325.5-856.3)	647.8 (424.7-1132.2)	896.6 (548.0-1633.7)
Other polyphenol classes	32.2 (19.9-72.0)	40.1 (26.5-93.5)	45 (28.3-106.4)	48.8 (29.5-117.5)	57 (34.8-134.3)

(Continues)

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TABLE 1 (Continued)

Category	Quintile of intake				
	Quintile 1 ($n = 69,832$)	Quintile 2 ($n = 69,826$)	Quintile 3 ($n = 69,826$)	Quintile 4 ($n = 69,841$)	Quintile 5 ($n = 69,840$)
Lignans	1.2 (0.9-3.1)	1.3 (1-4.6.0)	1.4 (1.1-4.5)	1.5 (1.2-3.8)	1.7 (1.4-3.7)
Stilbenes	0.2 (0.05-3.5)	0.4 (0.1-6.5)	0.7 (0.2-8.4)	1.1 (0.2-9.9)	1.4 (0.3-11.2)

Notes: Means ± SD are presented for continuous variables, and percentages are presented for categorical variables. Medians and percentiles (25th to 95th percentile) are presented for polyphenol intake.

Abbreviations: EPIC, European Prospective Investigation into Cancer and Nutrition; PANACEA, Physical Activity, Nutrition, Alcohol, Cessation of Smoking, Eating Out of Home and Obesity.

[a]Calculated as weight at follow-up minus weight at baseline divided by the follow-up time in years and multiplied by 5 years.

[b]Type 2 diabetes, cardiovascular disease, and cancer.

(caffeinated vs. decaffeinated) as exposure variables with body weight changes. Decaffeinated coffee intake was associated with a slightly greater body weight gain than caffeinated coffee (when modeled continuously; Supporting Information Table S6).

In the sensitivity analysis, after excluding participants with chronic disease at baseline ($n = 57,617$) and participants who quit smoking or started smoking during follow-up or with missing values ($n = 35,489$), we observed that the associations among total polyphenol intake and polyphenol classes and body weight change were similar to our main results (Supporting Information Tables S7 and S8).

DISCUSSION

In this large prospective study, a mean body weight gain of 2.6 kg during the 5 years of follow-up was observed. Progressive age-related weight gain in adulthood is a well-observed phenomenon in many nonobese populations such as in the Nurses' Health Study II cohort, which showed a weight change of 4.4 lb (2.0 kg) per 4.4 years of follow-up [27], and in NHANES, the weight change of which was 2.5 kg per 9.8 years of follow-up [28]. In the current study, a positive association among total polyphenol and phenolic acid intakes and body weight gain was observed. Conversely, higher intakes of flavonoids, including anthocyanins, dihydrochalcones, and dihydroflavonols, and other minor polyphenol classes such as tyrosols and stilbenes were inversely associated with body weight change, supporting the evidence from experimental studies that some polyphenol classes and subclasses may play a role in obesity prevention; several mechanisms have been proposed, such as activation of β oxidation processes, stimulation of energy expenditure, and inhibition of adipocyte differentiation [12]. Recently, it has been discussed that polyphenols may modulate type 2 taste receptors responsible for bitter taste recognition, which may play a role in energy/body weight homeostasis [29]. Similar to our findings, a cohort study by Adriouch and colleagues reported that high intakes of flavanones, flavones, and lignans were associated with lower waist circumference and lower BMI. In their study, total polyphenol and phenolic acid intakes were associated with both a lower body weight gain and a lower increase in adiposity over 6 years [15]. Our study showed that total polyphenols were positively related to body weight gain; however, after excluding phenolic acids, we observed an inverse association with body weight change. Such changes were driven by phenolic acids (specifically HCAs), the main contributors to total polyphenols; therefore, the results with total polyphenols need to be interpreted with caution.

Flavonoids are the most-studied polyphenol class in relation to their effects on body weight [13]. In our study, we observed that a higher intake of flavonoids, particularly anthocyanins, flavan-3-ol monomers, theaflavins, flavones, and flavonols, was strongly and inversely associated with body weight change over 5 years. Similarly, in a large prospective cohort, statistically significant inverse associations among subclasses of anthocyanins, flavanols (including proanthocyanidins), and flavonols and body weight change were observed after a 24-year follow-up [27]. Another cohort from the Netherlands observed an association among a higher intake of flavonol/flavone and catechin and a lower increase in BMI in women, but not in men [30]. Similarly, the Mediterranean healthy Eating, Aging and Lifestyle (MEAL) cohort study, with a follow-up over 14 years, reported that women with a high intake of total flavonoids were less likely to have obesity and that flavonol intake was inversely associated with obesity [31]. Although the magnitudes of body weight loss were small, they may contribute to body weight maintenance, which has been reported as a protective factor for diseases such as type 2 diabetes, hypertension, and cardiovascular disease [32]. Some trials have also investigated these body weight effects showing, in general, a body weight reduction after the intervention with supplements rich in polyphenols [11, 14].

Contrary to our expectations, this study found an inverse association among the minor subclasses of phenolic acids (i.e., hydroxybenzoic acids and hydroxyphenylacetic acids) and body weight change, whereas total phenolic acid and HCA intakes were associated with an increase in body weight. Their main food source is coffee [10] and, because other compounds of coffee such as caffeine, trigonelline, and magnesium may possess antiobesogenic properties [33], after we stratified by coffee consumption, non-coffee consumers showed a null association between HCA intake and body weight change, whereas, in coffee consumers, phenolic acid intake

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TABLE 2 Associations between intakes of total polyphenols, polyphenol classes, and subclasses (milligrams per day) and body weight change over 5 years in the EPIC-PANACEA study ($n = 349,165$)

	Quintile of intake					
Polyphenol (mg/d)	**Quintile 1, β (95% CI)**	**Quintile 2, β (95% CI)**	**Quintile 3, β (95% CI)**	**Quintile 4, β (95% CI)**	**Quintile 5, β (95% CI)**	***p* value for trend**
Total polyphenols	<720.1	720.1-983.5	983.6-1263.1	1263.2-1630.5	>1630.5	
Model 4	0 (ref)	0.009 (−0.044 to 0.063)	0.011 (−0.046 to 0.069)	0.095 (0.034 to 0.157)	0.205 (0.138 to 0.272)	<0.001
Flavonoids	<231.6	231.6-359.4	359.5-525.3	525.4-786.7	>786.7	
Model 4	0 (ref)	−0.069 (−0.122 to −0.016)	−0.136 (−0.194 to −0.079)	−0.183 (−0.244 to −0.122)	−0.195 (−0.262 to −0.128)	<0.001
Total flavanols	<142.8	142.8-238.4	238.5-369.7	369.8-595.7	>595.7	
Model 4	0 (ref)	−0.023 (−0.076 to 0.03)	−0.072 (−0.128 to −0.015)	−0.100 (−0.16 to −0.041)	−0.141 (−0.207 to −0.075)	<0.001
Flavan-3-ol monomers	<16.0	16.0-30.6	30.7-69.7	69.8-246.9	>246.9	
Model 4	0 (ref)	−0.044 (−0.098 to 0.009)	−0.069 (−0.127 to −0.01)	−0.114 (−0.175 to −0.053)	−0.200 (−0.265 to −0.134)	<0.001
Proanthocyanidins	<113.5	113.5-175.7	175.8-243.2	243.3-345.9	>345.9	
Model 4	0 (ref)	−0.060 (−0.112 to −0.007)	−0.086 (−0.141 to −0.030)	−0.124 (−0.183 to −0.065)	−0.071 (−0.136 to −0.005)	0.081
Theaflavins	0	<3.5	3.5-24.8	24.9-59.1	>59.1	
Model 4	0 (ref)	−0.011 (−0.071 to 0.050)	−0.068 (−0.125 to −0.011)	−0.197 (−0.261 to −0.134)	−0.170 (−0.233 to −0.106)	<0.001
Flavonols	<14.3	14.3-23.6	23.7-36.3	36.4- 63.5	>63.5	
Model 4	0 (ref)	−0.070 (−0.124 to −0.015)	−0.107 (−0.166 to −0.047)	−0.118 (−0.181 to −0.055)	−0.178 (−0.246 to −0.109)	<0.001
Anthocyanins	<10.8	10.8-20.2	20.3-35.7	35.8-64.7	>64.7	
Model 4	0 (ref)	−0.087 (−0.139 to −0.036)	−0.104 (−0.158 to −0.051)	−0.159 (−0.216 to −0.102)	−0.148 (−0.214 to −0.082)	<0.001
Flavanones	<7.7	7.7-17.0	17.1-32.0	32.1-64.7	>64.7	
Model 4	0 (ref)	−0.079 (−0.131 to −0.028)	−0.065 (−0.118 to −0.012)	−0.167 (−0.223 to −0.111)	−0.270 (−0.336 to −0.204)	<0.001
Flavones	<4.9	4.9-7.5	7.6-10.5	10.6-15.3	>15.3	
Model 4	0 (ref)	−0.125 (−0.177 to −0.073)	−0.143 (−0.198 to −0.088)	−0.200 (−0.258 to −0.141)	−0.201 (−0.269 to −0.133)	<0.001
Dihydrochalcones	0	<0.8	0.8-1.8	1.9-3.3	>3.3	
Model 4	0 (ref)	−0.048 (−0.182 to 0.086)	−0.085 (−0.133 to −0.037)	−0.124 (−0.172 to −0.075)	−0.187 (−0.240 to −0.134)	<0.001
Dihydroflavonols	0	<0.16	0.16-1.0	1.1-3.4	>3.4	
Model 4	0 (ref)	0.050 (−0.018 to 0.119)	−0.025 (−0.092 to 0.043)	−0.142 (−0.211 to −0.072)	−0.258 (−0.335 to −0.181)	<0.001
Isoflavonoids	0	>0-0.01	>0.01-0.03	0.04-0.10	>0.10	
Model 4	0 (ref)	−0.019 (−0.115 to 0.078)	−0.038 (−0.134 to 0.057)	0.001 (−0.095 to 0.097)	0.058 (−0.044 to 0.160)	0.004
Total phenolic acids	<298.3	298.3-458.8	458.9-618.9	619.1-881.2	>881.2	
Model 4	0 (ref)	−0.048 (−0.100 to 0.004)	0.006 (−0.047 to 0.059)	0.102 (0.047 to 0.156)	0.328 (0.268 to 0.386)	<0.001
Hydroxycinnamic	<240.6	240.6-416.2	416.3-570.6	570.7-838.2	>838.2	
Model 4	0 (ref)	−0.063 (−0.115 to −0.012)	−0.015 (−0.067 to 0.038)	0.094 (0.04 to 0.147)	0.324 (0.267 to 0.381)	<0.001

(Continues)

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TABLE 2 (Continued)

Polyphenol (mg/d)	Quintile of intake					
	Quintile 1, β (95% CI)	Quintile 2, β (95% CI)	Quintile 3, β (95% CI)	Quintile 4, β (95% CI)	Quintile 5, β (95% CI)	*p* value for trend
Hydroxybenzoic	<5.4	5.4-14.9	15.0-33.0	33.1-83.5	>83.5	
Model 4	0 (ref)	−0.083 (−0.141 to −0.025)	−0.104 (−0.171 to −0.037)	−0.147 (−0.218 to −0.077)	−0.244 (−0.317 to −0.170)	<0.001
Hydroxyphenyl acetic	<0.01	0.01-0.05	0.06-0.14	0.15-0.32	>0.32	
Model 4	0 (ref)	−0.037 (−0.088 to 0.014)	−0.176 (−0.228 to −0.124)	−0.219 (−0.274 to −0.163)	−0.204 (−0.275 to −0.132)	<0.001
Lignans	<1.0	1.0-1.2	1.3-1.6	1.7-2.1	>2.1	
Model 4	0 (ref)	−0.0003 (−0.054 to 0.053)	−0.070 (−0.128 to −0.012)	−0.010 (−0.077 to 0.056)	0.093 (0.013 to 0.174)	<0.001
Stilbenes	<0.09	0.09-0.33	0.34-1.1	1.2-2.6	>2.6	
Model 4	0 (ref)	−0.082 (−0.495 to 0.331)	−0.120 (−0.533 to 0.294)	−0.238 (−0.652 to 0.175)	−0.373 (−0.788 to 0.042)	<0.001
Other polyphenol classes	<23.6	23.6-36.3	36.4-50.8	50.9-70.9	>70.9	
Model 4	0 (ref)	0.053 (0.0004 to 0.106)	−0.003 (−0.059 to 0.053)	−0.074 (−0.134 to −0.013)	−0.073 (−0.145 to −0.002)	0.002
Alkylphenols	<5.3	5.3-19.7	19.8-35.2	>35.3-54.7	>54.7	
Model 4	0 (ref)	0.095 (0.037 to 0.152)	−0.005 (−0.071 to 0.060)	−0.112 (−0.183 to −0.041)	−0.167 (−0.247 to −0.086)	<0.001
Hydroxycoumarins	0	>0-0.01	>0.01-0.57	0.58-0.18	>0.18	
Model 4	0 (ref)	−0.052 (−0.134 to 0.030)	−0.083 (−0.172 to 0.006)	−0.214 (−0.303 to −0.124)	−0.270 (−0.367 to −0.174)	<0.001
Tyrosol	<1.1	1.1-2.5	2.6-5.1	5.2-11.4	>11.4	
Model 4	0 (ref)	−0.126 (−0.178 to −0.075)	−0.222 (−0.276 to −0.168)	−0.331 (−0.393 to −0.268)	−0.343 (−0.422 to −0.264)	<0.001
Alkymethoxyphenols	<0.9	0.9-1.9	2.0-2.8	2.9-4.2	>4.2	
Model 4	0 (ref)	−0.146 (−0.356 to 0.064)	−0.201 (−0.412 to 0.011)	−0.071 (−0.284 to 0.141)	0.135 (−0.079 to 0.348)	<0.001

Note: Overall mean 5-year weight gain corresponded to 2.6 kg (SD 5.0), and negative β values indicate less weight gain (kilograms) over the same period.

Model 4: generalized linear mixed models with random effect on the intercept and slope according to center and adjusted for age, sex, and BMI at baseline (three-knot restricted cubic spline), follow-up time in years (three-knot restricted cubic spline), educational level, smoking status, physical activity, alcohol consumption, menopausal status, energy intake, plausibility of dietary energy reporting, vitamin C, and total fiber intakes.

Abbreviations: EPIC, European Prospective Investigation into Cancer and Nutrition; PANACEA, Physical Activity, Nutrition, Alcohol, Cessation of Smoking, Eating Out of Home and Obesity; ref, reference.

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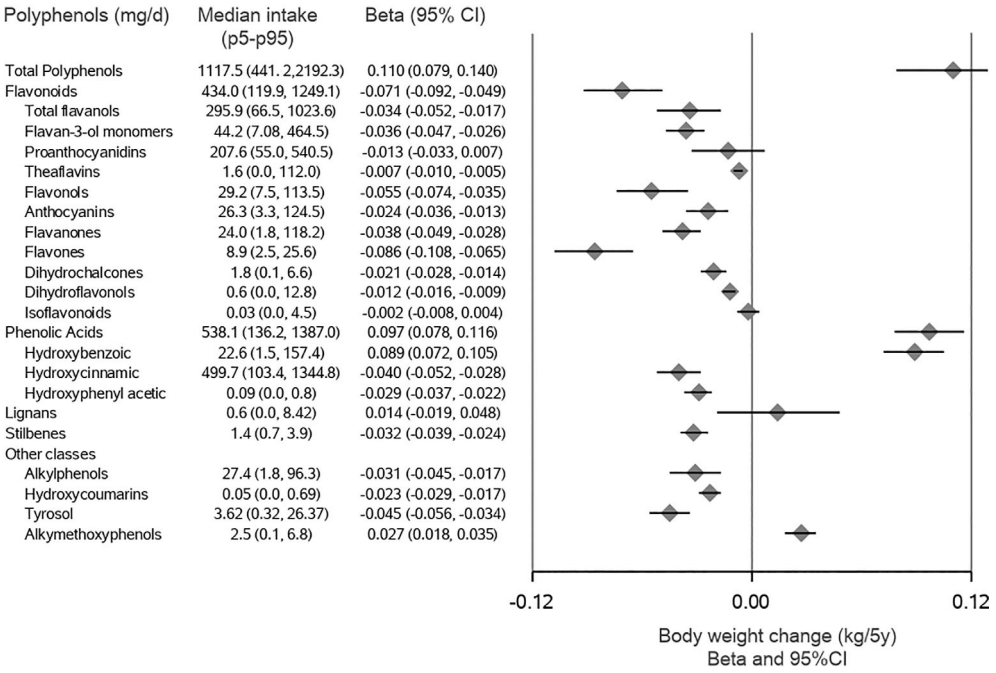

FIGURE 1 The association between intakes of total polyphenols, polyphenol classes, and subclasses (milligrams per day) as continuous variables (after $\log_2$ transformation) and body weight change (kilograms) over 5 years in the EPIC-PANACEA study. Model 4: generalized linear mixed models with random effect on the intercept and slope according to center and adjusted for age, sex, and BMI at baseline (three-knot restricted cubic spline), follow-up time in years (three-knot restricted cubic spline), educational level, smoking status, physical activity, alcohol consumption, menopausal status, total energy intake, plausibility of dietary energy reporting, vitamin C, and total fiber intakes

was positively associated with body weight gain. Some *in vivo* studies have suggested potential mechanisms of HCAs from coffee in weight loss through regulation of lipid and glucose metabolism, e.g., via sterol regulatory element binding transcription factor 1 (SREBP-1C), peroxisome proliferator activated receptor α (PPAR-α), increased fatty acid oxidation, and increased insulin secretion; however, there is not information reported about possible mechanisms of HCAs associated with body weight gain [34]. The direct role of coffee consumption on body composition has been studied in previous cohorts; however, the results are still inconclusive. For instance, two previous cohorts have concluded that higher coffee consumption was associated with lower weight gain, BMI, and waist circumference [26, 35], whereas consumption of more than six cups of coffee per day was associated with higher BMI compared with the group consuming less than two cups per day among Swedish women [35]. Similarly, other studies conducted in Asia have reported that higher coffee consumption (>3 cups/d) was associated with higher risk of obesity compared with lower coffee consumption [36, 37]. However, these results need to be taken with caution, as they considered instant coffee blends that contain sugar and cream. In this sense, the method of coffee preparation, the types of coffee varieties, roasting degree, the size of the serving, and use of milk or cream and sugar added to coffee are factors that may influence the coffee-obesity relationship [38]. For example, the types of coffee have been evaluated (caffeinated vs. decaffeinated), and it was found that decaffeinated coffee was associated with higher body weight gain compared with caffeinated coffee [39]. In our study, we observed an increase in body weight for both types of coffee; however, it is important to highlight that the consumption of caffeinated coffee was much higher (mean = 222.1 mL/d) compared with decaffeinated coffee (mean = 32.3 mL/d). Therefore, phenolic acids and caffeine seem to not have harmful effects on body weight, but it is unclear which potential coffee compounds, if any, might have an obesogenic effect.

The current study found an inverse association of stilbenes with body weight change, which is consistent with that reported in the HAPIEE study for change in waist circumference [18]. However, their results were not statistically significant. Furthermore, it has been previously observed that consumption of stilbenes from berries, red grapes, and wine has antiadipogenic and antilipogenic effects, improving changes in BMI and waist circumference [12, 40]. Future studies on the current findings are still warranted.

Our results also showed that tyrosols are inversely associated with body weight change. The main food sources of tyrosols include olives and olive oil, of which the principal component is hydroxytyrosol [10]. It has been largely studied for its protective effects on low-density lipoprotein oxidation and reduction of oxidative stress [41], and it may be responsible for the antiobesogenic properties of olive oil [41]. Moreover, extra-virgin olive oil is the main source of dressing and cooking fats in the Mediterranean diet, which has been reported to have a protective effect against weight gain, particularly in younger people [42]. The PREDIMED study evaluated the long-term effects of an unrestricted-calorie Mediterranean diet rich in extra-virgin olive oil

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on adiposity measures and observed a small reduction in body weight in participants given the Mediterranean diet interventions compared with the control groups [23]. However, more clinical and epidemiological evidence is needed in order to clarify the effect of tyrosols on body weight.

Results of the interaction analyses should be interpreted with caution because even very small body weight differences among subgroups are statistically significant because of our large sample size. We observed that women with perimenopause had a slightly greater weight gain associated with total polyphenol intake. Several polyphenols have estrogenic effects [12], and they would help to prevent body weight gain related to menopause. However, our results pointed out the opposite, probably because of reverse causality. Women with perimenopause might improve their diets and lifestyles [43], but, when they become menopausal, they tend to return to their regular habits [43]. Moreover, analyses by smoking status at follow-up showed that current smokers benefitted more from higher intakes of total polyphenols and phenolic acids, probably because of their ability to reduce tobacco oxidative stress [44]. Finally, interactions by BMI showed that flavonoid intakes were associated with a lower body weight in all groups, except those with obesity. Our hypothesis was that participants with obesity would benefit more from the intake of potential antiobesity compounds [12]. However, our contradictory results could be because participants with obesity tend to underestimate unhealthy foods and overestimate healthy foods more than those without obesity [45].

Strengths of our study include the multicenter prospective design, two measurements of body weight (to calculate body weight change), and a large sample size, which provided sufficient statistical power to perform multiple subgroup and sensitivity analyses. Another strength is the use of Phenol-Explorer, the most comprehensive database on polyphenol content in foods, to measure polyphenol intake. However, our study also had some limitations. First, weight was self-reported at follow-up in most centers; however, we improved the accuracy of these data by using a prediction equation, and the results in the two EPIC centers with measured weight (Cambridge and Doetinchem) were consistent with the rest of the cohort [21]. Second, the use of both self-report diet and lifestyle questionnaires with a single measurement at baseline did not allow us to consider dietary or lifestyle (except tobacco consumption) changes during follow-up. Third, participants diagnosed with severe diseases during follow-up might have changed their dietary and lifestyle habits. However, we performed sensitivity analyses excluding participants with preexisting conditions, and the results remained robust to those of the entire cohort. Fourth, the information regarding the method of preparation and type of coffee was limited, and the quantification of HCAs in coffee was probably underestimated [10]. Fifth, breastfeeding, a part of pregnancy, can also interfere in the standard body weight trajectory. Pregnant women were excluded from our analysis; therefore, most of the breastfeeding women were consequently excluded, except those lactating only at baseline. We assume that this number is very low because the mean average was 50 years old, and, in some centers (such as Spain and Italy), participants were mostly blood donors, and it is not possible to do a blood donation until 6 to 9 months after giving birth. For this reason, we recommend complementing the results from dietary questionnaires with nutritional biomarkers in future studies. Although validated center- and country-specific questionnaires were used to collect polyphenol-rich food data [19], we cannot exclude some measurement error leading to a potential underestimation of any true association. Finally, all models were adjusted for potential confounders; however, some potential residual bias cannot be ruled out.

In conclusion, this study identified a small inverse association between flavonoid intake and body weight change, specifically for anthocyanin, flavan-3-ol monomer, flavanone, flavone, and flavonol subclasses. These results suggest that flavonoids from foods may be promising compounds for weight control. Future randomized controlled trials using combinations of polyphenols or plant extracts mimicking polyphenol-rich diets may provide more definitive evidence to validate these results. In addition, HCAs from coffee showed a positive association with weight gain in coffee consumers. Future research related to coffee constituents, including HCAs, and weight change is warranted.O

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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DATA AVAILABILITY STATEMENT

For information on how to apply for getting access to EPIC data and/or biospecimens, please follow the instructions at the following link: http://epic.iarc.fr/access/index.php.

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