

Association between both total baseline urinary and dietary polyphenols and substantial physical performance decline risk in older adults: a 9-year follow-up of the InCHIANTI study

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ABBREVIATIONS: TUP: total urinary polyphenols; TDP: total dietary polyphenols; InCHIANTI: Invecchiare in Chianti; F-C: Folin-Ciocalteu; SPPB: Short Physical Performance Battery; GAE: gallic acid equivalents; BMI: body mass index; MMSE: Mini-Mental State Examination; CES-D: Center for Epidemiologic Studies Depression Scale; ADL: activities of daily living; IADL: instrumental activities of daily living; SD: standard deviation; IQR: interquartile range; OR: odds ratio; CI: confidence interval.

ABSTRACT

Importance: The decline in physical performance that occurs in many older subjects is a strong predictor of falls, hospitalization, institutionalization and mortality. Polyphenols are bioactive compounds that may play a preventive role against physical performance decline due to their antioxidant and anti-inflammatory properties.

Objective: To investigate the association between total urinary polyphenols (TUP) and total dietary polyphenols (TDP) and substantial physical performance decline over a nine-year period among older subjects.

Methods: This longitudinal study included 368 participants aged 65 years or older from the InCHIANTI (*Invecchiare in Chianti*) study, an Italian population-based cohort. TUP and TDP concentrations were assessed at baseline using the Folin-Ciocalteu (F-C) assay and a validated food frequency questionnaire, respectively. Physical performance was objectively measured at baseline and at nine-year follow-up using the Short Physical Performance Battery (SPPB). A substantial decline in physical performance was considered as a decrease of three or more points in the SPPB score.

Results: At the nine-year follow-up assessment, 71 participants had suffered a substantial decline in physical performance. In the fully adjusted logistic regression model, participants in the highest TUP tertile had a lower risk of substantial decline in physical performance than those in

the lowest tertile (OR, 0.40; 95% CI, 0.17–0.93; *P* trend=0.033). However, no significant association between TDP intake and physical performance decline was observed.

Conclusion: This study shows that high TUP concentrations, a biomarker of polyphenol-rich exposure, were associated with lower risk of substantial decline in physical performance in community-dwelling older subjects over a nine-year period. These results suggest that a polyphenol-rich diet may play a role in protecting against physical performance decline in older people.

INTRODUCTION

The decline in physical performance that occurs in many older people often marks the early stage of a process leading to disability⁽¹⁾ and is associated with increased morbidity and mortality⁽²⁻⁴⁾. The Short Physical Performance Battery (SPPB) is a standardized tool for assessing physical performance in both research and clinical geriatric settings⁽⁵⁾. It has an excellent reliability and is highly sensitive to clinically substantial changes, being a strong predictor of subsequent disability, nursing home admission, hospitalization and mortality in community-dwelling older subjects^(1, 4, 6). The causes of physical performance decline are complex and not completely understood. Aging, diseases and unhealthy life-style factors, mainly low physical activity and poor nutrition, can contribute to physical decline in older persons. There is increasing evidence suggesting that a healthy diet can reduce the risk of developing disability in older adults^(7, 8). A recent study on diet rich in fruits and vegetables, such as the Mediterranean diet, showed a beneficial role in mobility-related outcomes^(9, 10). Over the last few years, there has been an increasing interest in polyphenols, which are present in diets rich in fruits, vegetables and their derived products, due to their biological effects that could be beneficial to promote healthy aging, such as maintaining optimal physical and cognitive performance⁽¹¹⁾. However, to the best of our knowledge, no epidemiological study has evaluated the association between total polyphenol intake and physical performance decline in older subjects.

One of the reasons for the lack of studies in this field is the difficulty in assessing total dietary polyphenol (TDP) intake. This is mainly due to the well-known drawbacks of using self-reported dietary questionnaires and the limited food composition data on all polyphenol classes⁽¹²⁾. The use of a valid polyphenol biomarker, i.e. the concentration of total urinary polyphenols (TUP), provides a more accurate and objective measure of total polyphenol exposure than dietary questionnaires⁽¹²⁾. In a previous study by our group, TDP was moderately correlated with TUP, and it is currently utilized as biomarker of total polyphenol intake⁽¹³⁾. In the present study, our objective was to evaluate whether TUP concentrations and TDP intake were associated with a lower risk of physical performance decline over a nine-year follow-up in a community-dwelling older population.

METHODS

Study population

The InCHIANTI (*Invecchiare nel Chianti*) is a prospective population-based study aimed at investigating the factors contributing to the decline of mobility in older subjects living in two municipalities located in Tuscany (Italy). A description of the study rationale, design and methods is provided in detail elsewhere⁽¹⁴⁾. The study population comprised 1,155 participants aged 65–102 years, who were randomly selected from the residents' registry with the use of a multistage stratified sampling method. The response rate was 91.6%.

Data collected at baseline (1998–2000) and during the nine-year follow-up assessment (2007–2009) were used for the current analyses. Participants with missing data at baseline on TUP (n=346, individuals without 24-h urine sample), SPPB at baseline (n=30) or SPPB at nine-year follow-up (n=408, of whom 126 had no physical performance assessment, 225 died, 42 refused and 15 emigrated before the nine-year visit) were excluded. We also excluded participants with dementia at baseline (n=3), since they were not able to complete the questionnaires reliably^(9, 15). The final sample included 368 participants aged 65 years or older.

Total polyphenol exposure

At baseline, 24-h urine samples were obtained from participants. Urine samples were immediately aliquoted and stored at –80 °C until analysis. Samples were thawed on ice and analysed using the Folin-Ciocalteu (F-C) assay after a solid-phase extraction, which allows the elimination of interfering substances that could react with the F-C assay, as described previously⁽¹³⁾. TUP concentrations were expressed as mg of gallic acid equivalents (GAE) per 24-h urine.

A validated Italian version of food frequency questionnaire was self-administered to assess the intake of 236 food items (g/d) consumed in the preceding year⁽¹⁶⁾. TDP intake was estimated using a food composition database on polyphenols⁽¹⁷⁾ based on three USDA databases⁽¹⁸⁻²⁰⁾ and the Phenol-Explorer database⁽²¹⁾. TDP intake was calculated as the sum of flavonoids (anthocyanidins, flavonols, flavanones, flavones, flavanols and isoflavones), phenolic acids, lignans, stilbenes and other polyphenols expressed as aglycone equivalents (mg/d)⁽²¹⁾.

Short Physical Performance Battery (SPPB)

Physical performance was assessed at baseline and at nine-year follow-up using the SPPB, which comprises three different tests⁽⁴⁾: 4-metre walking speed, ability to rise from a chair, and standing balance in progressively more challenging positions. Each test has a score ranging from 0 to 4, with a value of 0 indicating inability to complete the test and 4 being the highest level of performance⁽¹⁾. The final score, which is the sum of the score in each of the three tests, ranges from 0 (worst performance) to 12 (best performance). A substantial decline in physical performance was defined as a decrease of three or more points in the SPPB score^(22, 23) over the nine years of follow-up.

Baseline covariates

Smoking status was self-reported and participants were classified as “current smokers” and “non-smokers” (including former and never smokers). Anthropometric measures were taken by trained personnel and body mass index (BMI) was calculated as weight/height² (kg/m²). Educational level was recorded as the number of years of schooling. Physical activity in the previous year was self-reported and classified as⁽²⁴⁾: 1) sedentary (completely inactive or light-intensity physical activity, i.e., walking), 2) light (light-intensity physical activity for 2 to 4 h/wk), and 3) moderate to intense (light-intensity physical activity of at least >4 h/wk or moderate-intensity physical activity of at least 1–2 h/wk). Dietary intakes of total energy (kcal/d) and alcohol (g/d) were estimated using an Italian food composition table⁽²⁵⁾. Medications were coded according to the Anatomical Therapeutic Chemical Codes⁽²⁶⁾. Diseases were ascertained by information from self-reported physician diagnoses, pharmacological treatments, medical history, clinical examinations and blood

tests. Renal function was classified as normal renal function (≥ 60 mL/min) and impaired renal function (< 60 mL/min) using the Cockcroft-Gault formula⁽²⁷⁾: $(140 - \text{Age}) \times \text{Weight} \times [0.85 \text{ if female}] / (72 \times \text{Serum Creatinine})$. Cognitive function was assessed by the Mini-Mental State Examination (MMSE). Participants with a MMSE score < 24 were considered to be cognitively impaired⁽²⁸⁾. Depressive symptoms were assessed using the Center for Epidemiological Studies Depression Scale (CES-D). A score of ≥ 20 was used to identify clinically relevant depressive symptoms⁽²⁹⁾. Functional status was evaluated using the Katz's Activities of Daily Living (ADL) (0-6)⁽³⁰⁾, and the Lawton and Brody for the Instrumental Activities of Daily Living (IADL) (0-8) scales⁽³¹⁾.

Statistical analysis

Descriptive analyses were conducted to provide information on baseline characteristics of the study population. Comparisons were calculated using age-adjusted generalized linear models. We analysed the associations between TUP and TDP and physical performance decline using two different statistical approaches: 1) Associations between TDP and TUP and substantial decline in physical performance over nine years of follow-up (difference \geq three points in SPPB score between nine-year follow-up and baseline, dichotomous variable) were analysed using logistic regression models. 2) Associations between TDP and TUP and decline in SPPB score (continuous variable) over nine years of follow-up were estimated using multivariable linear regression models. TUPs and TDPs were categorized as tertiles according to the following cut-off: 133 and 185 mg GAE/d, and 494 and 640 mg/d, respectively. Tests for linear trend were performed by considering the median of each tertile as an ordinal variable. TUP and TDP were analysed after a \log_2 transformation, since they were not normally distributed. Covariates in these statistical models were identified a priori as known risk factors or potential confounders and were included at the same time. Three separate statistical models were performed: model 1, adjusted for age and gender; model 2, additionally adjusted for baseline SPPB score (in order to correct for the "regression toward the mean"); and model 3, further adjusted for education, physical activity, current smoking, BMI, number of medications, energy and alcohol intakes, renal impairment, diabetes, hypertension, stroke, cognitive impairment and depressed mood. Interactions with gender, age, BMI, smoking status, physical activity, cognitive impairment and depressed mood were tested between TUP and TDP levels and SPPB score by including product terms in the fully adjusted model. There was no evidence of collinearity. In the sensitivity analysis, we excluded participants if they had an extreme energy intake (participant in the top or the bottom 1% of the distribution of the reported total energy intake) in models for TDP. In a second sensitivity analysis, participants with an extreme change in SPPB score, considered as a change of ≥ 9 points in the SPPB score over the 9 years of follow-up, were excluded in TUP and TDP models. All analyses were performed using the SPSS package program version 20.0 (SPSS, Chicago, IL). Two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Table 1 provides the baseline characteristics of the population sample according to tertiles of TUP and TDP, adjusted for age. The mean (SD) age of the participants was 71.3 (4.8) years and 54.1% were female. From the highest to the lowest tertiles of TUP, participants were likely to be older, took fewer medications and had lower BMI. Moreover, from the highest to the lowest tertiles of TDP, participants were likely to be older and women, less sedentary, had lower alcohol and energy intake, and had a higher prevalence of stroke and disability in more than one IADL. The change in SPPB score over the nine-year follow-up ranged from -12 to 4, with a mean (SD) change of -1.9 (3.1). Two hundred and thirteen (57.9%) participants suffered a decline in SPPB score, of whom 71 (19.3%) experienced a substantial decline in physical performance (a decrease of three or more points in the SPPB score). Participants with substantial physical performance decline over the 9-years of follow-up were older and more likely to be women, had a lower physical activity, daily alcohol intake, total urinary polyphenols and had a higher prevalence of depressed mood and cognitive impairment than those without a substantial physical performance decline (**Supplementary table 1**). Participants not included in the current study (n=787) were significantly older, more likely to be disabled, had poorer cognitive function, lower physical activity and higher depressed mood (all $P < 0.05$) than those included in the study.

The Spearman correlation between TUP and TDP at baseline was 0.140 ($P < 0.001$). The median (IQR) of TDP intake decreased during the follow-up being 556 (462-682), 539 (429-656), 513 (415-619) and 500 (407-595) mg/day, at baseline, three-, six-, and nine-year follow-up visits, respectively. The Spearman correlations of TDP intake at baseline with TDP at three-, six-, and nine-year follow-up visits were 0.50 ($P < 0.001$), 0.41 ($P < 0.001$), and 0.35 ($P < 0.001$), respectively. The difference in the intake of TDP was mainly due to a decrease in the consumption of fruits (279mg/d at baseline and 189mg/d after 9-y of follow-up) and vegetables (187g/d at baseline and 143g/d after 9-y of follow-up); while the intakes of total energy and macronutrients were stable along the 9 years of follow-up.

The association between TUP and TDP concentrations and substantial decline in physical performance over the nine-year follow-up is shown in **Table 2**. In logistic regression models adjusted for age and gender, participants in the highest tertile of TUP had a significant lower risk of substantial decline in physical performance than those in the lowest tertile (OR = 0.38; 95% CI = 0.18–0.80; P trend = 0.011). This association remained statistically significant after the adjustment for baseline SPPB score (OR = 0.38; 95% CI = 0.18–0.80; P trend = 0.011) and potential confounders (OR = 0.40; 95% CI = 0.17–0.93; P trend = 0.033). No association between TDP intake and substantial decline in physical performance was observed.

The associations between TDP and TUP concentrations and the decline in SPPB score at nine years of follow-up are presented in **Table 3**. In general linear models adjusted for age and gender, participants in the highest TUP tertile were associated with a significant lower decline of physical performance [mean difference (95% CI) comparing extreme tertiles, 0.99 (0.25–1.73), P trend = 0.008]. Further adjustment for baseline score and potential confounding factors did not change considerably the risk estimates [mean difference (95% CI) comparing extreme tertiles, 0.97 (0.23–1.70), P trend = 0.009] and [mean difference (95% CI) comparing extreme tertiles, 0.98 (0.23–1.73), P trend = 0.009], respectively. No association between TDP intake and decline in SPPB score was found.

We did not observe any statistically significant interactions between TUP and TDP concentrations and physical performance, using either of the two approaches, by gender, age, BMI, smoking status, physical activity and depressed mood interactions (all *P* values > 0.05).

Sensitivity analyses were performed by repeating the models after the exclusion of participants in the top or bottom 1% of the distribution of total energy intake for TDP (n=8). The associations between TDP intake and physical performance decline were non-significant and almost identical to results based on the whole population (data not shown). After the exclusion of 25 participants with extreme changes in SPPB score, the association between TUP and decline in physical performance was attenuated but still statistically significant (OR for log₂ = 0.49; 95% CI = 0.07-0.90).

DISCUSSION

This prospective study shows that older people with high TUP concentrations, a nutritional biomarker of polyphenol exposure⁽¹³⁾, had a lower risk of substantial decline in physical performance over a nine-year follow-up. In addition, high TUP concentrations were significantly associated with a lower physical performance decline. These results were clinically relevant since the difference in SPPB score was almost 1 point comparing participants in the extreme TUP tertiles⁽³²⁻³³⁾. No association was found with TDP, analogously to what was observed in our previous InCHIANTI studies regarding all-cause mortality⁽¹⁷⁾, substantial cognitive decline⁽³⁴⁾, and frailty syndrome⁽³⁵⁾. These differences in the results between TUP and TDP could be due to bioavailability and interactions of polyphenols with other compounds, such as caffeine⁽³⁶⁾. Thus, TUP measurement takes into account polyphenol bioavailability that highly varies between and within subjects⁽³⁷⁾.

Greater adherence to the Mediterranean diet was associated with a lower decline in body mobility over time and a lower risk of developing mobility disability in community-living older adults⁽⁹⁾. Mediterranean diet is associated with an adequate intake of certain nutrients with antioxidant capacity (such as vitamins and polyphenols), which has been related to a reduced risk of physical performance impairment in older subjects⁽⁷⁾. Several epidemiological studies have suggested protective associations between polyphenols and some age-related chronic diseases, and even total mortality^(17, 34-35, 38-42). These beneficial activities, which may be attributable to their ability to modulate oxidative stress and subsequent inflammation⁽⁴³⁻⁴⁴⁾, can translate in a protective effect against the development of physical performance decline. However, to date limited data exists on the potential effects of total polyphenol intake on skeletal muscle. Sarcopenia, a degenerative loss of skeletal muscle mass and strength associated with aging, is a major determinant of physical performance decline⁽⁴⁵⁾. A recent study has demonstrated that polyphenols are able to totally restore muscle maximal mitochondrial oxidative capacity, and decrease skeletal muscle ROS (reactive oxygen species) production in association with an enhancement of antioxidant defence in aging animals⁽⁴⁶⁾. Some polyphenols such as resveratrol also activate SIRT1 (sirtuin 1), leading to modulation of muscle gene expression and improving mitochondrial function⁽⁴⁷⁾.

Major strengths of this study included its prospective design and the selection of the participants among community-living older men and women. Another major strength was the measure of a validated biomarker, TUP concentrations in 24-h urine samples, to assess polyphenol exposure⁽¹³⁾. A further advantage was the use of a standardized and objective assessment test (the SPPB) to evaluate decline in physical performance. Finally, our models

were constructed taking into account potentially confounding variables of physical performance decline and polyphenol exposure; however, possible residual confounding cannot be excluded.

The present study also has some limitations. First, the number of subjects who suffered a substantial decline in physical performance was relatively small. However, this is the first prospective cohort study, with a reasonable sample size, to investigate the relationship between polyphenol exposure (TUP and TDP) and physical performance decline. Second, TUP was measured only once at baseline. Although there was a decrease in the polyphenol intake during the follow-up as in other studies with aging⁽⁴⁸⁾, we were interested in the long-term predicting ability of polyphenol exposure in the physical performance decline. Third, the TDP intake may be underestimated, although the dietary intake was assessed using a validated country-specific FFQ⁽¹⁶⁾ and a comprehensive database on polyphenols^(17, 34-35).

In conclusion, the current longitudinal study shows that higher concentrations of TUP, a nutritional biomarker of polyphenol-rich exposure, were associated with a lower risk of substantial decline in physical performance in older subjects living in a community. A polyphenol-rich diet seems to play an important preventive role against physical performance decline, and therefore in the delay of the onset of disability.

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AUTHOR CONTRIBUTIONS

The authors' contributions to the manuscript were as follows: CA-L, LF, SB, and AC designed the research; MR, RZ-R, CA-L and AC conducted the research; MR, CA-L and MU-S performed the samples analyses; MR and RZ-R conducted the statistical analysis; MR wrote the manuscript; RZ-R, AC, CA-L, MU-S, LF and SB provided critical revision, and CA-L and AC had primary responsibility for the final content. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

None of the authors had any financial or personal conflicts of interest.

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Table 1: Characteristics of the study participants 65 years or older at baseline according to tertiles of TUP and TDP

Characteristic	TDP					TUP			
	All	Tertile 1	Tertile 2	Tertile 3	<i>P</i> [†]	Tertile 1	Tertile 2	Tertile 3	<i>P</i> [*]
n (% of study population)	368 (100)	122 (33.2)	123 (33.4)	123 (33.4)		122 (33.2)	123 (33.4)	123 (33.4)	
Age, mean (SD), years	71.3 (4.8)	72.1 (5.6)	70.9 (4.2)	70.8 (4.6)	0.028	71.9 (4.9)	71.8 (5.5)	70.1 (3.8)	0.006
Female gender, n (%)	199 (54.1)	81 (66.4)	69 (56.1)	49 (39.8)	<0.001	69 (56.6)	67 (54.5)	63 (51.2)	0.55
BMI, mean (SD), kg/m ²	27.6 (3.7)	27.2 (4.1)	27.9 (3.7)	27.6 (3.4)	0.60	26.8 (3.7)	27.8 (3.7)	28.2 (3.7)	0.008
Education, mean (SD), years	6.2 (3.6)	5.8 (3.3)	6.4 (3.6)	6.5 (3.8)	0.20	6.1 (3.5)	6.3 (3.9)	6.2 (3.3)	0.85
Physical activity, n (%)					0.010				0.71
Sedentary	27 (7.4)	14 (11.5)	9 (7.3)	4 (3.3)		10 (8.2)	10 (8.3)	7 (5.7)	
Light	174 (47.5)	63 (51.6)	59 (48.0)	52 (43.0)		61 (50.0)	56 (46.3)	57 (46.3)	
Moderate to high	165 (45.1)	45 (36.9)	55 (44.7)	65 (53.7)		51 (41.8)	55 (45.5)	59 (48.0)	
Current smoker, n (%)	48 (13.0)	13 (10.7)	17 (13.8)	18 (14.6)	0.44	14 (11.5)	16 (13.0)	18 (14.6)	0.59
Number of medications, mean (SD)	2.0 (1.8)	2.2 (1.9)	1.9 (1.8)	1.9 (1.8)	0.43	1.5 (1.4)	2.2 (1.9)	2.2 (2.0)	<0.001
Daily total energy intake, mean (SD), kcal/d	1972 (577)	1654.0 (441.8)	1936.6 (470.1)	2321.2 (600.5)	<0.001	1922 (539)	1974 (618)	2018 (571)	0.44
Alcohol intake, mean (SD), g/d	16.5 (23.4)	10.2 (14.8)	16.0 (21.7)	23.1 (29.6)	<0.001	16.8 (24.7)	15.4 (24.2)	17.3 (21.4)	0.96
TUP, mg GAE/d	161 (122-203)	146 (115-190)	166 (120-209)	163 (129-212)	0.024	107 (87-122)	160 (145-171)	223 (202-251)	<0.001
TDP, mg/d	556 (462-683)	418 (328-462)	555 (521-597)	762 (683-823)	<0.001	529 (462-662)	533 (445-690)	592 (486-698)	0.73
Renal impairment, n (%)	200 (54.3)	72 (59.0)	66 (53.7)	62 (50.4)	0.52	77 (63.1)	63 (51.2)	60 (48.8)	0.19
Stroke, n (%)	12 (3.3)	7 (5.7)	4 (3.3)	1 (0.8)	0.035	3 (2.5)	3 (2.4)	6 (4.9)	0.27
Hypertension, n (%)	173 (47.0)	60 (49.2)	58 (47.2)	55 (44.7)	0.63	61 (50.0)	58 (47.2)	54 (43.9)	0.51

Diabetes Mellitus, n (%)	48 (13.0)	17 (13.9)	17 (13.8)	14 (11.4)	0.57	11 (9.0)	16 (13.0)	21 (17.1)	0.05
Depressed mood, CES-D score \geq 20, n (%)	58 (15.8)	24 (19.7)	17 (13.8)	17 (13.8)	0.28	25 (20.5)	20 (16.3)	13 (10.6)	0.07
Cognitive impairment, MMSE score < 24, n (%)	55 (14.9)	24 (19.7)	12 (9.8)	19 (15.4)	0.77	21 (17.2)	19 (15.4)	15 (12.2)	0.96
ADL disability, n (%)	3 (0.8)	3 (2.5)	0 (0.0)	0 (0.0)	>0.99	1 (0.8)	2 (1.6)	0 (0.0)	0.51
IADL disability, n (%)	24 (6.5)	16 (13.1)	6 (4.9)	2 (1.6)	0.001	10 (8.2)	7 (5.7)	7 (5.7)	0.75
SPPB score, mean (SD)	11.2 (1.3)	11.2 (1.3)	11.1 (1.5)	11.2 (1.2)	0.51	11.0 (1.6)	11.3 (1.1)	11.3 (1.4)	0.27
Change in SPPB score, mean (SD)	-1.9 (3.1)	-2.3 (3.4)	-1.5 (2.9)	-1.9 (3.1)	0.81	-2.5 (3.5)	-2.2 (3.2)	-1.1 (2.3)	0.007
Substantial SPPB decline, n (%)	71 (19.3)	31 (25.4)	17 (13.8)	23 (18.7)	0.52	33 (27.0)	26 (21.1)	12 (9.8)	0.009

Abbreviations: TUP, total urinary polyphenols; GAE, gallic acid equivalents; TDP, total dietary polyphenols; BMI, body mass index; CES-D, center for epidemiologic studies depression scale; MMSE, Mini-Mental State Examination; ADL, activities of daily living; IADL, instrumental activities of daily living.

Generalized linear models were adjusted for age, except when age is the evaluated characteristic.

Table 2. Logistic regression models evaluating the association of total urinary and dietary polyphenols with substantial decline of physical performance

	TDP				TUP			
	Cut-off <i>mg/d</i>	<i>n</i>	OR (95% CI)	<i>P</i> -value	Cut-off <i>mg GAE/d</i>	<i>n</i>	OR (95% CI)	<i>P</i> -value
Model 1*								
Tertile 1	<494	31	1 (reference)		<133	33	1 (reference)	
Tertile 2	494-640	17	0.61 (0.30–1.23)	0.16	133-185	26	0.70 (0.37–1.32)	0.27
Tertile 3	>640	23	0.98 (0.50–1.94)	0.96	>185	12	0.38 (0.18–0.81)	0.012
<i>P</i> trend [†]			0.95				0.012	
Continuous (log ₂)		71	0.80 (0.43–1.47)	0.46		71	0.52 (0.32–0.87)	0.012
Model 2[‡]								
Tertile 1	<494	31	1 (reference)		<133	33	1 (reference)	
Tertile 2	494-640	17	0.61 (0.30–1.24)	0.18	133-185	26	0.69 (0.36–1.31)	0.26
Tertile 3	>640	23	0.99 (0.50–1.95)	0.97	>185	12	0.38 (0.18–0.80)	0.011
<i>P</i> trend [†]			0.93				0.011	
Continuous (log ₂)		71	0.80 (0.43–1.48)	0.48		71	0.52 (0.32–0.87)	0.012
Model 3[§]								
Tertile 1	<494	31	1 (reference)		<133	33	1 (reference)	
Tertile 2	494-640	17	0.76 (0.36–1.64)	0.48	133-185	26	0.70 (0.34–1.42)	0.32
Tertile 3	>640	23	1.12 (0.49–2.55)	0.79	>185	12	0.40 (0.17–0.93)	0.034
<i>P</i> trend [†]			0.74				0.033	
Continuous (log ₂)		71	0.81 (0.38–1.71)	0.58		71	0.51 (0.29–0.90)	0.021

Abbreviations: TDP, total dietary polyphenols; TUP, total urinary polyphenols; OR, odds ratio; CI, confidence interval; GAE, gallic acid equivalents.

* Adjusted for age and gender.

[†] *P* trend obtained by assigning the median of each tertile as ordinal variable.

[‡] Adjusted for age, gender and baseline SPPB score.

§Fully adjusted for age, gender, baseline SPPB score, education, physical activity, current smoking, BMI, number of medications, energy and alcohol intakes, renal impairment, diabetes, hypertension, stroke, cognitive impairment and depressed mood.

Table 3. Multivariable linear regression models testing the association between TUP and TDP and change in physical performance over nine years of follow-up

	TDP			TUP		
	Cut-off <i>mg/d</i>	Mean difference (95% CI)	<i>P</i> -value	Cut-off <i>mg GAE/d</i>	Mean difference (95% CI)	<i>P</i> -value
Model 1*						
Lowest tertile	<494	1 (reference)		<133	1 (reference)	
Intermediate tertile	494-640	0.47 (-0.26–1.21)	0.21	133-185	0.29 (-0.44–1.02)	0.44
Highest tertile	>640	-0.05 (-0.80–0.71)	0.90	>185	0.99 (0.25–1.73)	0.009
<i>P</i> trend [†]		0.76			0.008	
Continuous (log ₂) [‡]		0.35 (-0.29–0.99)	0.28		0.70 (0.15–1.24)	0.012
Model 2[§]						
Lowest tertile	<494	1 (reference)		<133	1 (reference)	
Intermediate tertile	494-640	0.51 (-0.23–1.24)	0.18	133-185	0.27 (-0.46–1.00)	0.47
Highest tertile	>640	-0.04 (-0.80–0.71)	0.91	>185	0.97 (0.23–1.70)	0.010
<i>P</i> trend [†]		0.76			0.009	
Continuous (log ₂) [‡]		0.37 (-0.26–1.01)	0.26		0.70 (0.15–1.24)	0.012
Model 3						
Lowest tertile	<494	1 (reference)		<133	1 (reference)	

Intermediate tertile	494-640	0.32 (-0.42–1.06)	0.40	133-185	0.29 (-0.44–1.03)	0.43
Highest tertile	>640	-0.20 (-1.03–0.62)	0.63	>185	0.98 (0.23–1.73)	0.010
<i>P</i> trend [†]		0.54			0.009	
Continuous (log ₂) [‡]		0.41 (-0.32–1.13)	0.27		0.74 (0.19–1.30)	0.009

Abbreviations: TDP, total dietary polyphenols; TUP, total urinary polyphenols; CI, confidence interval; GAE, gallic acid equivalents.

* Adjusted for age and gender.

[†] *P* trend obtained by assigning the median of each tertile as ordinal variable.

[‡] Non-standardized regression coefficient (95% CI).

[§] Adjusted for age, gender and baseline SPPB score.

[¶] Fully adjusted for age, gender, baseline SPPB score, education, physical activity, current smoking, BMI, number of medications, daily energy and alcohol intakes, renal impairment, diabetes, hypertension, stroke, cognitive impairment and depressed mood.

Supplementary table 1. Baseline characteristics of the study participants according to presence or absence of substantial physical performance decline over 9 years of follow-up.

Characteristic [*]	No substantial physical performance decline (n=297)	Substantial physical performance decline (n=71)	P-value [†]
Age, years	70.4 (4.3)	74.8 (5.3)	<0.001
Female gender	151 (50.8)	48 (67.6)	0.043
BMI, kg/m ²	27.8 (3.6)	26.7 (4.0)	0.11
Education, years	6.4 (3.5)	5.4 (3.5)	0.3
Physical activity			0.012
Sedentary	17 (5.8)	10 (14.1)	
Light	133 (45.1)	41 (57.7)	
Moderate to high	145 (49.2)	20 (28.2)	
Current smoker	40 (13.5)	8 (11.3)	0.88
Number of medications	1.9 (1.8)	2.5 (2.0)	0.48
Daily caloric intake, kcal/d	2004.2 (592.5)	1834.3 (485.5)	0.3
Alcohol intake, g/d	18.3 (24.9)	8.9 (13.4)	0.005
TUP, mg GAE/d	165 (127-208)	135 (108-166)	0.013
TDP, mg/d	557 (465-688)	529 (455-669)	0.26
Renal impairment	148 (49.8)	52 (73.2)	0.15
Stroke	9 (3.0)	3 (4.2)	0.65
Hypertension	131 (44.1)	42 (59.2)	0.08
Diabetes Mellitus	37 (12.5)	11 (15.5)	0.61
Depressed mood, CES-D score \geq 20	38 (12.8)	20 (28.2)	0.015
Cognitive impairment, MMSE score < 24	29 (9.8)	26 (36.6)	0.001
Number of ADL disabilities	1 (0.3)	2 (2.8)	0.08
Number of IADL disabilities	14 (4.7)	10 (14.1)	0.12

^{*}Variables reported as means (SD), percentages or median (IQR) as appropriate.

[†]Generalized linear models were adjusted for age, except when age is the evaluated characteristic.