

## Original Contribution

### Flavonoid Intake and Cognitive Decline over a 10-Year Period

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In the PAQUID (Personnes Agées Quid) study, the authors prospectively examined flavonoid intake in relation to cognitive function and decline among subjects aged 65 years or older. A total of 1,640 subjects free from dementia at baseline in 1990 and with reliable dietary assessment were reexamined four times over a 10-year period. Cognitive functioning was assessed through three psychometric tests (Mini-Mental State Examination, Benton's Visual Retention Test, "Isaacs" Set Test) at each visit. Information on flavonoid intake was collected at baseline. A linear mixed model was used to analyze the evolution of cognitive performance according to quartiles of flavonoid intake. After adjustment for age, sex, and educational level, flavonoid intake was associated with better cognitive performance at baseline ( $p = 0.019$ ) and with a better evolution of the performance over time ( $p = 0.046$ ). Subjects included in the two highest quartiles of flavonoid intake had better cognitive evolution than did subjects in the lowest quartile. After 10 years' follow-up, subjects with the lowest flavonoid intake had lost on average 2.1 points on the Mini-Mental State Examination, whereas subjects with the highest quartile had lost 1.2 points. This gradient persisted after adjustment for several other potential confounders. This study raises the possibility that dietary flavonoid intake is associated with better cognitive evolution.

antioxidants; cognition; flavonoids; nutrition assessment

Abbreviations: BVRT, Benton's Visual Retention Test; IST, "Isaacs" Set Test; MMSE, Mini-Mental State Examination; SD, standard deviation.

The most frequent cause of dementia is Alzheimer's disease, an irreversible condition with our present state of knowledge (1). It is therefore necessary to identify protective factors on which we could act to postpone the onset of dementia. The role of nutrition in dementia and Alzheimer's disease is a promising area of research (2), with particular interest in the role of antioxidants (3). The brain is particularly susceptible to oxidative stress because of, on one hand, its high content in easily peroxidizable long-chain polyunsaturated fatty acids, in particular docosahexaenoic acid, and, on the other hand, the high level of in-site production of free radicals. In Alzheimer's disease patients, the accumulation of  $\beta$ -amyloid protein is associated with

increased free radical production and increased lipoperoxidation (3).

Several studies have investigated the relation among antioxidants, cognitive decline, and dementia. Most studies analyzed the risk of Alzheimer's disease. Results from prospective observational studies relating intake of antioxidants, vitamins, and Alzheimer's disease are conflicting (refer to the review by Luchsinger and Mayeux (2)). For instance, in the Washington Heights-Inwood Columbia Aging Project (4), no relation between antioxidants and incident Alzheimer's disease was found. Engelhart et al. (5) found that dietary intake of vitamins C and E, but not supplement intake, was associated with a lower risk of Alzheimer's

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disease. In addition, high intake of  $\beta$ -carotene and flavonoids was associated with reduced risk of Alzheimer's disease in smokers. Commenges et al. (6) found that higher dietary flavonoid intake was related to lower risk of Alzheimer's disease.

The association between antioxidant and cognitive decline was less frequently studied. Morris et al. (7) found that vitamin E was inversely related to cognitive decline measured by several psychometric tests. In a sample of 342 men, Kalmijn et al. (8) found no association between intake of vitamins C/E and the risk of cognitive decline but observed a nonsignificant inverse association between flavonoid intake and risk of cognitive decline. Flavonoids are powerful antioxidant molecules (9). They are found mainly in fruits, vegetables, tea, and red wine. However, the association between flavonoid intake and cognitive impairment was rarely studied in humans. To our knowledge, no epidemiologic study analyzed the risk of cognitive decline as a function of overall dietary flavonoid intake in older persons. We investigated this association in a prospective cohort study over a 10-year period.

## MATERIALS AND METHODS

### Study design and sample

The data come from the PAQUID (Personnes Agées Quid: "what about older persons") study on functional and cerebral aging (10). This prospective epidemiologic study included at baseline 3,777 community dwellers aged 65 years or older. Participants were randomly recruited from electoral rolls, and selection was stratified by sex, age, and size of the urban unit throughout Gironde and Dordogne, two administrative areas of southwest France. Subjects who agreed to participate in the study gave their informed consent. The study was approved by the Ethics Committee of the University Hospital of Bordeaux (France). The initial participation rate was 68 percent, and the sample was representative of the age-sex distribution of the elderly community dwellers of the area (11).

The participants were visited at home by a psychologist for the baseline interview in 1988–1989. A set of psychometric tests was administered, including an evaluation of global mental status by the Mini-Mental State Examination (MMSE) (12), visual memory by Benton's Visual Retention Test (BVRT) (13), verbal fluency by the test known as "Isaacs" Set Test (IST) (14), visuospatial attention by Zazzo's cancellation test (15), and simple logical reasoning and attention by Wechsler's Digit Symbol Test (16). Subjects suspected of dementia according to the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised (DSM-III-R) (17), were visited by a neurologist to document the diagnosis of dementia and to ascertain its etiology following the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association) criteria (18) for Alzheimer's disease and the "Hachinski score" (19) for vascular dementia. The participants were interviewed in the same manner 1 (in Gironde only), 3, 5, 8, 10, and 13 years after baseline assessment. At each

follow-up, the cognitive evaluation was similar to that conducted at baseline (i.e., including the same psychometric tests and diagnosis of dementia with a two-step procedure). At the 3-year follow-up, a food frequency questionnaire was proposed to 1,795 participants. The subjects were asked to report the usual frequency of consumption of a selected number of foods, which included citrus fruits, kiwis, other fruits, dried fruits, cabbage, spinach, French beans, asparagus, sweet pepper, oats flakes, chocolate, tea, coffee, soup, and fruit juice. These subjects were participants from Gironde ( $n = 1,626$ ) who agreed to participate in this follow-up (of the 2,792 participants of Gironde, 58 percent agreed to participate in this follow-up, 30 percent refused or had moved, and 12 percent were dead) and a subsample of subjects from Dordogne ( $n = 169$ ). In this subsample of 169 subjects, a dietary survey (3-day food record and dietary history) was administered. With this subsample, we were able to collect precise food quantity intakes that were used to impute intakes from the food frequency questionnaire. By use of the quantities of food recorded during the dietary survey, quantitative values of each food were imputed for the categories recorded in the food frequency questionnaire (refer to Commenges et al. (6) for a detailed description of the method). We then estimated the total flavonoid intake for the 1,795 subjects using the composition tables of Hertog et al. (20). In this composition table, five major flavonoids were described: quercetin, kaempferol, myricetin, luteolin, and apigenin. Once the quantities of each food were determined, the quantities of flavonoids were computed. We considered four categories of flavonoid intake based on the quartiles of the distribution. As flavonoid intake was collected only at the 3-year follow-up, the evolution of cognitive performance was analyzed over a 10-year period between the 3-year (considered as the baseline visit) and the 13-year follow-ups. The study sample was composed of 1,640 nondemented participants (78 prevalent cases of dementia excluded) for whom nutritional data were available at the 3-year visit and who completed at least one psychometric test at one of the visits (77 subjects with insufficient data on the psychometric tests excluded).

### Statistical analysis

Univariate associations between flavonoid intake and explanatory variables were tested with the chi-square test or analysis of variance when appropriate. We then used linear mixed models (21) to estimate the prediction of flavonoid intake on the baseline MMSE score and the annual rate of change in MMSE score. The model makes use of individual trajectories of MMSE scores over time to simultaneously estimate the effects of variables on the initial level of MMSE score and the change in score while taking into account the correlation among repeated measures of the score. As the distribution of MMSE scores was not normal, we analyzed the square root of the number of errors, as proposed by Jacqmin-Gadda et al. (22). Indeed, these authors stated that, after transformation, graphical examination of residuals indicated that the hypotheses of normality and homoscedasticity were acceptable. Therefore, we chose to apply the same transformation to our data. Because this

**TABLE 1. Baseline characteristics of the sample according to flavonoid intake, PAQUID\* study (*n* = 1,640), France, 1991–2001**

	Flavonoid quartile (mg/day)								<i>p</i> value
	0–10.39		10.40–13.59		13.60–17.69		17.70–36.94		
	No.	%	No.	%	No.	%	No.	%	
Sex (men)	128	31.2	147	35.8	223	54.4	194	47.3	<0.0001
Low educational level	167	40.7	105	25.6	83	20.2	60	14.6	<0.0001
Smoking status									<0.0001
Smokers	32	7.8	32	7.8	47	11.5	49	11.9	
Former smokers	87	21.2	97	23.7	140	34.1	127	31.0	
Never smokers	291	71.0	281	68.5	223	54.4	234	57.1	
	0–10.39		10.40–13.59		13.60–17.69		17.70–36.94		
	Mean	SD*	Mean	SD	Mean	SD	Mean	SD	
Age (years)	77.74	6.55	76.55	6.41	76.73	6.17	76.92	5.84	<0.036
Body mass index (kg/m <sup>2</sup> )	24.48	4.01	24.83	3.85	24.73	3.89	24.74	3.81	0.60
Fruits (g/day)	175.2	108.2	286.9	106.0	333.7	111.4	348.8	148.9	<0.0001
Vegetables (g/day)	187.6	112.1	241.8	109.3	259.6	123.9	280.7	144.5	<0.0001
Mini-Mental State (score)	26.54	2.71	27.01	2.45	27.33	2.26	27.53	2.11	<0.0001
“Isaacs” Set Test (score)	27.84	5.94	28.85	6.21	29.31	5.83	29.76	5.44	<0.0001
Benton’s Visual Retention Test (score)	10.71	2.58	11.12	2.32	11.26	2.39	11.38	2.18	<0.0007

\* PAQUID, Personnes Agées Quid; SD, standard deviation.

transformation is not linear, a formula given by Jacqmin-Gadda et al. (22) was used to compute the MMSE expectation. The adjusted model included terms for flavonoid intake; age at baseline (65–69, 70–74, 75–79, ≥80 years); sex; education (subjects achieving at least the Certificat d’Etudes Primaires, i.e., the first French diploma after primary school, vs. the less educated (23)); time (time in years since the baseline visit); and interaction terms between time and each covariate. The parameters for time interactions represent the estimated effect of the covariate on the annual rate of change since baseline. Each estimated parameter significance was tested by Wald’s test (coefficient/standard error(coefficient)). Log-likelihood ratio tests were performed for tests for trend.

Several potential confounders were considered in the analyses. Because energy intake was not available in our database, body mass index was chosen as a proxy variable. Body mass index was considered in four categories (<21, 21–26, 27–30, >30) as described by Larrieu et al. (24), with the category 21–26 kg/m<sup>2</sup> being the referent category. Smoking status was also included (smokers or former smokers vs. never smokers). As dietary data include many correlated variables, it is very difficult to identify the effect of specific nutrients. An attempt to solve this problem was to control for the quantity of fruits and vegetables consumed per day. We estimated the specific effect of flavonoids, independently of the other nutrients found in fruits and vegetables.

As several cognitive tests were administered to the subjects, we aimed at exploring the influence of flavonoid intake on a global measure of cognitive function using a nonlinear model for multivariate longitudinal data (25). In this approach, the dependent variable is an unobserved latent pro-

cess that can be viewed as the actual cognitive performance of each subject. The cognitive tests are measures with errors of a nonlinear transformation of this common underlying process. In this model, normality of cognitive tests is not required, since the link function between the tests and the latent process is estimated. Therefore, the psychometric scores are included in their original scale. Interpretation of the results is similar to that of linear mixed models. We introduced the same explanatory variables and their interactions with time to assess the effects of covariates on the baseline latent cognitive performance and on the evolution of the latent cognitive performance. We used three cognitive tests (MMSE, BVRT, IST) in this analysis because the number of missing data was too large over time for the other tests.

## RESULTS

The general description of the 1,640 subjects according to flavonoid intake is given in table 1. The mean flavonoid intake was 14.33 (standard deviation (SD): 5.85) mg/day. The quartiles of flavonoid intake were 0–10.39, 10.40–13.59, 13.60–17.69, and 17.70–36.94 mg/day. Age was slightly higher in the first quartile. The proportion of men was greater among the two highest quartiles. The proportion of subjects with a low educational level decreased as flavonoid intake increased. The proportion of smokers was greater in the two highest quartiles of flavonoid intake than in the two lowest ones. Body mass index was not associated with flavonoid intake. As expected, the mean quantity of fruits or vegetables increased as flavonoid intake increased. The mean MMSE score at baseline was 27.1 (SD: 2.4) and

increased as flavonoid intake increased. The same pattern was observed for the other cognitive tests. The mean time of follow-up was 6.18 (SD: 3.6) years (minimum = 0, maximum = 10.54). The median number of visits was four (minimum = 1, maximum = 5, interquartile range = 2–5). The median number of MMSE evaluations by subject was four (minimum = 1, maximum = 5, interquartile range = 2–5); for the Benton and Isaacs tests, the median number was three (minimum = 0, maximum = 5, interquartile range = 2–5).

A linear mixed model was fitted to analyze the evolution of the square root of the number of errors to the MMSE over a 10-year period (table 2). After adjustment for age, sex, and education, flavonoid intake was significantly associated with the baseline score (model 1, flavonoid:  $p_{\text{trend}} = 0.019$ ). The three flavonoid parameters were negative, and this indicated that the number of errors at baseline tended to be lower as flavonoid intake increased. The time parameter ( $\beta = 0.0482$ ) showed an increase of the number of errors over time in the referent category (i.e., the first quartile of flavonoid intake). A gradient of change over time for the scores (model 1, flavonoid  $\times$  time:  $p_{\text{trend}} = 0.046$ ) was found, since the slopes of the number of errors decreased as flavonoid intake increased. Subjects in the two highest quartiles had a significantly better evolution than did subjects in the first quartile.

Further adjustments for body mass index, smoking, fruit intake, and vegetable intake are displayed in model 2 (table 2). No modification effect was observed for smoking status. Smoking was not associated with baseline cognitive performance or its evolution. At baseline, under- or overweight subjects tended to make more errors on the MMSE than did subjects in the 21–26 kg/m<sup>2</sup> category. No association of the evolution of the performance with body mass index was found. Fruit and vegetable intakes were not associated with cognitive performance. After controlling for these variables, we found it to be remarkable that the associations between cognitive performance and flavonoid intake were similar to those found in model 1. The flavonoid  $\times$  time coefficients were not confounded and increased substantially and fairly regularly for the second through fourth quartiles. At baseline in the referent group (men aged 65–70 years, high educational level, nonsmokers, normal body mass index, and average fruit (286.15 g/day) and vegetable (242.44 g/day) consumption), the predicted mean MMSE score ranged from 28.26 in the lowest quartile to 28.58 in the highest one. After 5 years of follow-up, it ranged from 27.44 to 28.14, and after 10 years, from 26.19 to 27.38. Therefore, over a 10-year period, the mean MMSE score changed by 2.1 points in subjects with the lowest flavonoid intake and changed by 1.2 points in subjects with the highest flavonoid intake. The mean evolutions of the MMSE score according to flavonoid intake are displayed in figure 1. It shows the general decrease of the scores over time but also the steeper slopes as flavonoid intake decreases.

In order to confirm these results with another approach, we used a model for multivariate longitudinal data to analyze the common factor underlying the psychometric tests (i.e., the global cognitive performance). MMSE, BVRT, and IST were introduced in their natural scale (table 3). After

adjustment for age, sex, and education, flavonoid intake markedly improved the model (test of baseline and change over time coefficients: chi-square = 22.6, 6 df;  $p < 0.001$ ). Baseline cognitive performance increased with flavonoid intake (flavonoid: chi-square = 12.6;  $p_{\text{trend}} < 0.005$ ). In this model, the greater the coefficient, the better was the latent cognitive performance. The latent cognitive performance at baseline increased from 0.00454 in the second quartile of intake to 0.0216 in the highest quartile. The evolution of cognitive performance also increased linearly as a function of flavonoid intake (flavonoid  $\times$  time: chi-square = 7.6;  $p_{\text{trend}} = 0.06$ ); the greater the coefficient, the higher was the performance. Subjects in the third and fourth quartiles performed significantly better over time than did subjects in the lowest quartile.

## DISCUSSION

We found that high intake of flavonoid from food is associated with a better cognitive functioning at baseline and also with a more favorable evolution of cognitive performance over a period of 10 years. These associations persisted after controlling baseline and longitudinal data for a number of potentially confounding variables, such as age, sex, education, body mass index, smoking status, and fruit and vegetable intakes.

Several methodological issues should be considered. First, although we adjusted for several potential confounding factors, the possibility of residual confounding cannot be completely excluded. We were not able to adjust for caloric intake that was not available. We chose to adjust for a proxy variable (body mass index with four categories), and no confounding effect was observed. Body mass index is a very remote indicator of caloric intake, but it has been linked to the risk of developing dementia (26) and should be considered as a potential confounder. Dietary data include many correlated variables, and it is very difficult to identify the effect of specific nutrients. We included the quantity of fruits and vegetables consumed as further adjustment. We thus estimated the specific effect of flavonoids, independently of the other nutrients found in fruits and vegetables. The magnitude of the effect of flavonoids was virtually unchanged in the fully adjusted model. A gradient of change over time of the cognitive performance with flavonoid quartiles was still found, and no confounding was detected in the fully adjusted model. We were not able to control for other nutrients, because they were not available in our database.

Second, even in longitudinal studies, one cannot exclude the possibility of changing dietary reporting or dietary habits because of cognitive impairment. To minimize this potential source of confounding, we excluded demented subjects at the moment dietary habits were recorded. In addition, the length of the follow-up (10 years) limits this potential confounding effect. Third, because dietary assessment was performed only once, it may not have precisely reflected the participant's long-term dietary habits. However, this may have led to dilution and thus to underestimating the association of flavonoid intake and cognitive performance, since it

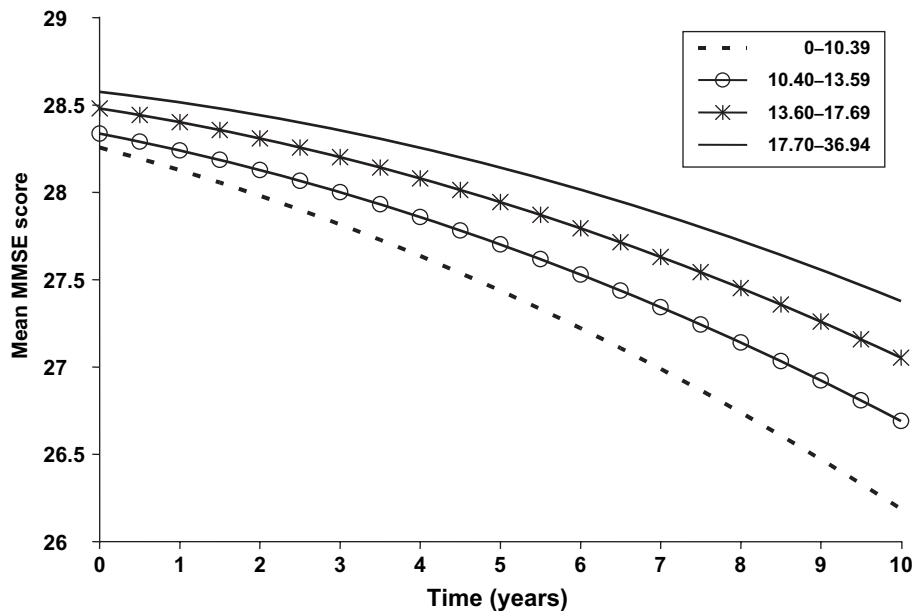
**TABLE 2. Linear mixed-model estimates of the square root of the number of errors to the Mini-Mental State Examination for several categories of flavonoid intake, PAQUID\* study ( $n = 1,617$ ), France, 1991–2001**

Variable	$\beta$ -coefficient	Standard error	Wald's test $p$ value	$P_{\text{trend}}$
<b>Model 1†</b>				
Intercept	1.154	0.0569	<0.0001	
Time	0.0482	0.0109	<0.0001	
Flavonoid (mg/day)				0.019
0–10.39 (quartile 1)	Referent			
10.40–13.59 (quartile 2)	–0.0181	0.0461	0.69	
13.60–17.69 (quartile 3)	–0.0903	0.0469	0.054	
17.70–36.94 (quartile 4)	–0.127	0.0470	0.0071	
Flavonoid $\times$ time				0.046
Quartile 1 $\times$ time	Referent			
Quartile 2 $\times$ time	–0.0139	0.00943	0.14	
Quartile 3 $\times$ time	–0.0195	0.00974	0.045	
Quartile 4 $\times$ time	–0.0267	0.00964	0.0056	
<b>Model 2‡</b>				
Intercept	1.038	0.0699	<0.0001	
Time	0.0460	0.0138	0.0009	
Flavonoid (mg/day)				0.06
0–10.39 (quartile 1)	Referent			
10.40–13.59 (quartile 2)	–0.0369	0.0491	0.453	
13.60–17.69 (quartile 3)	–0.106	0.0527	0.045	
17.70–36.94 (quartile 4)	–0.153	0.0545	0.0049	
Flavonoid $\times$ time				0.24
Quartile 1 $\times$ time	Referent			
Quartile 2 $\times$ time	–0.0126	0.0102	0.21	
Quartile 3 $\times$ time	–0.0187	0.0110	0.089	
Quartile 4 $\times$ time	–0.0267	0.0114	0.019	
Fruits	0.0164	0.0139	0.24	
Fruits $\times$ time	–0.00217	0.00288	0.45	
Vegetables	0.0135	0.0134	0.31	
Vegetables $\times$ time	0.00452	0.00276	0.10	
Smoker	–0.0202	0.0419	0.63	
Smoker $\times$ time	0.0111	0.0086	0.20	
Body mass index (kg/m <sup>2</sup> )				0.13
<21	0.172	0.0468	0.0002	
27–30	0.0845	0.0454	0.062	
>30	0.109	0.0579	0.059	
Body mass index $\times$ time				0.61
<21 $\times$ time	–0.00503	0.00997	0.61	
27–30 $\times$ time	–0.0123	0.00937	0.19	
>30 $\times$ time	–0.00332	0.0122	0.78	

\* PAQUID, Personnes Agées Quid.

† Model 1 adjusted for age, sex, education, and their interactions with time ( $n = 1,640$ ).

‡ Model 2 adjusted for age, sex, education, tobacco use, body mass index, and their interactions with time.



**FIGURE 1.** Evolution of the mean MMSE score for persons in quartiles 1–4 of flavonoid intake estimated with a linear mixed model, PAQUID study, France, 1991–2001. Examples for men aged 65–70 years at baseline, who had a high educational level, were nonsmokers, and had a normal body mass index and average fruit (286.15 g/day) and vegetable (242.44 g/day) consumption. MMSE, Mini-Mental State Examination; PAQUID, Personnes Agées Quid.

is expected that, with aging, dietary diversity diminishes and subjects classified in the highest quartiles at baseline tend to consume fewer quantities of flavonoid afterwards. The clas-

**TABLE 3.** Multivariate model estimates for several categories of flavonoid intake, PAQUID\* study ( $n = 1,640$ ), France, 1991–2001†,‡

Variable	Coefficient	Standard error	Wald's test $p$ value
Intercept	0.634	0.00974	<0.001
Time	–0.00945	0.00129	<0.001
Flavonoid (mg/day)			
0–10.39 (quartile 1)	Referent		
10.40–13.59 (quartile 2)	0.00454	0.00644	0.48
13.60–17.69 (quartile 3)	0.0131	0.00656	0.046
17.70–36.94 (quartile 4)	0.0216	0.00658	0.0010
Flavonoid by time			
Quartile 1 $\times$ time	Referent		
Quartile 2 $\times$ time	0.00195	0.00112	0.081
Quartile 3 $\times$ time	0.00242	0.00116	0.037
Quartile 4 $\times$ time	0.00296	0.00114	0.0097

\* PAQUID, Personnes Agées Quid.

† The global measure of cognitive function is measured through three cognitive tests: Mini-Mental State Examination, “Isaacs” Set Test, and Benton’s Visual Retention Test.

‡ Model adjusted for age, sex, education, and their interactions with time.

sification of subjects into quartiles was preferred to including directly the quantity of flavonoid intake because this estimate may not be accurate. Ranking subjects into quartiles minimized this aspect, especially because the influence of outlying data points was cancelled (27). Ranking flavonoid intake allowed us to show a dose-response relation. The coefficient estimates showed a gradient associated with cognitive performance. As flavonoid intake increased, cognitive performance at baseline and its evolution were better. The method used to estimate flavonoid intake might not be accurate. A subsample of subjects had a detailed dietary survey (3-day record) supervised by a dietician and a food frequency questionnaire. It enabled us to make a conversion of food frequencies into flavonoid quantities. The quantities estimated might not be accurate, but the ranking of flavonoid intake is respected. This procedure allowed performing such analyses at a lower cost, since only a subsample of the cohort needed a detailed questionnaire.

Finally, we used two approaches to explore the association between flavonoid intake and the evolution of cognitive performance. The first approach was a linear mixed model that is commonly used to analyze longitudinal quantitative data. This model needs to handle normally distributed data, and we transformed the MMSE score into the square root of the number of errors to get closer to a normal distribution. The second approach has two advantages compared with the linear mixed model. The normality of the data is not required, and psychometric scores can be used in the natural scale. This approach allows combining into a single analysis several psychometric tests that are imperfect measures of a common process (i.e., cognitive performance). This

approach is supposed to be more powerful since it includes more information, but it is not in the present case since MMSE is already a global composite test that explores several aspects of cognition. Both approaches gave similar results, indicating that the observed association is not due to a given transformation of the data or to a possible misspecification of the model.

Few studies have analyzed the association between flavonoid intake and cognitive performance. Engelhart et al. (5) analyzed the effect of several antioxidants, including flavonoids, on the risk of developing Alzheimer's disease. They found a nonsignificant decreased risk of Alzheimer's disease as flavonoid intake increased, but they included flavonoid intake as a continuous variable, and the linearity of the relation was not ensured. They also showed an interaction between flavonoid intake and smoking status, with a higher reduction of the risk of Alzheimer's disease among current smokers. We did not find any confounding or effect modification by smoking in our analyses. Kalmijn et al. (8) analyzed the effect of flavonoid intake on the risk of cognitive decline in a sample of 342 men. Subjects classified in the medium or highest intake tertile showed a nonsignificant decreased risk of cognitive decline defined as a drop of more than two points in the MMSE over a 3-year period. The nonsignificant association is probably due to the small number of subjects included and the short period of follow-up of the sample.

In conclusion, we showed that higher intake of flavonoids from food may be associated with a better cognitive evolution over a 10-year period. Whether this reflects a causal association remains to be elucidated. Polyphenols and flavonoids have been linked to a lower risk of developing several pathologies, from cardiovascular diseases (reduction of mortality risk up to 65 percent) and cancers (inverse association between lignans and breast cancer risk) to asthma (inverse association between asthma and intake of flavonols, flavones, and flavanones) (28). We cannot exclude that the flavonoid intake measured in our study is a global marker of specific dietary habits that are more favorable for cognitive aging. Since flavonoids are found mainly in fruits and vegetables, subjects classified in the highest quartiles are likely to eat more fruits and vegetables that are known to be associated with a lower risk of several diseases, including cognitive decline (29). More cohort studies are needed to further investigate the relation between flavonoid intake and cognitive evolution, including other antioxidant molecules.

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