Pattern of polyphenol intake and the long-term risk of dementia in older persons

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Authors' Contributions

S. Lefèvre-Arbogast performed statistical analyses and drafted the manuscript. C. Samieri contributed to the -drafting of the manuscript and supervised the research project. L. Letenneur and J.-F. Dartigues participated in the design and the protocol of the 3C study. D. Gaudout, L. Letenneur, J.-F.Dartigues, C. Delcourt, and C. Samieri obtained funding. All authors critically reviewed the manuscript and approved the final version of the manuscript.

Disclosures

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ABSTRACT

Objective: To investigate the optimal combination of dietary polyphenols associated with the long-term risk of dementia in a large prospective French cohort of older persons, the Three-City (3C) Study.

Methods: We included 1,329 non-demented older adults from the 3C Study with assessment of intake of 26 polyphenol subclasses and followed for 12 years for dementia. Using Partial Least Square for Cox models, we identified a pattern of polyphenol intake associated with dementia risk.

Results: The pattern combined several flavonoids (dihydroflavonols, anthocyanins, isoflavonoids, flavanones), stilbenes (including resveratrol), lignans and other subclasses (hydroxybenzaldehydes, naphtoquinones, furanocoumarins). Compared with participants in the lower quintile of pattern score, those in the higher quintile had a 50% lower risk of dementia (95% CI 20%; 68%, p-trend <0.01) in multivariate models.

Conclusions: In this French cohort, a polyphenol pattern provided by a diet containing specific plant products (nuts, citrus, berries, leafy vegetables, soy, cereals, olive oil) accompanied with red wine and tea was associated with lower dementia risk.

Key words: Diet, Polyphenols, Flavonoids, Stilbenes, Aged, Dementia, Alzheimer's Disease, Epidemiology

INTRODUCTION

Polyphenols are a large family of phytochemical compounds (>500 species grouped into 5 large classes: flavonoids, phenolic acids, stilbenes, lignans and other polyphenols)[1] provided by various plant foods and beverages in the habitual diet. The cumulative intake of all dietary polyphenols may reach 1g/day, which is 10 to 100 times higher than the intake of most vitamins.[1]

Polyphenols may constitute very promising targets for the prevention of cognitive aging and Alzheimer's disease (AD). Some polyphenols (or their metabolites) can cross the blood brain barrier and may promote normal functioning and plasticity of the aging brain.[2,3] Moreover, some polyphenol species (e.g., resveratrol, a stilbene provided by grape products) appear to exert anti-amyloid properties.[4]

Epidemiological studies have reported associations of total flavonoids/polyphenols or of specific subclasses (e.g., anthocyanins) to: better memory;[5] reduced cognitive decline;[6,7] lower risk of dementia;[8] and higher odds of healthy aging.[9] However, inconsistent findings have also been found.[10–14] Cumulative exposures to multiple polyphenols, which may exert synergistic and/or complementary biological effects on the brain and may be more relevant than a single compound to prevent a disease with multiple pathological components such as AD,[15] have been unexplored in relation to the risk of dementia. We thus conducted an exploratory study to examine whether a pattern of polyphenol intake (based on a weighted combination of 26 flavonoid and non-flavonoid subclasses) would be associated with the risk of dementia and AD over 12 years in a large prospective French cohort of older persons, the Three-City (3C) Study.

METHODS

Study Population

The 3C study is a French population-based cohort on dementia that started in 1999-2000, including 9,294 non-institutionalized community dwellers aged 65 years or older from three French cities:[16] Bordeaux (n=2,104), Dijon (n=4,931) and Montpellier (n=2,259).

At recruitment, participants provided sociodemographic, lifestyle and medical information, neuropsychological testing and blood sampling during in-person interviews. Follow-up examinations including repeated cognitive tests have been performed every 2 to 3 years. In 2001-2002, a comprehensive dietary survey was conducted in the Bordeaux center, including a 24-hour recall administered during a face-to-face interview by trained dieticians. The present study was based on participants from the Bordeaux 3C sample who participated in both the screening procedure for dementia and the dietary survey (n=1,658, see flow chart in **(Dryad, Figure 1)**). Among them, we excluded (i) prevalent dementia cases (n=76), (ii) participants who were not re-examined after baseline (n=109), and (iii) participants with missing data for the main covariates (education and apolipoprotein E [ApoE] genotype) (n=144). Our study sample thus included 1,329 participants followed for up to 12 years after dietary assessment.

Standard Protocol Approvals, Registrations, and Patient Consents

The Consultative Committee for the Protection of Persons participating in Biomedical Research at Kremlin-Bicêtre University Hospital (Paris, France) approved the 3C study protocol and a written informed consent was obtained from each participant.

Diagnosis of Dementia

Incident dementia was ascertained through a three-stage protocol. At each follow-up visit, participants were administered a battery of neuropsychological tests during home interviews conducted by a trained psychologist. Participants suspected of cognitive impairment were then examined by a neurologist to establish a clinical diagnosis of dementia. Finally, an independent committee of neurologists reviewed all potential cases of dementia to validate diagnosis of dementia according to the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition).[17] Dementia cases were classified as probable or possible AD based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association Alzheimer's criteria.[18]

Assessment of polyphenol intakes

Nutrient and polyphenol intakes were ascertained through a 24-hour dietary recall.[19] Participants were invited to report all meals and beverages consumed the day prior the interview (excluding week-end meals) along with quantities of intake using a manual of portion size photographs. We estimated individual daily intakes in polyphenols as the sum of estimated intakes of each food/beverage multiplied by its polyphenol content using Phenol-Explorer, the first comprehensive database on polyphenol content in foods (http://phenol-explorer.eu).[20,21] Here, we focused on intakes of 26 main polyphenol classes/subclasses.

Other variables

Sociodemographic and lifestyle information included age at baseline, sex, level of education, alcohol intake, tobacco consumption and regular physical activity (defined as practicing a

sport or an intensive leisure activity [e.g., hiking] ≥1hour per week or engaging in a more moderate activity [e.g., walking or household] ≥1hour per day). ApoE-ε4 genotype was defined as carrying at least one ε4 allele vs no ε4 allele. Cardiovascular risk factors included Body Mass Index (BMI, weight (kg) divided by height^2 (m²)), history of cardiovascular diseases, hypertension (blood pressure ≥140/90 mmHg or treated), hypercholesterolemia (total cholesterol ≥6.2 mmol/L or treated) and diabetes (fasting glucose ≥7.2 mmol/L or treated). Moreover, the number of medications regularly consumed was used as a general indicator of comorbidities. High depressive symptomatology was assessed using the Center for Epidemiological Studies-Depression (CES-D) scale.[22]

Statistical analyses

Identification of a pattern of polyphenol intake associated with the long-term risk of dementia

We used Partial Least Square regression for Cox models (PLS-Cox)[23] to investigate whether a specific pattern of polyphenol intake was associated with the risk of incident dementia over the 12 years following ascertainment of diet. PLS-Cox belongs to PLS regression methods[24] – a family of dimension reduction approaches (such as Principal Component Analysis [PCA]) which aims to extract summary components of a set of p predictors X that best explain the variability in a set of q outcomes Y (see **(Dryad, Appendix)**); PLS-Cox is an extension of PLS method for time-to-event data.[23] We adapted the original PLS-Cox algorithm to allow covariate adjustment in the construction of the components.

In the present analyses, the predictors X were the standardized intakes of 26 polyphenol subclasses and the response variable Y was the age of onset of dementia. As indicated by a five-fold cross-validation, we retained the first PLS-Cox component only (interpreted as a

pattern of polyphenol intake oriented toward the association with incident dementia). PLS components can be interpreted using their Pearson correlations with the original X; in this study, we primarily considered polyphenol subclasses with an absolute correlation with the component score ≥0.25.

Multivariate associations between the pattern of polyphenol intake and the risk of dementia

We used Cox proportional hazards models with delayed entry and age as time scale to evaluate the multivariate associations between quintiles of the polyphenol pattern score and the risk of dementia, adjusting for potential confounders. First, we controlled for the variables used in PLS-Cox (sex, education, ApoE-ε4, total energy intake and season of the 24h recall; model 1). We further adjusted for lifestyle factors, cardiovascular and health-related risk factors and other nutrients (vitamins C, D, and E, carotene, folate, long-chain omega 3 fatty-acids and saturated fats) (model 2). We examined linear trends across quintiles of polyphenol pattern by using median values of each quintile as a continuous variable. We secondarily analyzed AD specifically. Moreover, we investigated the interaction of the polyphenol pattern score with ApoE-ε4 genotype on incident dementia/AD.

To limit exclusions due to missing values, we only excluded participants with missing values for the main potential confounders (model 1). For other covariates, data were missing for <3% of the sample, we thus assigned to missing data the reference category (for categorical variables) or the median value (for continuous variables), except for regular exercise that was missing for 11.8% of the sample and for which we created a specific missing category. In all Cox models, the proportional hazards and the log-linearity assumptions were satisfied. Statistical analyses were performed using SAS software version 9.3 and the R software

version 3.3.2 (R script used for PLS-Cox available at https://github.com/slefevarb/plscox_adapted).

Supplementary analyses

We conducted sensitivity analyses to assess the robustness of our findings to potential reverse causation (which occurs when incipient dementia modifies dietary habits) by: (1) further adjusting the models for global cognitive performance at baseline, represented by the Mini Mental State Examination (MMSE) score;[25] (2) excluding participants with baseline MMSE<26 and those who developed dementia within the 5 years following dietary assessment.

In addition, we investigated the foods most contributive of our polyphenol pattern; we described average intakes of top food contributors across quintiles of the pattern score, and we computed the correlation between these foods and the pattern score.

Data availability

Additional material can be accessed via the Dryad Digital Repository: https://doi.org/10.5061/dryad.gp126fv.[26] Anonymized data will be shared by request to the 3C scientific committee.

RESULTS

Characteristics of the sample

The 1,329 study participants were 75.8 years old on average at baseline. A total of 256 participants were diagnosed with dementia, including 169 AD cases, during a median follow-up of 11.7 years (range 0.9-13.1 years).

Compared to participants who remained free of dementia over the follow-up, those who developed the disease were older at baseline (**Table 1**); they were also more likely to be ApoE-ε4 carrier and diabetics, and they consumed more medications.

On average, participants consumed a total of 1,071 mg/day of polyphenols at baseline (**Table 2**); with higher total intakes reported in men compared to women (see **(Dryad, Table 1)** for average absolute and energy-adjusted polyphenol intakes stratified by sex). Intakes of the large polyphenol classes at baseline did not differ significantly between participants diagnosed with dementia and those who remained free of dementia (**Table 2**; see **(Dryad, Table 2)** for energy-adjusted polyphenol intakes), although future dementia cases tended to have slightly lower intakes in all 5 main classes of polyphenols. Likewise, none of the 26 polyphenol subclasses were significantly associated with the risk of dementia when considered individually (results not shown in tables).

Pattern of polyphenol intake associated with the risk of dementia

When we combined the 26 subclasses of polyphenols using PLS-Cox, we found a pattern of polyphenol intake strongly associated with a lower risk of dementia (see **Figure 1** for cumulative risk of dementia by quintiles of the polyphenol pattern score).

The pattern score was associated with higher intakes of hydroxybenzaldehydes, dihydroflavonols, stilbenes and lignans (all correlations >0.50; **Table 3**); other important contributors to the pattern (with correlations between 0.25 and 0.40) included naphtoquinones, anthocyanins, isoflavonoids, flavanones and furanocoumarins (see **Table 4** for average polyphenol intakes and **(Dryad, Table 3)** for baseline characteristics across quintiles of score).

In multivariate analyses, the polyphenol pattern score remained associated with a lower risk of dementia (p for trend <0.007 in model 2; **Table 5**). The score was also associated with a lower risk of AD (p for trend=0.047 in model 2). For example, compared with participants in the lower quintile of score, those in the higher quintile had a 50% lower risk of dementia over 12 years (95% CI=20% to 68%), and a 48% lower risk of AD (95% CI=7% to 71%). These associations were not modified by ApoE-ε4 status.

Supplementary analyses

In sensitivity analyses, associations were virtually unchanged when we further adjusted for baseline cognition; likewise, findings were not modified when we excluded the n=163 participants with MMSE<26 at baseline, or the n=65 participants diagnosed with dementia within the first five years of follow-up, suggesting that reverse causation was not likely to explain our findings.

We secondarily investigated the top dietary sources of the pattern of polyphenol intake. In this cohort from South West of France, red wine was an important source of polyphenols, including those most representative of our pattern, i.e., hydroxybenzaldehydes, dihydroflavonols, stilbenes, lignans and anthocyanins (for which red wine contributed to 40 to 100% of the intakes, **Figure 2A**; correlation of red wine intake with the PLS-Cox

component=0.66; **Figure 2B**). Other important contributors were nuts, soy products, citrus fruits, leafy vegetables, olive oil and berries (**Figure 2 A and B**). Accordingly, for those top contributors there was a strong gradient of increasing intakes across quintiles of the pattern score (**Table 4**). For example, participants in the higher quintile of score reported daily consumptions equivalent to: 2.5 standard glasses (125 mL) of red wine; 1 cup of tea; half a handful of nuts (or 5 walnuts); 1 small orange and 4 strawberries; 1.5 medium stalks of celery; and a portion of cooked cereals (added to small amounts of olive oil and soy products; **Table 4**).

DISCUSSION

In this large cohort of older persons, we identified a pattern of polyphenol intake associated with a decreased risk of all-cause dementia and of AD over 12 years. Compared with participants in the lower quintile of the polyphenol pattern score, those in the higher quintile had an approximately 50% lower risk of both dementia and AD, independently of major potential confounders. The pattern was mostly characterized by 9 polyphenol subclasses including specific flavonoids (dihydroflavanols, anthocyanins, isoflavonoids and flavanones), stilbenes (including resveratrol), lignans and additional isolated polyphenols (hydroxybenzaldehydes, naphtoquinones and furanocoumarins). It was associated with a diet rich in specific plant products including nuts, citrus and berries, leafy vegetables, soy products and cereals, accompanied with red wine and tea and regular consumption of olive oil.

The few epidemiological studies which have investigated polyphenol intakes in relation to cognitive aging or dementia yielded conflicting results. Primary results from the PAQUID cohort showed an association between total flavonoid intake and a lower risk of dementia and cognitive decline over 10 years.[7,8] These findings were replicated in the large Nurses' Health Study;[6] yet no association was found either with the risk of dementia or AD in the Rotterdam study,[10,11] or with cognitive decline in both the Zutphen Elderly and The Invecchiare in Chianti studies.[12,13] Likewise, cohorts which examined total flavonoid/polyphenol intakes in midlife in relation to cognition or dementia risk in older ages found inconsistent results.[5,14] Total polyphenol intake was significantly associated with better global cognitive performance at baseline in our cohort (results not shown in the manuscript and available upon request), yet it was not associated with a lower incidence of dementia. Total polyphenol intake is determined by the polyphenol species most consumed in the diet rather than the species biologically linked to brain health, and thus, it may incompletely reflect brain-protective

polyphenol exposures. The strong relationship between a polyphenol pattern and dementia risk (yet no significant association with either individual subclasses or total polyphenol intake) found here suggests that combining specific polyphenols may be more relevant for brain health than a simple addition of polyphenols in the diet.

Our polyphenol pattern partly reflects plant-based healthy diets which have been previously associated with a lower risk of dementia outcomes. For example, the Mediterranean diet (MeDi), which combines several polyphenol-rich components, has been associated with lower risk of AD,[27] and with preserved global cognition in persons at high vascular risk in a large trial.[28] Interestingly, our findings showing associations of polyphenol subclasses to dementia only when combined in a pattern are similar to what previously reported with the MeDi (with individual components inconsistently related to dementia outcomes in studies unless combined in a global pattern score).[27] Most foods represented in our polyphenol pattern are also found in the MIND (Mediterranean-dietary approach to stop hypertension Intervention for Neurodegenerative Delay) diet, which was associated with slower cognitive decline and lower risk of AD in the Rush Memory and Aging Project.[29] Thus overall, the results obtained here through a statistical learning approach, without formulating any a priori hypothesis, reinforces these previous associations found with several plant-based dietary scores.

Most of the polyphenols constituting our pattern have documented clinical effects in cognitive aging and AD. For example, in moderately-sized trials (N<150), moderate to high doses of resveratrol (ie, 200-2000 mg/day) increased hippocampal connectivity and memory in older adults, [30,31] and decreased plasma and cerebrospinal fluid amyloid-β levels in AD patients.[32] Moreover, a few small trials demonstrated efficacy of flavanols in increasing hippocampal

vascular plasticity,[33] and of both citrus flavanones and soy isoflavonoids in improving cognition in older persons.[34,35] Moreover, it is plausible that the combination of polyphenols within foods/beverages (e.g., grape products) or the overall diet may exert additive and/or synergistic effects on brain health. Indeed, the bioavailability of polyphenols, which is relatively restricted, depends on the polyphenol matrix present in the gut. For example, phenolic compounds (from blueberries) are more efficiently absorbed when consumed with a grape product.[36] In addition, polyphenols may be involved in complementary neuroprotective pathways. For instance, catechin (a flavanol) and resveratrol display complementary neuroprotective effects against amyloid-induced toxicity in vitro.[37] Overall, interactions between various polyphenols in the food matrix are still largely unknown and deserve further investigation.

Our study is limited by the availability of a single 24h recall to assess polyphenol intake. A reported single day of intake may not fully capture individual variations in dietary habits and might lead to misclassifications. However, when sample size is sufficiently large, a single 24h recall can be used to assess average intakes in subgroups of a population.[38] Accordingly, in our sample, estimated average intakes of the main polyphenol classes were very similar to those reported in another large French population-based cohort (the SU.VI.MAX study[21]) based on several 24h records, which certainly supports the validity of our estimations. Moreover, using a single 24h recall, we found expected associations of several nutrients/diet patterns with brain aging outcomes in our previous research.[39,40] Besides, our findings based on an older population from the French Bordeaux area with specific cultural habits (including a regular consumption of red wine) might not be generalizable to populations with other dietary habits.

Our study has also major strengths, including use of the most comprehensive polyphenol database to date, a longitudinal population-based design with more than a decade of follow-up and a clinical diagnosis of dementia validated by an independent committee of neurologists. The long lag period between the dietary survey and the diagnosis of dementia and sensitivity analyses suggested that reverse causation is unlikely to explain our results. Finally, we were able to control for a large set of potential confounders, including other antioxidants and healthy nutrients (although we cannot exclude that residual confounding still persists).

In this large cohort of French older persons, we identified a pattern of polyphenol intake reflecting a diet providing specific plant products including nuts, certain fruits (berries and citrus) and leafy vegetables, soy products and cereals, accompanied with red wine and tea and regular consumption of olive oil, strongly associated with a lower risk of both dementia and AD. The weighted combination of polyphenols evidenced in this exploratory study deserves investigation in relation to dementia outcomes and pathways in further experimental research.

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Table 1. Baseline characteristics of the participants according to incident all-cause dementia over 12 years, the 3C Bordeaux cohort (N=1,329).

Baseline characteristics	Overall sample	Incident dementia (n=256)	No dementia (n=1,073)	p-value [a]
Age (years)	75.8 (4.8)	78.1 (4.6)	75.3 (4.7)	<.001
Sex, female	62.1	69.9	60.2	0.56
Education, ≥ high school	40.9	35.2	42.2	0.07
ApoE-ε4 carrier	18.3	22.3	17.3	0.003
Alcohol consumption categories				0.12
0 g/day	19.3	16.9	19.9	
≤12 g/day	44.6	51.6	42.9	
]12-24] g/day	18.7	19.7	18.5	
>24 g/day	17.4	11.8	18.7	
Tobacco consumption categories				0.84
0 pack-year	64.6	70.2	63.3	
<10 pack-years	12.0	10.7	12.3	
[10-20[pack-years	6.4	6.3	6.4	
[20-30[pack-years	5.4	3.6	5.9	
≥ 30 pack-years	11.5	9.1	12.1	
Regular exercise	35.5	31.0	36.5	0.62
BMI (kg/m²)	26.6 (4.1)	26.2 (4.4)	26.6 (4.1)	0.42
Hypercholesterolemia	57.8	63.7	56.4	0.14
Diabetes	9.5	15.2	8.1	<.001

History of cardiovascular diseases	32.4	30.5	32.8	0.45
Hypertension	75.5	77.6	75.0	0.77
High depressive symptomatology	7.5	10.7	6.7	0.13
Number of drugs consumed	4.8 (2.9)	5.6 (3.2)	4.6 (2.8)	<.001

Values are mean (standard deviation) or percentages (of non-missing values).

[a] Univariate Cox Proportional Hazards models with delayed entry and age as time scale (except for age which use a standard Cox Proportional Hazards model).

Abbreviations: ApoE-ε4, allele ε4 for the apolipoprotein E gene; BMI, Body Mass Index.

Table 2. Average intakes of total polyphenol and of the main classes of polyphenols at study baseline according to incident all-cause dementia over 12 years, the 3C Bordeaux cohort (N=1,329).

Polyphenol classes	Overall sample	Incident dementia (n=256)	No dementia (n=1,073)	p-value[a]
Total polyphenols	1071 (570)	1029 (542)	1081 (576)	0.52
Flavonoids	500 (353)	472 (304)	506 (363)	0.43
Phenolic acids	546 (396)	534 (414)	549 (392)	0.87
Stilbenes	4.46 (5.59)	3.80 (4.52)	4.62 (5.81)	0.27
Lignans	0.38 (0.27)	0.35 (0.25)	0.38 (0.27)	0.45
Other polyphenols	20 (18)	19 (16)	21 (18)	0.70

Values are mean (standard deviation). Intakes are expressed in milligrams per day.

[a] Univariate Cox Proportional Hazards models with delayed entry and age as time scale

Table 3. Correlation coefficients of the 26 polyphenol subclasses with the pattern of polyphenol intake associated with a reduced risk of dementia with Partial Least Square for Cox model[a], the 3C Bordeaux cohort (N=1,329).

Polyphenol subclasses	Pearson correlation coefficients
Flavonoids	
Dihydroflavonols	0.65[b]
Anthocyanins	0.35[b]
Isoflavonoids	0.31[b]
Flavanones	0.27[b]
Flavanols	0.21
Flavones	0.15
Flavonols	0.09
Chalcones	-0.10
Dihydrochalcones	-0.21
Phenolic acids	
Hydroxybenzoic acids	0.21
Hydroxyphenylacetic acids	0.15
Hydroxycinnamic acids	-0.01
Hydroxyphenylpropanoic acids	-0.23
Stilbenes	0.65[b]
Lignans	0.51[b]
Other polyphenols	
Hydroxybenzaldehydes	0.68[b]
Naphtoquinones	0.39[b]

Furanocoumarins	0.25[b]
Tyrosols	0.22
Other polyphenols	0.05
Hydroxyphenylpropenes	0.02
Alkylphenols	-0.03
Methoxyphenols	-0.07
Alkylmethoxyphenols	-0.14
Hydroxybenzoketones	-0.16
Hydroxycoumarins	-0.24

Polyphenol subclasses are classified within the 5 main classes of polyphenols by descending correlation with the PLS-Cox component.

[a] The PLS-Cox included adjustment of univariate relationships between each individual polyphenol and incident dementia for age, sex, level of education, ApoE-ε4, total energy intake and season of the 24h recall.

[b] Polyphenol subclasses with an absolute Pearson correlation ≥0.25 with the PLS-Cox component were primarily considered for interpretation of the pattern.

Table 4. Average intakes of polyphenol subclasses representative of the pattern of polyphenol intake associated with a reduced risk of dementia and of top food sources across quintiles of pattern score, the 3C Bordeaux cohort (N=1,329).

	Quintiles of polyphenol pattern score				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
Polyphenol subclasses (mg/day)					
Hydroxybenzaldehydes	0.26 (0.45)	0.23 (0.41)	0.56 (0.53)	1.29 (0.78)	2.51 (1.43)
Dihydroflavonols	1.7 (3.3)	1.4 (3.0)	3.9 (4.0)	9.4 (6.0)	18.1 (11.0)
Stilbenes	1.2 (2.1)	1.0 (1.9)	2.6 (2.5)	6.0 (3.7)	11.5 (7.0)
Lignans	0.22 (0.18)	0.26 (0.17)	0.32 (0.21)	0.46 (0.26)	0.62 (0.27)
Naphtoquinones	0.01 (0.11)	0.0 (0.07)	0.02 (0.21)	0.06 (0.42)	0.91 (2.57)
Anthocyanins	17.6 (45.7)	22.6 (45.7)	45.6 (75.5)	66.7 (91.1)	117.0 (123.2)
Isoflavonoids	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.19 (2.21)	3.65 (20.18)
Flavanones	4.8 (15.2)	9.0 (23.8)	20.7 (30.5)	31.9 (42.2)	41.0 (51.8)
Furanocoumarins	0.0 (0.01)	0.01 (0.08)	0.01 (0.08)	0.01 (0.07)	0.12 (0.83)
Top food sources (g/day)					
Red wine	30 (60)	26 (54)	72 (73)	173 (110)	333 (203)
Nuts	0.2 (2.2)	0.9 (5.6)	0.6 (4.7)	1.6 (8.6)	11.4 (30.3)
Soy products	0 (0)	0 (0)	0.1 (1.2)	0.9 (12.0)	5.4 (30.0)
Citrus	15 (48)	28 (71)	57 (79)	78 (102)	91 (122)
Leafy vegetables	52 (84)	55 (81)	60 (93)	65 (108)	83 (135)
Olive oil	1.0 (3.3)	1.9 (4.7)	2.1 (5.2)	2.6 (6.3)	2.4 (5.6)
Berries	14 (53)	36 (99)	33 (88)	35 (91)	46 (117)
Tea and infusion	77 (177)	136 (207)	138 (262)	112 (206)	115 (243)

Cereals	156 (111)	155 (105)	150 (100)	178 (108)	174 (99)

Values are mean (standard deviation).

Table 5. Multivariate associations between the polyphenol pattern score obtained by PLS-Cox and the risk of all-cause dementia and Alzheimer's disease over 12 years, the 3C Bordeaux cohort (N=1,329).

	Incident all-cause dementia		Incident Alzheimer's Disease	
	Model 1	**Model 2**	**Model 1**	**Model 2**
Pattern score				
Quintile 1	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Quintile 2	0.73 (0.50-1.06)	0.71 (0.49-1.04)	0.79 (0.50-1.24)	0.76 (0.48-1.22)
Quintile 3	0.73 (0.50-1.05)	0.64 (0.43-0.95)	0.75 (0.47-1.19)	0.67 (0.41-1.10)
Quintile 4	0.72 (0.49-1.05)	0.65 (0.43-0.97)	0.81 (0.50-1.29)	0.75 (0.46-1.23)
Quintile 5	0.57 (0.37-0.86)	0.50 (0.32-0.80)	0.54 (0.32-0.93)	0.52 (0.29-0.93)
p for trend	0.016	0.007	0.045	0.047

Values are HR (95% CI) for Cox Proportional Hazards models with delayed entry using age as time-scale.

Model 1: adjusted for sex, level of education, ApoE-ε4, total energy intake and season of the 24h recall.

Model 2: covariates from model 1 plus alcohol and tobacco consumptions, regular exercise, Body Mass Index, hypercholesterolemia, diabetes, history of cardiovascular diseases, hypertension, depressive symptomatology and number of drugs consumed, intakes of vitamins C, D, E, carotene, folate, saturated fatty acids and long-chain omega 3 fatty acids.

Figure legend

Figure 1. Kaplan-Meier curves for the cumulative risk of incident all-cause dementia by quintiles of the polyphenol pattern score identified by PLS-Cox (quintile 1, dotted line; quintile 3, solid line; quintile 5, dashed line)

Figure 2. Top food sources of the pattern of polyphenol intake associated with a reduced risk of dementia, the 3C Bordeaux cohort (N=1,329).

A) Top food sources for the polyphenol subclasses representative of the pattern of polyphenol intake (i.e., subclasses with an absolute Pearson correlation ≥0.25 with the PLS-Cox component score). Polyphenol subclasses are classified in descending order for their correlation on the x axis.

B) Pearson correlation coefficients of the candidate food contributors (i.e., top food sources of the polyphenol subclasses representative of the polyphenol pattern) with the PLS-Cox component score.