Association between higher intake of flavonols and lignans and better mood: evidence from dietary and biomarker evaluation in healthy individuals

RESEARCH ARTICLE

Molecular Nutrition & Food Research
www.mnf-journal.com

Association between Higher Intake of Flavonols and Lignans and Better Mood: Evidence from Dietary and Biomarker Evaluation in Healthy Individuals

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Scope: The aim of this study is to investigate associations between (poly)phenol consumption, circulating (poly)phenol metabolites, and mood states in healthy individuals.
Methods and results: The study included 333 healthy individuals. Mood state was assessed with the Positive and Negative Affect Schedule questionnaire. Dietary (poly)phenol intake was estimated matching food consumption data collected using a Food Frequency Questionnaire(FFQ) with a comprehensive in-house (poly)phenol database. A total of 102 (poly)phenol metabolites were quantified in fasting plasma and 24 h urine samples by Liquid Chromatography-Mass Spectrometry using a validated method. A higher intake of lignans, flavanones, and flavonols estimated from FFQs was associated with positive mood after adjusting for age and sex (β: 0.118 to 0.134). A total of 11 urinary (poly)phenol metabolites, including lignan and flavonol metabolites were associated with less negative mood (β: −0.387 to −0.205). No association was found between mood and plasma (poly)phenols.
Conclusion: A higher consumption of lignans flavanones and flavonols is associated with a better mood, while certain urinary metabolites are associated with less negative mood. The lack of associations between fasting plasma (poly)phenols and mood may be due to their transient nature incirculation compared with 24 h urinary metabolites, which reflect longer-term exposure.

1. Introduction

(Poly)phenols are abundant phytochemicals present in plant-based foods, including fruits, vegetables, nuts, cereals, and plant-derived beverages such as coffee and tea. (Poly)phenols and their main subclasses flavonoids, phenolic acids, stilbenes, and lignans have gained increasing attention in recent times for their potential to prevent diseases such as cancer, cardiovascular disorders, and impaired cognitive function.[1] Epidemiological and clinical evidence suggests that higher dietary intake of (poly)phenols may also be inversely associated with depressive symptoms,[2,3] possibly due to their anti-inflammatory and neuroprotective properties.[4,5] Two recent systematic reviews have proposed a protective role of dietary (poly)phenols, including soy isoflavones, tea and cocoa flavanols, curcumin, and coffee hydroxycinnamic acid, on depressive symptoms.[6,7]

Although existing studies have proposed a beneficial effect of (poly)phenol intake on mental health,[6] the evidence

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The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/mnfr.202400112

DOI: 10.1002/mnfr.202400112

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for their effect on generic mood states remains scarce. The mood states measured by Positive and Negative Affect Schedule (PANAS) Scales has been suggested to reflect a simple and conceptually straightforward measure of general psychological distress in non-clinical populations, compared to other clinically commonly used measures, such as the Hopkins Symptom Checklist (HSCL), Beck Depression Inventory (BDI), and State-Trait Anxiety Inventory (STAI).[8] The mood states measured by PANAS have also been confirmed to represent an important general correlate of psychiatric disorders,[9] as the presence of negative affect and symptoms and diagnoses of both anxiety and depression are highly correlated, whereas reduced positive affect is related primarily to symptoms and diagnosis of depression.[10] However, few randomized controlled trials investigating the effects of (poly)phenol intake on mood states in healthy adults and children have been reported. Those that have are limited by small sample sizes (less than 55) and a short-term intervention with a specific polyphenol-rich food—for example, blueberry[11] and dark chocolate.[12] Additionally, no study has explored the relationship between habitual (poly)phenol consumption and mood state in the general population.

Evidence on the specific role of (poly)phenols in relation to mood, and mental health disorders in general, is further limited due to common methods of assessing (poly)phenol intake. Particularly, retrospective dietary assessment tools (such as food frequency questionnaires [FFQs] and food records) are subjective and inaccurate.[13] The possibility of assessing (poly)phenol intake using more objective biological markers is therefore very attractive and has been previously proposed.[14] However (poly)phenol metabolism is complex and, the few studies using objective methods have only measured a small selection of metabolites. These cannot capture all the different (poly)phenol types present in the diet. To overcome these limitations, we have recently developed a fast and high throughput method to quantify more than 100 (poly)phenol metabolites in plasma and complete 24 h urine samples,[15] which represent the most abundant (poly)phenols present in the diet. Using this method, we investigated for the first time the relationship between (poly)phenol intake and mood states in a general population sample by estimating (poly)phenol intake using food frequency questionnaires and plasma and 24 h urinary (poly)phenol metabolites. We hypothesized that dietary (poly)phenols as well as its corresponding (poly)phenol metabolites and better mood states would be positively associated when adjusted potential confounders.

2. Experimental Section

2.1. Study Population

The study included baseline data from six dietary intervention studies conducted at the Department of Nutritional Sciences, King's College London from 2018 to 2021. Although the studies involved different dietary interventions, in this analysis the study used standard measures of habitual dietary intake and current mood data obtained at baseline before these interventions were started, which had been reported in the previous study.[16] All studies were conducted in accordance with the guidelines stated in the current revision of the Declaration of Helsinki. All procedures were approved by King's College London Ethics Committee (references HR-18/19-8999, HR-18/19-9036, HR-17/18-5338, HR-18/19-9091, HR-17/18-5353, HR-17/18-5703), and were registered at ClinicalTrials.gov (NCT04179136, NCT03995602, NCT03592966, NCT04084457, NCT03573414, NCT03553225). Written informed consent was provided by all participants, and all participants consented for data to be used in future research.

A total of 333 participants were eligible for the analysis of FFQ-estimated (poly)phenols intake and mood by the inclusion criteria: 1) completed both dietary intake and mood assessments; 2) females whose daily intake was between 500 and 3500 kcal and males whose daily intake was between 800 and 4000 kcal; 3) within two standard deviations (SD) of the mean of Energy intake/Basal metabolic rate (EI/BMR), as reported in previous studies.[16,17] The age of the whole sample ranged from 8 to 79 years (19 aged 8–17 years and 314 aged 18–79 years; mean 40.6 years, SD = 19.9), with 66.1% of participants being female and 74.5% being White (**Table 1**). Of these, $n = 132$ individuals also provided complete 24 h urine samples and $n = 101$ provided fasting plasma samples at the first study visit, and these were included in the metabolite analysis (**Figure 1**). The demographic differences between the subsample included in biomarker analysis and those who were not included are shown in Table S1, Supporting Information.

2.2. Habitual Dietary (Poly)phenol Intake

Dietary (poly)phenol intake was calculated by matching food consumption data from the European Prospective Investigation into Cancer (EPIC) Norfolk Study food frequency questionnaires (FFQ) with the database of food (poly)phenols. Participants completed this 130-item semiquantitative questionnaire about their habitual diet in the previous year,[18] and parents of children participants completed the questionnaire on behalf of their children. The original data were analyzed with the FFQ EPIC Tool for Analysis (FETA) software, which calculated daily intake for main food groups and individual nutrients.[19] The food energy and nutrients data were from McCance and Widdowson's the Composition of Foods (5th Edition) and its supplements.[20] Dietary (poly)phenol intake were calculated by an in-house database as previously described,[17] involving food (poly)phenol content data from the Phenol-Explorer database 3.0,[21] the United States Department of Agriculture (USDA) databases,[22–24] and published papers.[17]

2.3. Urinary and Plasma (Poly)phenol Metabolites Analysis

A 24 h urine sample was collected during the 24 h before the first study visit, and a blood sample was collected after an overnight fast and plasma was obtained from the supernatant of the centrifugated ETDA blood samples. No dietary restrictions were imposed upon the participants. Both complete 24 h urine and plasma samples were spiked with 2% formic acid (the LC-MS grade formic acid [24 µL for urine and 12 µL for plasma] was added to urine/plasma samples in tubes [1200 µL for urine and 600 µL for plasma], yielding 2% of formic acid in each sample) before storing at -80 °C in labeled cryovials until analysis.

Table 1. FFQ-estimated polyphenol intakes by participants' characteristics ($N = 333$).

	N [%]	Total (poly)phenols			Flavonoids			Phenolic acids			Stilbenes			Lignans			Other (poly)phenols		
		Mean (SD) [mg day^{-1}]	*t*/*F* value	*p* value	Mean (SD) [mg day^{-1}]	*t*/*F* value	*p* value	Mean (SD) [mg day^{-1}]	*t*/*F* value	*p* value	Mean (SD) [mg day^{-1}]	*t*/*F* value	*p* value	Mean (SD) [mg day^{-1}]	*t*/*F* value	*p* value	Mean (SD) [mg day^{-1}]	*t*/*F* value	*p* value
Sex			−2.014	0.045		−1.255	0.210		−1.802	0.073		−0.719	0.473		1.979	0.049		1.129	0.260
Male	113 (33.9)	1314 (861)			619 (459)			671 (618)			0.11 (0.16)			1.89 (1.05)			22 (20)		
Female	220 (66.1)	1514 (860)			687 (478)			806 (699)			0.12 (0.13)			1.67 (0.81)			19 (17)		
Ethnicity			2.819	0.039		0.880	0.451		2.238	0.084		4.600	0.004		5.054	0.002		4.896	0.002
White	246 (74.5)	1522 (855)			686 (482)			812 (679)			0.13 (0.15)			1.83 (0.95)			22 (19)		
Black	14 (3.5)	1398 (1063)			681 (385)			699 (824)			0.05 (0.04)			1.73 (0.45)			16 (9)		
Asian	57 (17.5)	1164 (833)			591 (481)			559 (579)			0.07 (0.12)			1.34 (0.60)			13 (12)		
Mixed	16 (4.5)	1330 (780)			565 (340)			747 (713)			0.10 (0.08)			1.93 (0.98)			17 (11)		
Age group			10.832	<0.001		10.112	<0.001		5.121	<0.001		6.163	<0.001		19.550	<0.001		1.840	0.121
< 18 years	19 (5.7)	712 (509)			511 (351)			186 (171)			0.05 (0.03)			1.88 (1.25)			12 (11)		
18–25 years	80 (24.0)	1228 (794)			500 (361)			706 (663)			0.10 (0.08)			1.57 (0.75)			21 (21)		
26–45 years	105 (31.5)	1346 (794)			584 (451)			742 (657)			0.09 (0.10)			1.53 (0.78)			19 (15)		
46–64 years	54 (16.2)	1732 (992)			803 (525)			908 (729)			0.13 (0.15)			1.68 (0.67)			20 (15)		
≥ 65 years	75 (22.5)	1801 (797)			890 (489)			885 (675)			0.17 (0.20)			2.26 (1.04)			24 (22)		
Smoking history			1.466	0.144		1.106	0.270		1.074	0.283		1.893	0.062		0.895	0.372		0.945	0.345
Yes	71 (21.3)	1580 (919)			719 (489)			837 (677)			0.16 (0.21)			1.83 (0.94)			22 (21)		
No	262 (78.7)	1410 (844)			649 (468)			740 (674)			0.11 (0.11)			1.72 (0.89)			20 (17)		
Alcohol use			−3.198	0.002		−0.747	0.455		−3.542	<0.001		−5.750	<0.001		−1.265	0.207		−1.275	0.203
< 3 units per w	221 (66.4)	1340 (869)			650 (478)			669 (664)			0.08 (0.10)			1.70 (0.88)			19 (19)		
≥ 3 units per w	112 (33.6)	1656 (818)			691 (462)			941 (660)			0.18 (0.17)			1.83 (0.94)			22 (16)		
BMI			0.113	0.953		1.590	0.192		0.304	0.822		2.808	0.040		2.772	0.042		0.558	0.643
Underweight	15 (4.5)	1404 (761)			488 (374)			898 (754)			0.17 (0.22)			1.81 (0.99)			17 (14)		
Ideal	221 (66.4)	1433 (865)			645 (476)			766 (681)			0.10 (0.09)			1.67 (0.84)			21 (19)		
Overweight	76 (22.8)	1470 (853)			730 (453)			720 (623)			0.15 (0.21)			1.83 (0.97)			18 (17)		
Obese	21 (6.3)	1530 (1012)			760 (537)			749 (760)			0.10 (0.18)			2.22 (1.01)			22 (15)		
Physical activity			1.295	0.276		1.100	0.334		0.791	0.454		0.472	0.624		0.629	0.534		0.806	0.448
Low	10 (3.0)	1295 (719)			686 (518)			580 (474)			0.08 (0.06)			1.42 (0.77)			28 (32)		
Moderate	76 (23.4)	1339 (815)			590 (432)			727 (648)			0.11 (0.13)			1.71 (0.79)			20 (16)		
High	213 (66.4)	1506 (851)			682 (479)			801 (680)			0.12 (0.14)			1.74 (0.88)			20 (19)		

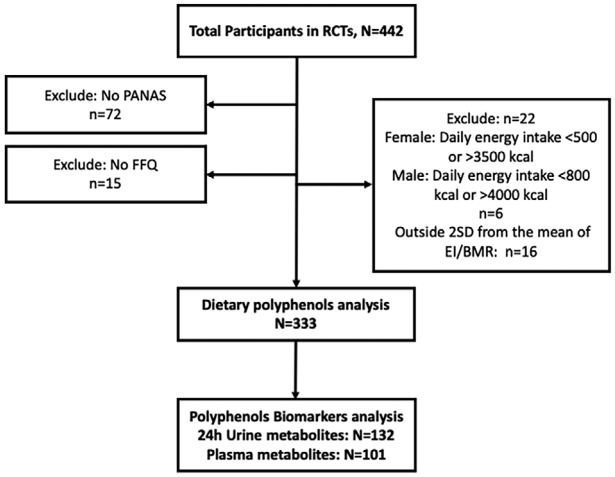

Figure 1. Study participant selection process. EI/BMR, energy intake/basal metabolic rate; FFQ, food frequency questionnaires; PANAS, the Positive and Negative Affect Schedule; RCTs, randomized controlled trials.

No enzymatic treatment was performed so the analyzed phase II metabolites were in conjugated form. Both 24 h urine and plasma samples were processed with micro-solid-phase extraction (μ-SPE) and analyzed with a validated ultra-performance liquid chromatography and triple-quadrupole mass spectrometry (UPLC-Q-q-Q MS) method, a previously validated method developed by the lab.[15] The metabolites were selected based on the current knowledge of the most abundant (poly)phenol in human diet and availability of the authentic analytical standards. All compounds in the method were quantified by using authentic standards. A total of 102 phenolic metabolites, including 15 flavonoids, 66 phenolic acids, 5 lignans, 5 stilbenes, and 11 others (3 tyrosols, 3 benzene diols and triols, 3 benzaldehydes and 2 hydroxycoumarins) were identified and quantified with authentic chemical standards.[15] The detailed list of (poly)phenol metabolites analyzed from 24 h urine and plasma samples were shown in Table S2, Supporting Information.

2.4. Mood Assessment

The Positive and Negative Affect Schedule - Short Form (PANAS - SF) and PANAS - Children (PANAS - C) were used to assess current mood state for adults and children, respectively. The PANAS - SF was a 20-item (10 positive and 10 negative mood states),[8] and PANAS-C was a 30-item (15 positive and 15 negative mood states) self-report measure of Positive Affect (PA) and Negative Affect (NA).[25] Participants rated the degree to which they were currently experiencing each item on a five-point Likert scale (Very slightly or not at all, A little, Moderately, Quite a bit, Extremely). The ratings of positive and negative items were summed to calculate an overall positive mood score and negative mood score, ranging from 10 to 50 for PANAS-SF and 15–75 for PANAS-C, with lower scores indicating lower levels of positive or negative mood. The PANAS-SF and PANAS-C had both demonstrated good reliability, with a Cronbach's alpha of 0.88 for PA and 0.87 for NA in PANAS-SF,[8] and an alpha of 0.90 and 0.94 for PA and NA in PANAS-C,[25] respectively. To allow inclusion of PANAS-SF and PANAS-C data in the same models, the study transformed these outcomes to Z-scores separately within each scale.

2.5. Sociodemographic and Lifestyle Factors

Sociodemographic and lifestyle information were collected with a questionnaire at baseline, and included details of participants' age, sex, ethnicity, height, weight, smoking history, alcohol use (units per week), and physical activity. Ethnicity was self-reported and categorized into White, Black, Asian, Mixed, and Other ethnic group according to the list of ethnic groups from the 2021 Census of England and Wales.[26] Body mass index (BMI) was calculated as weight divided by height squared (kg m^{-2}) and participants were grouped into the following categories: underweight (<18.5 kg m^{-2}), healthy weight (18.5–24.9 kg m^{-2}; 18.5–23.0 kg m^{-2} for Asian), overweight (25.0–29.9 kg m^{-2}; 23.0–27.5 kg m^{-2} for Asian), and obese (≥30 kg m^{-2}; >27.5 kg m^{-2} for Asian) according to WHO standards.[27,28] Children (aged under 18) were grouped according to BMI-for-age percentile, as underweight (on the 2nd centile or below), healthy weight (between the 2nd and 91st centiles), overweight (91st centile or above), and obese (98th centile or above), based on UK-WHO growth charts.[29] Participants aged 15 and above also completed the International Physical Activity Questionnaire (IPAQ) and were categorized into low, moderate, and high levels of activity.[30] Details had been described in the previous study.[16]

2.6. Statistical Analysis

All statistical analyses were performed using R 4.2.1 (https://www.R-project.org/). Descriptive statistics were generated for sociodemographic and lifestyle characteristics. Data were reported as mean and standard deviation (SD), and statistical differences in dietary (poly)phenol intake between different groups were evaluated using parametric tests (one-way ANOVA and *t*-test). Pairwise differences in group means were explored post-hoc with the Turkey test. Urinary and plasma metabolite levels were log-transformed and adjusted for batch effects using the ComBat method[31] using the sva package.[32] The ComBat method was an empirical Bayes method originally developed to remove batch effects in microarray data in gene sequencing and now also applied to metabolomics analysis.[33] Spearman correlation analysis was used to assess the relationship between FFQ-estimated (poly)phenols, and urinary and plasma metabolites, as well as the correlation between (poly)phenol metabolites and mood. When looking at the correlation between (poly)phenols and mood states, the total FFQ-estimated (poly)phenols will be tested at first, then followed by the main groups (flavonoids, phenolic acids, lignans, stilbenes, and other (poly)phenols), and subgroupings at last. Significance was adjusted for multiple comparisons using the False Discovery Rate (FDR) method.[34] Furthermore, a linear regression analysis was conducted to explore relationship between individual (poly)phenols and (poly)phenol metabolites with mood, after adjusting for potential confounders (sex and age), as described in the previous study.[16] As there was no significant association between BMI or physical activity and mood, these factors were not considered among potential

Table 2. Linear regression analysis between FFQ-estimated (poly)phenols and positive mood.

	Model 1		Model 2		Model 3		Model 4		Model 5	
	β	*p* value	*β*	*p* value	*β*	*p* value	*β*	*p* value	*β*	*p* value
Sex[a)]	−0.106	0.050	−0.121	0.024	−0.137	0.011	−0.128	0.018	−0.131	0.016
Age	0.167	0.003	0.202	<0.001	0.189	<0.001	0.179	0.002	0.193	<0.001
FFQ-estimated lignans	0.134	0.016								
FFQ-estimated flavanones			0.113	0.035						
FFQ-estimated flavonols					0.118	0.029				
FFQ-estimated flavan-3-ols							0.071	0.212		
FFQ-estimated proanthocyanidins									0.077	0.158
R^2	0.069		0.065		0.066		0.057		0.058	
Adjusted R^2	0.060		0.056		0.057		0.048		0.049	
F	8.084***		7.593***		7.706***		6.574***		6.730***	

Linear regression analysis was conducted to explore relationship between individual dietary (poly)phenols with positive mood, after adjusting for potential confounders (sex and age). Models 1–5 included each listed FFQ-estimated (poly)phenols, respectively. [a)] Reference group: Males. ***$p < 0.001$.

confounders,[16] which might be due to the very low percentage of participants whose BMIs fell into the obese group (6.3%) and even in the obese group only 13 participants (3.9%) had a BMI equal to or more than 30.

3. Results

3.1. FFQ-Estimated (Poly)phenol Intake

In the total sample, the average FFQ-estimated total dietary (poly)phenol intake was 1447±864 mg day^{-1}, ranging from 97 to 4014 mg day^{-1}. The distributions of FFQ-estimated intakes of dietary (poly)phenols could be found in Figure S1, Supporting Information. Females, White participants, and those aged 45 and above had a higher total (poly)phenol intake compared to males (1514 ± 860 mg day^{-1} vs 1314 ± 861 mg day^{-1}, $p = 0.045$), Asian participants (1522 ± 855 mg day^{-1} vs 1164 ± 833 mg day^{-1}, Turkey $p = 0.024$), and those younger than 45 years of age (1772 ± 881 mg day^{-1} vs 1241 ± 789 mg day^{-1}, $p < 0.001$) (Table 1). More specifically, White participants had higher dietary intakes of stilbenes (0.13 ± 0.15 mg day^{-1} vs 0.07 ± 0.12 mg day^{-1}, Turkey $p = 0.007$) and lignans than Asians (1.83 ± 0.95 mg day^{-1} vs 1.34 ± 0.60 mg day^{-1}, Turkey $p = 0.001$), while participants older than 45 years of age had a higher dietary intake of flavonoids (853 ± 504 mg day^{-1} vs 544 ± 409 mg day^{-1}, $p < 0.001$) and phenolic acids (894 ± 696 mg day^{-1} vs 676 ± 648 mg day^{-1}, $p = 0.002$), and participants older than 45 years of age had a higher dietary intake of stilbenes (0.16 ± 0.18 mg day^{-1} vs 0.09 ± 0.09 mg day^{-1}, $p < 0.001$) and lignans (2.02 ± 0.95 mg day^{-1} vs 1.58 ± 0.82 mg day^{-1}, $p < 0.001$) than participants younger than 45 years.

3.2. Associations between FFQ-Estimated (Poly)phenol Intake and Mood

The correlation between the total FFQ-estimated (poly)phenol intake and positive or negative mood was not significantly correlated (Spearman rho = 0.097, $p = 0.077$ and rho = 0.022, $p = 0.691$, respectively). Considering the five main classes of (poly)phenols, better positive mood and higher reported dietary intake of flavonoids and lignans were positively correlated (rho = 0.171, FDR $p = 0.010$ and rho = 0.181, FDR $p = 0.010$, respectively). Considering the subclasses of flavonoids, better positive mood and higher dietary intake of flavanones, flavonols, flavan-3-ols, and proanthocyanidins were all positively correlated (rho = 0.156, 0.150, 0.143, 0.142, respectively, all FDR $p < 0.05$), while less negative mood and higher dietary intake of chalcones was correlated (rho = −0.137, FDR $p < 0.05$) (**Figure 2**). These significant Spearman correlations are visualised in Figure S2, Supporting Information. Correlations between subclasses of

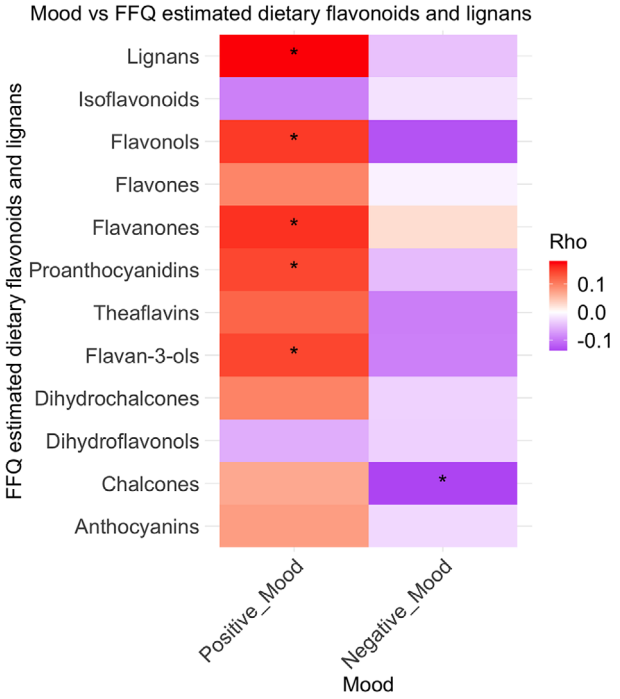

Figure 2. Spearman correlations between mood and FFQ-estimated (poly)phenols. *FDR adjusted *p*-value < 0.05.

Table 3. Linear regression analysis between urinary (poly)phenols and negative mood.

	Model 1		Model 2		Model 3		Model 4		Model 5	
	β	p value	β	p value	β	p value	β	p value	β	p value
Urinary flavones	−0.205	0.028								
Urinary tyrosols			−0.133	0.138						
Urinary benzoic acids					−0.258	0.013				
Urinary hydroxyphenylacetic acids							−0.183	0.064		
Urinary stilbenes									−0.080	0.413
R^2	0.087		0.068		0.097		0.077		0.057	
Adjusted R^2	0.066		0.047		0.076		0.056		0.035	
F	4.088**		3.135*		4.596**		3.578*		2.588	

Linear regression analysis was conducted to explore relationship between (poly)phenol metabolites with negative mood, after adjusting for potential confounders (sex and age). Models 1–5 included each listed urinary (poly)phenols, respectively. *$p < 0.05$. **$p < 0.01$.

phenolic acids, stilbenes, and other (poly)phenols and positive or negative mood were not significant.

After adjusting for sex and age, the simple linear models indicated that the association of better positive mood with higher intake of lignans, flavanones, and flavonols significantly remained (β = 0.134, 113 and 0.118, respectively, all $p < 0.05$) (**Table 2**). Nonetheless, no significant association was seen between dietary intake of chalcones and negative mood in the simple linear model (β = -0.090, p = 0.100).

3.3. Associations between Urinary and Plasma (Poly)phenol Metabolites and Mood

Higher levels of five urinary (poly)phenol subclasses and less negative mood were significantly correlated, including flavones (rho = −0.332, FDR p = 0.004), tyrosols (rho = −0.235, FDR p = 0.048), benzoic acids (rho = −0.251, FDR p = 0.037), hydroxyphenylacetic acids (rho = −0.286, FDR p = 0.020), and stilbenes (rho = −0.248, FDR p = 0.037). When looking into urinary individual metabolites, we found that 16 urinary individual (poly)phenols were significantly correlated with less negative mood (Figure S3, Supporting Information). No significant associations were found between urinary (poly)phenols and positive mood. Distributions of urinary and plasma levels of (poly)phenols can be found in Figures S4 and Figure S5, Supporting Information, respectively.

After adjusting for potential confounders (sex and age), the simple linear models suggested that higher levels of urinary flavones and benzoic acids and less negative mood were associated, with the largest standardized effect seen for urinary benzoic acids (β = −0.258, p = 0.013) (**Table 3**). When considering individual urinary metabolites, the simple linear regressions showed that after adjusting for sex and age, higher levels of 11 urinary metabolites and less negative mood were still significantly associated as shown in **Figure 3**, including quercetin (β = −0.261, p = 0.005), enterodiol (β = −0.320, p = 0.002), 4-hydroxy-3,5-dimethoxybenzoic acid (β = −0.222, p = 0.024), 3-(3′-methoxyphenyl)propanoic acid-4′-sulfate (β = −0.251, p = 0.010), 4′-hydroxycinnamic acid-3′-glucuronide (β = −0.234, p = 0.030), cinnamic acid-4′-sulfate (β = −0.387, p < 0.001), 3,4-dihydroxybenzaldehyde (β = −0.347, p = 0.004), 4-hydroxybenzoic acid-3-sulfate (β = −0.303, p = 0.002), 3-hydroxybenzoic acid-4-sulfate (β = −0.260, p = 0.005), dihydroresveratrol (β = −0.386, p = 0.001), and flavone (β = −0.205, p = 0.028).

In contrast to what was observed for urinary metabolites, plasma (poly)phenols metabolites were not significantly correlated with negative or positive mood (Figure S6, Supporting Information).

3.4. Correlation between FFQ-Estimated (Poly)phenol Intake and Circulating (Poly)phenol Metabolites

Urinary rather than plasma (poly)phenol levels and the FFQ-estimated (poly)phenols in the same class or subclasses were significantly correlated. This was seen for total (poly)phenols (rho = 0.440, FDR p < 0.001), phenolic acids (rho = 0.433, FDR p < 0.001), stilbenes (rho = 0.315, FDR p = 0.003), and lignans (rho = 0.228, FDR p = 0.035). Furthermore, as shown in Figures S7 and S8, Supporting Information, more significant correlations were seen between FFQ-estimated (poly)phenols and urinary (poly)phenols than plasma (poly)phenols. Notedly, we found that both urinary and plasma levels of 3-hydroxy-4-methoxybenzoic acid-5-sulfate were persistently correlated with dietary theaflavins (rho = 0.60 and 0.44, respectively) and dietary flavan-3-ols (rho = 0.51 and 0.44, respectively), while both urinary and plasma levels of 3′-hydroxycinnamic acid-4′-glucuronide were persistently correlated with dietary total (poly)phenols (rho = 0.55 and 0.42, respectively).

3.5. (Poly)phenol-Rich Foods' Correlations with Mood States, FFQ-Estimated (Poly)phenol Intake, and (Poly)phenol Metabolites

We did not find any significant correlation between any (poly)phenol-rich food groups and either positive or negative mood (Figure S9, Supporting Information). However, various (poly)phenol-rich food groups and FFQ-estimated (poly)phenols were found to be highly correlated (FDR p < 0.05) (Figure S10, Supporting Information). As main sources of (poly)phenols, the daily average intakes of coffee, tea, wine were 1.8 serving

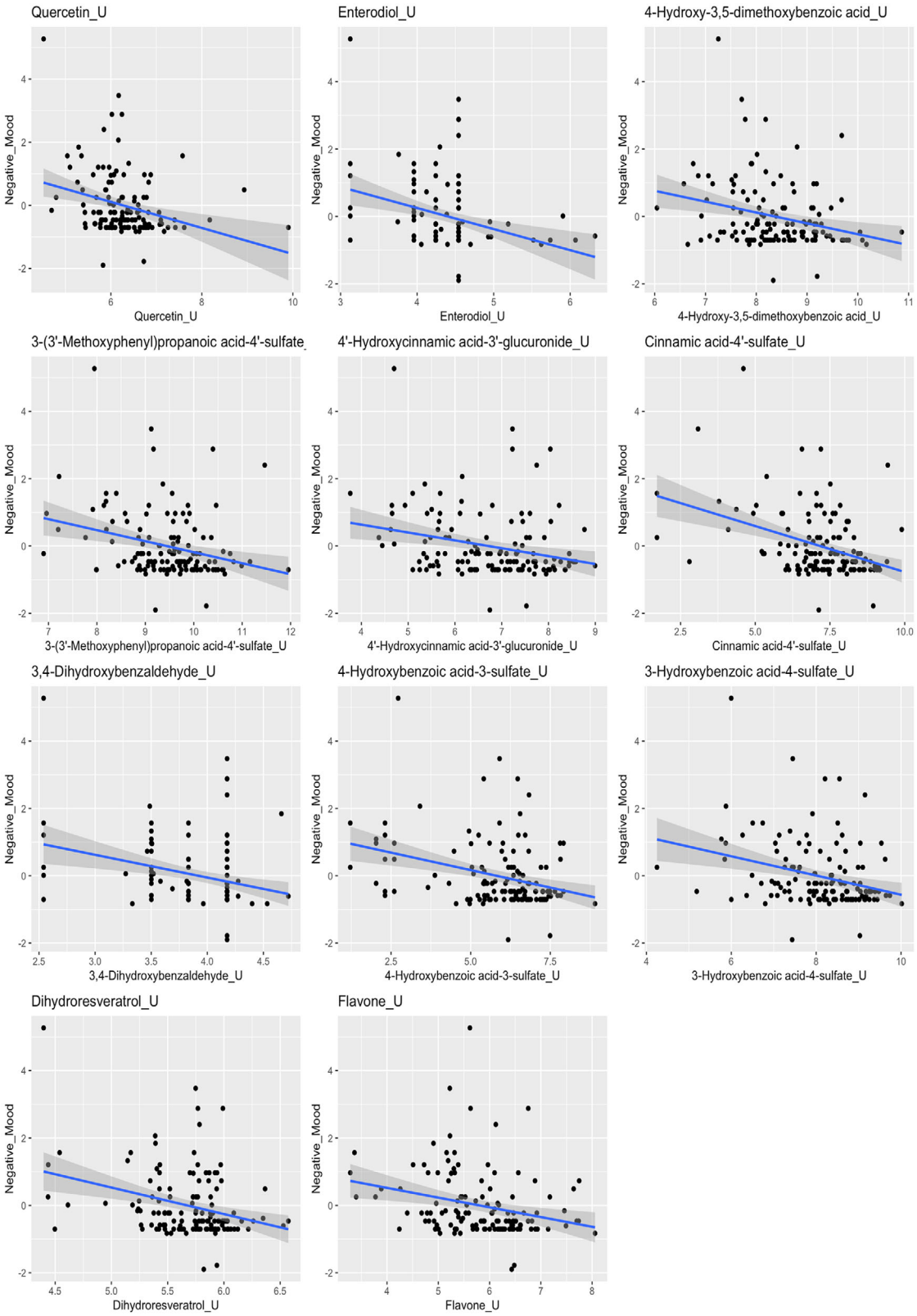

Figure 3. Significant associations between individual urinary metabolites and negative mood: linear regression analysis adjusted for age and sex.

(SD = 1.1 serving), 1.3 serving (SD = 1.4 serving), and 0.1 serving (SD = 0.3 serving), respectively, standardized as 190 g per serving according to default portion size in the EPIC-FFQ. Additionally, the average daily intake of fruits, vegetables, cereals, and fiber were 244.7 g (SD = 197.4 g), 289.1 g (SD = 164.6 g), 229.2 g (SD = 114.9 g), and 16.2 g (SD = 6.9 g), respectively. As a reference of the nutritional status of this sample, the daily nutritional profile with the main sources of (poly)phenol intake is illustrated in Table S3, Supporting Information.

We also explored the correlation of FFQ-estimated (poly)phenol-rich food groups with (poly)phenol metabolites (Figures S11 and S12, Supporting Information). The results indicated that more than 70 urinary individual (poly)phenols were significantly associated with daily intakes of tea, coffee, red wine, and whole grains, suggesting that tea, coffee, wine and whole grains are the main contributors to levels of urinary (poly)phenols in the complete 24 h urine samples. In contrast, only five plasma metabolites and FFQ-estimated daily intakes of tea, whole grain, and onion were correlated, which was in line with the results above that (poly)phenols in fasting plasma and estimates of FFQ-estimated (poly)phenols are less correlated than 24 h urinary levels.

4. Discussion

This is the first study exploring the association between mood states and habitual (poly)phenol intake estimated with both self-reported intake and plasma and urinary metabolites in a group of healthy individuals. Our results indicated that higher FFQ-estimated dietary intake of lignans, flavanones, and flavonols was independently associated with more positive mood. We also found that higher levels of 16 urinary (poly)phenol metabolites were significantly associated with less negative mood, with 11 remaining significant after controlling for age and sex, including the lignan metabolite enterodiol and the flavonol metabolite quercetin, which point to these particular (poly)phenol subclasses as promising potential contributors to better mood states.

Our findings suggest that higher FFQ-estimated dietary intake of lignans as well as urinary levels of the lignan metabolite enterodiol were both associated with better positive mood, which are in agreement with previous research showing that urinary enterodiol was significantly lower in depressed than in non-depressed women in a study of 193 perimenopausal US women.[35] Urinary lignans were also inversely associated with the prevalence of depressive symptoms in a large-scale (n = 3430) cross-sectional study of the US general population.[36] The potential mechanism underlying the association between lignan consumption and mood could be its anti-inflammatory properties indicated by decreasing pro-inflammatory mediators (COX-2, TNF-α, and IL-1β) and increasing hippocampal brain-derived neurotrophic factor (BDNF) to attenuate neuroinflammation, which has been investigated in animal models.[37,38] However, this has not been confirmed in humans yet. Additionally, our study reports for the first time a positive association between dietary flavonols and positive mood, as well as a significant association between negative mood and lower urinary quercetin (a type of flavonol, mainly from vegetables and tea). This is consistent with a US nurse cohort study of 82 643 women that found significant associations between higher flavonol intake and lower depression risk in a 10-year follow up.[39] This could also be explained by the fact that flavonols could modify physiological aspects of the serotonergic system (a key system involving in mood regulation) via increasing levels of serotonin and its availability, which has been confirmed in preclinical studies.[40] Nonetheless, the precise mechanism is still not replicated in clinical studies, calling for future studies to explore.

Our report of an association between higher dietary flavanones and more positive mood is in line with an observational study of 1572 Italian adults which showed a significant inverse dose response association between flavanone intake and depressive symptoms.[3] As citrus fruit is the main source of flavanone intake, significant correlation was also found between citrus fruit intake and positive mood. However, we were not able to see any significant association between plasma or urinary flavanone metabolites (hesperetin, rac-hesperetin-7-sulfate, rac-hesperetin-3′-glucuronide, and naringenin-4′-glucuronide) and mood, despite being present in 24 h urine in most volunteers. Besides, a poor correlation was found between habitual dietary flavanone intake and urinary flavanones in this study, which is consistent with a previous study suggesting that urinary flavanones, such as hesperetin and naringenin, may be a good estimation of acute but not habitual intake of flavanones.[41] Additionally, some of the abundant gut microbial metabolites of flavanones, including 4′-hydroxyhippuric acid, 3′-methoxycinnamic acid-4′-sulfate, 4′-methoxycinnamic acid-3′-glucuronide, 3-(4′-hydroxyphenyl)propanoic acid-3′-sulfate,[42] are not specific of flavanones and come from multiple (poly)phenol sources, which is reflected in the fact that they were correlated to other (poly)phenol-rich foods, like tea, coffee, and red wine, so we could not conclude that these metabolites specifically reflect citrus consumption.

Interestingly, we have found that a less negative mood was associated with higher levels of urinary flavones but not with FFQ-estimated flavone intake (mainly from cereals). This discrepancy could be explained by two facts that: 1) there is only one flavone measured in metabolites, which might not be representative for all flavone metabolites; 2) the FFQ does not include major food source of flavones (soups) compared to 7-day food diaries.[17] Our finding is not consistent with a US cohort study (n = 82 643) that found that higher intake of flavones could reduce risk of depression in 10 years.[39] This discrepancy could be explained by the different calculations for intake of flavones and the smaller sample size of our study, which might have limited the ability to detect an association between dietary flavones and negative mood. It is also possible that the evaluation of the urinary biomarker might be more sensitive to detect the association between urinary flavones and negative mood.

As a metabolite of anthocyanins and proanthocyanidins among others,[43] urinary 3,4-dihydroxybenzaldehyde (associated with tea, coffee, and red wine consumption in this study) was associated with less negative mood in our study. This might be explained by preclinical evidence that 3,4-dihydroxybenzaldehyde plays an anti-neuroinflammatory effect by reducing the production of inflammatory cytokines in rats.[44] More studies are needed to replicate these results and further confirm whether this is indeed the case in humans. Moreover, our results are also the first time to report that urinary dihydroresveratrol, one of the gut microbial catabolites of resveratrol, is negatively associated

with negative mood. However, dietary intake of stilbenes (mainly consisting of resveratrol) did not show the same association with mood. A recent meta-analysis of 22 animal studies concluded that resveratrol had positive effects in animal models of depression, comparable to the effects of antidepressants. However, very few human studies exist to replicate these findings.[45] In addition, the low intake of resveratrol in the diet is unlikely to lead to significant effects on human health, unless is taken as a dietary supplement. Dihydroresveratrol in this case might represent the intake of foods rich in other (poly)phenols, such as anthocyanins and flavan-3-ols, with red wine being the main source.

We also found a significant correlation between less negative mood and higher levels of six urinary phenolic compounds, including 4-hydroxy-3,5-dimethoxybenzoic acid (syringic acid), 4-hydroxybenzoic acid-3-sulfate (protocatechuic acid-3-sulfate), 3-hydroxybenzoic acid-4-sulfate (protocatechuic acid-4-sulfate), 3-(3′-methoxyphenyl)propanoic acid-4′-sulfate (dihydroferulic acid-4′-sulfate), cinnamic acid-4′-sulfate (p-coumaric acid-4′-sulfate) and 4′-hydroxycinnamic acid-3′-glucuronide (caffeic acid-3′-glucuronide), which are mainly derived from flavonoids and phenolic acids. Although not confirmed in humans yet, syringic acid could reduce the progression of Parkinson's disease in rats via its neuroprotective and anti-inflammatory effects.[46] This evidence could be one explanation of our finding that urinary syringic acid and less negative mood was correlated. In addition, other phenolic acid metabolites including 4-hydroxybenzoic acid-3-sulfate (protocatechuic acid 3-O-sulfate), 3-hydroxybenzoic acid-4-sulfate (protocatechuic acid-4-O-sulfate), 3-(3′-methoxyphenyl)propanoic acid-4′-sulfate (dihydroferulic acid-4′-sulfate), cinnamic acid-4′-sulfate (p-coumaric acid-4′-sulfate), and 4′-hydroxycinnamic acid-3′-glucuronide (caffeic acid-3′-glucuronide) were associated with less negative mood, and the correlations between these metabolites and coffee, red wine, and green vegetable consumption were significant. The association with berry intake was positively significant but became non-significant after multiple comparison adjustment. These metabolites could come from many different (poly)phenols including caffeoylquinic acids, anthocyanins, and proanthocyanidins, which are indeed abundant in coffee, red wine, berries, and vegetables such as artichokes.[47] Future clinical and preclinical studies are needed to investigate the potential relationship between these metabolites and mental health.

In terms of (poly)phenol sources, we did not find any significant association between individual (poly)phenol-rich foods and mood. Nonetheless, previous studies have indicated that higher intakes of tea, citrus, and grapes are associated with better mood.[48–50] Although there is evidence of a protective effect of dietary consumption of tea and fruits on mood, more studies are needed to establish the specific role of (poly)phenol metabolites detected in urine, which seems to reflect (poly) -phenol intake more objectively, in regulating mood and general mental health.

The levels of FFQ-estimated (poly)phenol intake found in our study are comparable to the ones estimated in the UK National Diet and Nutrition Survey (NDNS) 2008–2014.[51] We also found some consistent patterns with NDNS, such as total (poly)phenol intake being higher in people with higher alcohol consumption, and higher in older adults, as they consumed more tea, alcohol, and fruits, as well as less meat. Compared to the NDNS data,[51] we found flavonoid intake to be similar across all age groups. However, the intake of phenolic acids in our sample was higher and the intake of stilbenes was lower in all age groups, compared to the NDNS data.[51] This may be since our sample had a higher intake of non-alcoholic beverages (coffee in particular, main source of phenolic acids) and a very low alcohol consumption (28.2 g day^{-1}). Additionally, the average intake of fruits (244.7 g) and vegetables (289.1 g) was similar to the levels estimated in the UK EPIC-Norfolk cohort study (n = 11 577), which were 257 and 275 g day^{-1} for fruits and vegetables, respectively.[52] Although the average fiber intake (16.2 ± 6.9 g day^{-1}) in our sample was much lower than the UK recommendation (30 g day^{-1}), it was still higher than that from the UK NDNS.[53] Interestingly, we found different demographic patterns in terms of (poly)phenol intake. For instance, we found that females had a higher (poly)phenol intake than males, while the UK national analysis found this to be the case in males in all age groups, except for adults aged 19–34 and 50–64 years, where intakes were marginally higher in females. This might be because our sample had an unbalanced sex distribution (66.1% females in our study vs 54.1% females in NDNS) and more Asian participants (17.5% in our study vs 7.3% in NDNS) who consumed less alcohol.

Finally, more significant correlations were seen between FFQ-estimated (poly)phenol intake and 24 h urinary (poly)phenol metabolites than fasting plasma metabolites. Notably, the FFQ reflects habitual intake, whereas 24 h urine and fasting plasma should represent (poly)phenol intake in the previous 24–48 h. The lack of correlation between the plasma metabolites and the FFQ-estimated intake may be explained by the fact that the fasting plasma can only capture metabolites with a relatively long half-life from food sources that are frequently taken.[54] Dietary (poly)phenols undergo extensive metabolism after ingestion, with a small fraction of (poly)phenol absorbed in the small intestine and the majority reaching colon and being metabolized by the gut microbiota and further absorbed.[55] Some compounds that could be absorbed in the small intestine, usually reach peak concentrations in plasma 1–4 h post consumption[1,55,56] before being cleared from the blood stream and excreted in urine, therefore, these metabolites could be more abundant in 24 h urine. Fasting plasma, on the other side, can only capture (poly)phenol metabolites with relatively long half-lives, such as gut microbial metabolites. This is also an explanation for the fact that we did not find any associations between plasma (poly)phenol metabolites and mood, as most (poly)phenol we found to be associated with mood have a short T_{max}, which could not be found in fasting plasma. Overall, the correlations between FFQ-estimated dietary (poly)phenol intakes and metabolites in plasma were weak (Spearman's rho < 0.4), whereas some correlations between FFQ-estimated dietary (poly)phenol intakes and metabolites in urine were moderate with Spearman's rho ranging between 0.5 and 0.6. For instance, the Spearman rho between dietary theaflavins and urinary 3-Hydroxy-4-methoxybenzoic acid-5-sulfate was 0.60 and the rho between dietary total (poly)phenols and urinary 3′-hydroxycinnamic acid-4′-glucuronide was 0.55. Although these two metabolites in urine and plasma showed persistently correlations with dietary (poly)phenol intakes, we were unable to draw the conclusion that they could be specific biomarkers of dietary (poly)phenol intake. This is because that these phenolic

compounds could also be generated by the gut-microbiota from various types of (poly)phenols.[17]

To the best of our knowledge, this is the first study exploring the relationship between mood states and (poly)phenol metabolites in a wide age range of free-living healthy individuals. We for the first time have found that both dietary and urinary lignans and flavonols are associated with better mood states, providing solid evidence in this field and highlighting the importance of future studies to investigate it in a longitudinal design and further explore the biological mechanism. However, a number of limitations should be considered. First, the FFQ, although widely used, has a limited ability to capture and discriminate food sources of (poly)phenols due to the defined list of food items and its nature of self-report resulting in recall bias. Second, the sample is heterogenous in terms of the age distribution (range: 8–79 years), despite of the validation of EPIC-FFQ in children,[57] adults,[58] and older individuals,[18] the results need to be interpreted with caution due to the limited generalization. Third, the phenolic metabolites in 24 h urine and fasting plasma only reflect the intake of the last 24–48 h while the FFQ estimates the habitual diet of the previous year. Thus, variations between recent and habitual intake might influence the correlation between dietary intake and metabolite levels. Fourth, some of the phenolic metabolites we included are not specific to (poly)phenols and can derive from other sources or other endogenous metabolic pathways, such as the benzoic acid derivatives, that can come from multiple sources such as food preservatives.[59] This could result in bias when using (poly)phenol biomarkers to reflect exposure from diet. Lastly, although we used the same analytical method and device for all samples, we cannot exclude the presence of a batch effect that might have influenced the levels of metabolites, although this was minimized by using the ComBat method.

5. Conclusions

In conclusion, this study for the first time has reported the potential effects of dietary (poly)phenols on modulating mood, in particular flavonoids and lignans, raising the need for more studies to further investigate causality. Regarding the best way of examining (poly)phenol exposure, as currently there is no gold-standard method and both dietary and biomarker assessment approaches have limitations, we propose that the use of a combination of validated dietary assessment tools and biomarkers is the optimal approach in the future. We are also aware that this is difficult to achieve and reporting both results from dietary assessment and biomarkers (ideally in 24 h urine samples) might be an acceptable compromised approach for (poly)phenol intake estimation.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Acknowledgements

The authors extend their gratitude to all participants involved in the study. X.M., Y.X., and Y.L. have received King's-China Scholarship Council (K-CSC) joint scholarship.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Conceptualization: X.M., C.N, P.D., and A.R.M.; Data curation: X.M., Y.X., and Y.L.; Formal analysis: visualization, and writing - original draft, X.M.; Methodology and validation: Y.X., A.R.M., and R.G.; Statistics advice: A.J.L.; Writing – review & editing: R.G., C.W., A.J.L., C.N., P.D., and A.R.M.; Supervision: C.N., P.D., and A.R.M.; Project administration and funding acquisition: A.R.M. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

The data that support the findings of this study is not available to share due to ethical restrictions

Keywords

general population, mood, plasma metabolites, (poly)phenols, urinary metabolites

Received: February 12, 2024
Revised: August 17, 2024
Published online:

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