The Journal of Nutrition
Nutritional Epidemiology

Intake of Flavonoid-Rich Wine, Tea, and Chocolate by Elderly Men and Women Is Associated with Better Cognitive Test Performance[1–3]

Eha Nurk,[4] Helga Refsum,[4,5] Christian A. Drevon,[4] Grethe S. Tell,[6] Harald A. Nygaard,[6,7] Knut Engedal,[8] and A. David Smith[5]*

[4]Department of Nutrition, University of Oslo, 0316 Oslo, Norway; [5]Oxford Project to Investigate Memory and Ageing and Department of Physiology, Anatomy and Genetics, University of Oxford, OX1 3QX Oxford, United Kingdom; [6]Department of Public Health and Primary Health Care, University of Bergen, 5020 Bergen, Norway; [7]NKS Olaviken Hospital for Old Age Psychiatry, 5306 Erdal, Norway; and [8]Department of Geriatric Medicine, Norwegian Centre for Dementia Research, Ullevål University Hospital, 0407 Oslo, Norway

Abstract

In a cross-sectional study, we examined the relation between intake of 3 common foodstuffs that contain flavonoids (chocolate, wine, and tea) and cognitive performance. 2031 participants (70–74 y, 55% women) recruited from the population-based Hordaland Health Study in Norway underwent cognitive testing. A cognitive test battery included the Kendrick Object Learning Test, Trail Making Test, part A (TMT-A), modified versions of the Digit Symbol Test, Block Design, Mini-Mental State Examination, and Controlled Oral Word Association Test. Poor cognitive performance was defined as a score in the highest decile for the TMT-A and in the lowest decile for all other tests. A self-reported FFQ was used to assess habitual food intake. Participants who consumed chocolate, wine, or tea had significantly better mean test scores and lower prevalence of poor cognitive performance than those who did not. Participants who consumed all 3 studied items had the best test scores and the lowest risks for poor test performance. The associations between intake of these foodstuffs and cognition were dose dependent, with maximum effect at intakes of ~10 g/d for chocolate and ~75–100 mL/d for wine, but approximately linear for tea. Most cognitive functions tested were influenced by intake of these 3 foodstuffs. The effect was most pronounced for wine and modestly weaker for chocolate intake. Thus, in the elderly, a diet high in some flavonoid-rich foods is associated with better performance in several cognitive abilities in a dose-dependent manner. J. Nutr. 139: 120–127, 2009.

JN THE JOURNAL OF NUTRITION

Introduction

The pathogenesis of neurodegenerative disorders, especially Alzheimer's disease, leading to cognitive decline and dementia is multifactorial with a complex combination of genetic and nongenetic components. Environmental agents are at least as likely to contribute to neurodegenerative diseases as genetic factors (1). The role of micronutrients in age-related cognitive decline is being increasingly studied (2–7).

Polyphenols are abundant micronutrients in our plant-derived foods and are powerful antioxidants. Fruits and beverages such as tea, red wine, cocoa, and coffee are major dietary sources of polyphenols. The largest subclass of dietary polyphenols is flavonoids (8,9). A significant inverse relationship between dementia or cognitive performance and the intake of flavonoids has been reported (9–11).

Wine and tea are flavonoid-rich beverages that may have dual effects on health and cognitive function. Moderate alcohol consumption is associated with better cognitive function (12) and reduced risk of Alzheimer's disease and dementia in general (4,10,12–15). In contrast, heavy alcohol intake has been considered to be one of many causes of dementia (4,12). Tea consumption is associated with a reduced risk of cognitive impairment (16,17) and of cognitive decline (17) and components in green tea may be associated with neuroprotection (5,9). But in cellular models, a dual action of tea polyphenols, e.g. (-) epigallocatechin-3-gallate, on cell survival has also been demonstrated: they protect at low micromolar concentrations, whereas they become pro-

[1] Supported by the Charles Wolfson Charitable Trust, the Norman Collisson Foundation (United Kingdom), the Advanced Research Programme of Norway, the Johan Throne Holst Foundation for Nutrition Research, University of Oslo.
[2] Author disclosures: E. Nurk, H. Refsum, C. A. Drevon, G. S. Tell, H. A. Nygaard, K. Engedal, and A. D. Smith, no conflicts of interest.
[3] Supplemental Table 1 is available with the online posting of this paper at jn.nutrition.org.
* To whom correspondence should be addressed. E-mail: david.smith@pharm.ox.ac.uk.

Manuscript received 26 June 2008. Initial review completed 29 August 2008. Revision accepted 21 October 2008.
First published online December 3, 2008; doi:10.3945/jn.108.095182.

oxidant and pro-apoptotic at concentrations over 10–20 μmol/L (18).

Dark chocolate, like other cocoa products, may contain greater amounts of flavonoids, depending on the processing, per serving than teas and red wines (19). Acute (20) as well as chronic (21) ingestion of flavanol-rich cocoa is associated with increased blood flow to cerebral gray matter and it has been suggested that cocoa flavanols might be beneficial in conditions with reduced cerebral blood flow, including dementia and stroke (21).

The aim of this study was to examine the relation of the performance, in a variety of cognitive tests, to habitual intake during the previous year of certain types of flavonoid-rich food intake (chocolate, wine, and tea). A subset of elderly participants within the Hordaland Health Study (HUSK)[9] afforded the opportunity to examine these issues among >2000 older men and women.

Methods

Study population. The HUSK study was conducted from 1997 to 1999 as a collaboration between the University of Bergen, University of Oslo, local health services and the Norwegian Institute of Public Health. Details of the study and of recruitment to the Cognitive Sub-study has been described previously (22,23). Briefly, a total of 2841 participants out of 3341 attendees in the HUSK born in 1925–1927 were invited to participate in cognitive tests; 2197 (77.3%) of these agreed and constitute the Cognitive Sub-study. In this report, we have confined the analysis to cross-sectional data for 2031 (71.5%) individuals who also completed a FFQ.

All participants gave their written, informed consent. The study protocol was approved by the Regional Committee for Medical Research Ethics of Western Norway.

Data collection. Cognitive testing was performed at the study location by trained nurses after the standard cardiovascular examinations of the National Health Screening Service were completed. The cognitive test battery included 6 tests (24): Kendrick Object Learning test (KOLT; episodic memory) (25); Trail Making test, part A (TMT-A) (26); a modified version of Digit Symbol test (m-DST; perceptual speed) (27); Block Design, short form (m-BD; visuospatial skills) (27); a modified version of the Mini-Mental State Examination (m-MMSE; global cognition) (28); and an abridged version of Controlled Oral Word Association test (S-task) (access to semantic memory) (29).

Dietary habits. To asses the habitual food consumption, a comprehensive FFQ created at the Department of Nutrition, University of Oslo (30,31) was handed out on the day of examination, filled out later at home by the participants, and then mailed to the HUSK Project Centre in Bergen. The FFQ has been validated in several previous studies, including the correlation between self-reported dietary intake of fish and essential (n-3) fatty acids in plasma phospholipids among 579 men and women (31) and 14-d weighed diet records with the intakes calculated from the FFQ in a group of 38 elderly women (30). The questionnaire included 169 food items that were grouped according to Norwegian meal patterns. It was designed to obtain information on usual food intake during the last year. The frequency of consumption was given per day, week, or month. The portion sizes were defined as follows: chocolate (type not specified), 60 g (the approximate amount in a standard chocolate bar in Norway); wine (type not specified), 1 glass (120 mL); and tea [an infusion of the leaves of *Camellia sinensis* (the most common type at the end of the 1990s in Norway was black tea)], 1 cup (200 mL). Precise information on the type of chocolate consumed was not recorded, but at that time in Norway, the most common type purchased was milk chocolate.

Dichotomous variables were created considering individuals who reported the use of chocolate, wine, or tea, whereas all others reporting that they never consumed the actual product were considered nonusers. To identify the individuals who never had these items and individuals who consumed at least 1 or 2 or all of them, all dichotomous variables were combined. The amount of each item in g or mL/d and total energy intake were calculated by using a food database and software system developed at the Department of Nutrition, University of Oslo (Kostberegningssystem, version 3.2, University of Oslo, Norway).

Covariates. The FFQ also included questions about dietary supplement intake, in which the product names of the most used supplements in Norway were considered. Use of dietary supplements was reported as "seasonal use" (during the whole year or only winter half of the year), frequency per week, and amount per time.

Self-reported information on diabetes and history of myocardial infarction, angina pectoris, stroke, thrombosis, phlebitis, and hypertension was recorded in 1992–1993 and 1997–1999. On the basis of information from both surveys, the participants were categorized as with or without a history of cardiovascular disease (CVD) (including the diseases and conditions mentioned above). About four-fifths (79%) of the self-reported CVD cases were validated with hospitalization records used in our earlier study (32), whereas the remaining 21% of CVD cases were presumably less severe and did not require hospitalization or occurred before 1992.

Educational level was self-reported and recorded in 5 categories: primary school (≤9 y), vocational secondary school (10–12 y), theoretical secondary school (10–12 y), college or university ≤4 y, and university of ≥4 y. Smoking was considered in 3 categories: nonsmokers, ex-smokers, and current smokers (including daily smoking of cigarettes, cigars, cigarillos, or pipe). The depression score was assessed by a 7-item subscale for depression from the Hospital Anxiety and Depression Scale (33). Intake of coffee was reported as the number of cups (120 mL) consumed per day.

Statistical analysis. Cutoff points for poor cognitive test scores were set at about the 10th percentile of the cognitive test score, except for the TMT-A, where the 90th percentile was used. Preliminary analyses showed that cognitive test scores and intake of chocolate, wine, and tea were significantly correlated with 1 or more of the following background variables: sex, education, use of vitamin supplements, coffee intake, smoking status, history of CVD, diabetes, depression score, and total energy intake (**Supplemental Table 1**). Although the depression score was significantly correlated with most of the cognitive test scores, it made little difference when introduced in the statistical models and because inclusion of the depression score significantly reduced the numbers of participants due to missing data, it was excluded from final models. The results were almost identical when the use of vitamin supplements such as multivitamins, folate, B vitamins (not specified), and vitamins C, D, and E was included as covariates in separate variables or was combined into 1 variable. Consequently, in the present paper, the use of all these vitamin supplements was combined. Similarly, inclusion of coffee intake as a covariate in statistical models made very little difference and is therefore omitted from the final models. Thus, the final fully adjusted models used throughout the present paper were controlled for sex, education, history of CVD, smoking status, vitamin supplement use, diabetes, and total energy intake. Due to potential over-adjustment, we selected both a simple (sex-adjusted) model and a fully adjusted model in the table presenting mean values of cognitive test scores and when demonstrating dose-response associations. Given the narrow age range, adjustment for age did not change the results and has not been included.

For comparison between the groups of chocolate, wine, and tea intake, the χ^2 test or ANOVA was used. Estimated mean values of cognitive scores by combined intake of chocolate, wine, and tea, adjusted according to our final model of cofactors, were obtained from the univariate ANOVA, and risk ratios for poor cognitive test perfor-

[9] Abbreviations used: CVD, cardiovascular disease; HUSK, Hordaland Health Study; KOLT, Kendrick Object Learning Test; m-BD, a short form of Block Design; m-DST, a modified version of Digit Symbol Test; m-MMSE, a modified version of the Mini-Mental State Examination; OR, odds ratio; S-task, an abridged version of Controlled Oral Word Association Test; TMT-A, part A from the Trail Making Test.

TABLE 1 Characteristics of elderly men and women classified by consumption of chocolate, wine, and tea

	Consumers		Nonconsumers		
	n	*n* (%) or mean [95% CI]	*n*	*n* (%) or mean [95% CI]	*P*-value[1]
Gender (male)					
Chocolate	1036	474 (45.8)	995	444 (44.6)	0.624
Wine	882	422 (47.8)	1149	496 (43.2)	0.039
Tea	1083	419 (38.7)	948	499 (52.6)	<0.001
Education (≤9 y)					
Chocolate	1028	352 (34.2)	969	450 (46.4)	<0.001
Wine	875	243 (27.8)	1122	559 (49.8)	<0.001
Tea	1072	382 (35.6)	925	420 (45.4)	<0.001
Current smoking					
Chocolate	1036	145 (14.0)	995	123 (12.4)	0.294
Wine	882	117 (13.3)	1149	151 (13.1)	0.947
Tea	1083	114 (10.5)	948	154 (16.2)	<0.001
Ex-smoking					
Chocolate	1036	449 (43.3)	995	445 (44.7)	0.532
Wine	882	457 (51.8)	1149	437 (38.0)	<0.001
Tea	1083	465 (42.9)	948	429 (45.3)	0.303
Vitamin supplement use					
Chocolate	1036	414 (40.0)	995	281 (28.2)	<0.001
Wine	882	357 (40.4)	1149	338 (29.4)	<0.001
Tea	1083	416 (38.4)	948	279 (29.4)	<0.001
Folate and B vitamins					
Chocolate	1036	114 (11.0)	995	78 (7.8)	0.047
Wine	882	95 (10.8)	1149	97 (8.4)	0.118
Tea	1083	119 (11.0)	948	73 (7.7)	0.017
Vitamin C					
Chocolate	1036	139 (13.5)	995	102 (10.2)	0.027
Wine	882	123 (14.0)	1149	118 (10.2)	0.033
Tea	1083	145 (13.4)	948	96 (10.1)	0.002
Vitamin D					
Chocolate	1036	34 (3.2)	995	16 (1.6)	0.008
Wine	882	21 (2.3)	1149	29 (2.5)	0.961
Tea	1083	30 (2.8)	948	20 (2.1)	0.121
Vitamin E					
Chocolate	1036	102 (9.9)	995	69 (6.9)	0.009
Wine	882	98 (11.1)	1149	73 (6.3)	0.001
Tea	1083	113 (11.4)	948	58 (6.2)	<0.001
Multivitamins					
Chocolate	1036	290 (28.0)	995	14.8 (17.5)	<0.001
Wine	882	246 (27.9)	1149	218 (19.0)	<0.001
Tea	1083	284 (26.2)	948	180 (19.0)	0.001
Coffee intake, *mL/d*					
Chocolate	1036	372 [358, 386]	995	373 [357, 388]	0.971
Wine	882	360 [345, 375]	1149	382 [368, 396]	0.031
Tea	1083	328 [315, 341]	948	424 [408, 439]	<0.001
Total energy intake, *kJ/d*					
Chocolate	1036	8124 [7972, 8276]	994	6771 [6614, 6928]	<0.001
Wine	882	7843 [7679, 8008]	1148	7168 [7015, 7321]	<0.001
Tea	1083	7701 [7550, 7851]	947	7188 [7019, 7356]	<0.001
History of CVD					
Chocolate	1013	315 (31.1)	961	346 (36.0)	0.022
Wine	861	283 (32.9)	1113	378 (34.0)	0.631
Tea	1058	341 (32.2)	916	320 (34.9)	0.214
Diabetes					
Chocolate	1017	32 (3.1)	977	94 (9.6)	<0.001
Wine	869	44 (5.1)	1125	82 (7.3)	0.051
Tea	1062	58 (5.5)	932	68 (7.3)	0.097
Depression score					
Chocolate	991	3.4 [3.2, 3.6]	888	3.6 [3.4, 3.8]	0.204
Wine	844	3.4 [3.2, 3.6]	1035	3.6 [3.4, 3.7]	0.164
Tea	1017	3.4 [3.3, 3.6]	862	3.5 [3.3, 3.7]	0.433

[1] Pearson χ^2-test or ANOVA.

mance (based on cross-sectional data on habitual consumption of chocolate, wine, and tea during the previous year) were obtained from logistic regression analysis. Gaussian generalized additive regression models, as implemented in S-PLUS 6.2 for Windows (Insightful Corporation), were used to generate graphic representations of the dose-response relationships using a sex-adjusted model. On the vertical axis, the model generates a reference value of 0 that approximately corresponds to the value of cognitive test score associated with the mean of the average intake of flavonoid-rich food in g or mL/d for all participants. Multiple linear regression analyses were used to examine significant associations between the cognitive test scores and average chocolate, wine, and tea intake using both a sex-adjusted model and a model adjusted for the variables referred to in the final model. Except for generalized additive models, all statistical analyses were performed using SPSS, 12.0 for Windows. *P*-values < 0.05 were considered significant.

Results

Mean intakes among the 2031 participants were 3.8 (95% CI: 3.5, 4.2) g/d for chocolate, 22 (20, 25) mL/d for wine, and 222 (209, 235) mL/d for tea. When nonconsumers were excluded, the mean intakes doubled: 7.5 (6.9, 8.1) g/d for chocolate (n = 1036), 51 (46, 57) mL/d for wine (n = 882), and 417 (399, 435) mL/d for tea (n = 827). Approximately 30% of total tea intake was attributed to herbal tea [mean intake, 68 (60, 76) mL/d; mean intake among tea drinkers, 127 (114, 141) mL/d].

The proportion of wine drinkers was higher in men than in women, whereas the proportion of tea drinkers was higher among women than men (**Table 1**). The use of vitamin supplements was more frequent, and total energy intake and educational level (≥9 y) were higher among chocolate, wine, and tea consumers than nonconsumers. Current smoking was more prevalent among those who did not drink tea, whereas there were more ex-smokers among wine drinkers than among nondrinkers. Wine and tea drinkers drank less coffee than nondrinkers. Chocolate users had lower prevalence of CVD history and diabetes than nonusers and the prevalence of diabetes was lower among wine drinkers than nondrinkers.

The performance on all 6 cognitive tests was better among chocolate, wine, and tea consumers than among nonconsumers (**Table 2**).

In multivariate models, including adjustments for sex, education, smoking status, vitamin supplement use, history of CVD, diabetes, and total energy intake, the mean scores of all 6 cognitive tests remained significantly better among wine drinkers. Chocolate consumers also had significantly better test scores (except for m-BD) compared with nonconsumers, and tea drinkers had significantly better scores in 4 out of 6 tests (TMT-A, m-DST, m-BD, and m-MMSE) than nondrinkers in the multiple adjusted models.

The multiple-adjusted mean values of various cognitive tests and the risk ratios for poor cognitive test performance are presented in **Table 3** in relation to how many of the 3 flavonoid-rich foods (chocolate, wine, or tea) were consumed. For each of the 6 cognitive tests, the test performance improved as an increasing number of these products were consumed.

Odds ratios (OR) for poor cognitive performance were assessed in relation to habitual intake of chocolate, wine, and tea. The risk for poor test performance in all cognitive tests decreased significantly as an increasing number of the 3 flavonoid-rich foods (chocolate, wine or tea) were consumed (Table 3). The reduction in risk of poor test performance for those who consumed all 3 flavonoid-rich foods ranged from 64 to 74% compared with those who did not report consuming any of these foods.

TABLE 2 Cognitive test performance among elderly men and women classified by consumption of chocolate, wine, and tea

	Consumers		Nonconsumers			
	n	Mean[1] (95% CI)	*n*	Mean[1] (95% CI)	*P*-value[1]	*P*-value[2]
KOLT score						
Chocolate	1036	36.1 (35.6, 36.6)	991	34.6 (34.1, 35.1)	<0.001	0.020
Wine	880	36.8 (36.3, 37.3)	1147	34.3 (33.8, 34.7)	<0.001	<0.001
Tea	1079	35.8 (35.3, 36.2)	948	34.9 (34.4, 35.4)	0.015	0.292
TMT-A score						
Chocolate	1036	52.3 (50.3, 54.3)	988	60.1 (58.1, 62.2)	<0.001	<0.001
Wine	879	50.3 (48.1, 52.4)	1145	60.6 (58.7, 62.5)	<0.001	<0.001
Tea	1080	53.0 (51.0, 55.0)	944	59.7 (57.6, 61.8)	<0.001	<0.001
m-DST score						
Chocolate	1034	10.9 (10.7, 11.2)	988	9.7 (9.5, 10.0)	<0.001	0.001
Wine	878	11.4 (11.1, 11.6)	1144	9.5 (9.3, 9.8)	<0.001	<0.001
Tea	1080	10.9 (10.6, 11.1)	942	9.7 (9.4, 10.0)	<0.001	0.004
m-BD score						
Chocolate	1033	15.2 (15.1, 15.4)	985	14.8 (14.7, 15.0)	<0.001	0.176
Wine	878	15.3 (15.1, 15.4)	1140	14.8 (14.7, 15.0)	<0.001	0.005
Tea	1078	15.2 (15.1, 15.4)	940	14.8 (14.7, 15.0)	<0.001	0.033
m-MMSE score						
Chocolate	1029	11.6 (11.6, 11.7)	981	11.4 (11.4, 11.5)	<0.001	0.006
Wine	875	11.6 (11.6, 11.7)	1135	11.4 (11.4, 11.5)	<0.001	<0.001
Tea	1074	11.6 (11.5, 11.6)	936	11.5 (11.4, 11.5)	<0.001	0.046
S-task score						
Chocolate	1036	15.8 (15.5, 16.2)	988	14.5 (14.1, 14.8)	<0.001	0.010
Wine	880	16.5 (16.1, 16.9)	1144	14.1 (13.8, 14.5)	<0.001	<0.001
Tea	1079	15.7 (15.4, 16.0)	945	14.6 (14.2, 14.9)	<0.001	0.091

[1] ANOVA adjusted for sex.
[2] ANOVA adjusted for sex, education, vitamin supplement use (multivitamins, folate, and vitamins B, C, D, or E), smoking status, history of CVD, diabetes, and total energy intake.

In the sex-adjusted models, independent of cognitive test, the risk for poor performance decreased significantly among consumers of chocolate, wine, and tea when compared with nonconsumers (data not shown). In the fully adjusted models, the strongest risk-reducing effect for poor cognitive performance was related to wine intake: compared with nondrinkers, the wine drinkers had a 41–53% reduced risk for poor test performance in all 6 cognitive tests (**Table 4**). Among the chocolate eaters, the risk-reducing effect in 4 out of 6 tests (TMT-A, m-DST, m-MMSE, and S-task) remained significant when the models were controlled for multiple risk factors, but the tea drinkers had significantly reduced risk for poor performance only in the TMT-A and S-task.

The performance on all cognitive tests improved with increasing intake of wine up to 75–100 mL/d and then leveled off (**Fig. 1**). Similarly, improved cognitive performance with increasing chocolate intake reached a plateau at ~10 g/d in all cognitive tests, except KOLT. The sharpest dose-response effect of tea on cognitive performance was up to ~200 mL/d, after which it reached to plateau or tended to be linear. Linear regression analyses adjusted only for sex indicated that the dose-response associations with chocolate, wine, and tea were present for each of the cognitive tests, except for the association between chocolate and KOLT. In the fully adjusted models, several of the associations related to wine (KOLT, TMT-A, m-DST, and S-task) and tea intake (TMT-A, m-DST, and S-task) remained significant. Dose-response relationships also remained significant between intake of chocolate and S-task.

We studied an effect of tea (an infusion of the leaves of *Camellia sinensis*) and herbal tea on cognition separately and found that the positive associations were slightly stronger when intake of herbal tea was not included (data not shown). Analyses with herbal tea alone showed significant association only with TMT-A score; the mean score among users was 52 (95% CI: 48, 55) and among nonusers was 57 (56, 59), (P adjusted for gender $= 0.002$, multiple adjusted $P = 0.015$).

To determine whether the effect of particular flavonoid-rich foods on cognitive performance is independent, we repeated all statistical models adding chocolate, wine, and tea as covariates. This did not affect our results; all significant associations remained, except for the fully adjusted linear association (Fig. 1) between tea and S-task (P-value changed to 0.080).

Discussion

In a population-based study of elderly people, we showed that habitual intake of flavonoid-rich foods such as chocolate, wine, and tea is associated with better cognitive performance. The associations were dose dependent and applied for most of the cognitive tests used in the study. The associations were also additive in the sense that the risk of poor cognition was lower the greater the number of the 3 flavonoid-rich foods consumed the previous year.

Although elderly Norwegians were modest in their habitual wine consumption (~50% of users drank <1 glass/wk and ~5% drank >1 glass/d), the strongest beneficial effect on cognitive test performance was related to wine intake. Earlier studies have shown that light-to-moderate alcohol consumption might have a protective effect on cognitive impairment compared with total abstention or heavy consumption (1,12,34–36).

TABLE 3 Mean values of different cognitive tests and hazard ratios for poor cognitive test performance in elderly men and women classified by number of flavonoid-rich foods (chocolate, wine, and tea) consumed[1]

Cognitive test	Intake of chocolate, wine, or tea, *n* items	*n*	Mean (95% CI)	*P*	Poor test performance *n* (%)	OR (95% CI)	*P*-trend
KOLT	0	331	33.7 (32.8, 34.5)	Ref	50 (15.1)	1.00	
	1	634	35.1 (34.5, 35.7)	0.008	73 (11.5)	0.77 (0.52, 1.14)	
	2	624	36.2 (35.6, 36.8)	<0.001	50 (8.0)	0.54 (0.35, 0.83)	
	3	328	36.4 (35.5, 37.3)	<0.001	16 (4.9)	0.36 (0.19, 0.67)	<0.001
TMT-A	0	328	64.5 (61.0, 68.1)	Ref	54 (16.5)	1.00	
	1	634	58.6 (56.1, 61.1)	0.007	72 (11.4)	0.69 (0.47, 1.02)	
	2	624	52.0 (49.5, 54.5)	<0.001	38 (6.1)	0.37 (0.24, 0.59)	
	3	328	49.5 (46.0, 53.1)	<0.001	12 (3.7)	0.26 (0.13, 0.52)	<0.001
m-DST	0	328	9.4 (9.0, 9.8)	Ref	46 (14.0)	1.00	
	1	633	10.2 (9.9, 10.5)	0.002	61 (9.6)	0.70 (0.46, 1.07)	
	2	623	10.7 (10.4, 11.0)	<0.001	37 (5.9)	0.49 (0.30, 0.79)	
	3	328	11.3 (10.9, 11.7)	<0.001	10 (3.0)	0.31 (0.15, 0.64)	<0.001
BD	0	327	14.8 (14.6, 15.1)	Ref	24 (7.3)	1.00	
	1	631	14.9 (14.7, 15.1)	0.796	43 (6.8)	1.08 (0.64, 1.84)	
	2	624	15.2 (15.0, 15.4)	0.023	24 (3.8)	0.69 (0.38, 1.27)	
	3	327	15.3 (15.1, 15.6)	0.008	6 (1.8)	0.40 (0.15, 1.03)	0.029
m-MMSE	0	327	11.4 (11.3, 11.5)	Ref	49 (15.0)	1.00	
	1	625	11.5 (11.4, 11.6)	0.077	62 (9.9)	0.72 (0.48, 1.08)	
	2	623	11.6 (11.5, 11.6)	0.001	42 (6.7)	0.57 (0.36, 0.90)	
	3	327	11.7 (11.6, 11.7)	<0.001	10 (3.1)	0.33 (0.16, 0.69)	0.001
S-task	0	328	14.4 (13.8, 15.0)	Ref	56 (17.1)	1.00	
	1	634	14.6 (14.2, 15.0)	0.528	83 (13.1)	0.82 (0.56, 1.20)	
	2	624	15.9 (15.5, 16.3)	<0.001	40 (6.4)	0.44 (0.28, 0.69)	
	3	328	16.0 (15.5, 16.6)	<0.001	13 (4.0)	0.34 (0.18, 0.66)	<0.001

[1] All values are adjusted for sex, education, vitamin supplement use (multivitamins, folate, and vitamins B, C, D, or E), smoking status, history of CVD, diabetes, and total energy intake.

The most potent effects have been attributed to wine intake, because in several studies, moderate wine drinkers have shown strikingly low OR of 0.15–0.19 for Alzheimer's disease and dementia compared with nondrinkers (12,15,34,35). In our study, all wine consumers were grouped together, independent of dose, but the effect of wine intake was still evident (OR varied from 0.46 to 0.57 depending on cognitive test). Furthermore, we observed a plateau effect of wine at an intake of ~0.5 glass/d, which is comparable with the protective effect of moderate intake observed in the studies cited above. Because there were few people who reported high wine intake in our population (14 reported consuming >4 glasses/d), we could not study the effect of heavy consumption.

Several mechanisms by which moderate wine consumption might protect against cognitive impairment have been proposed, including reduced cardiovascular risk, antiinflammatory effects, and the antioxidant actions of its flavonoids (12,35,36). However, moderate wine intake may be a marker of a healthier diet or of a complex set of favorable social and lifestyle factors (15,34,37), which themselves are protective for cognitive impairment. In our study, we have tried to adjust for potentially relevant factors, but we cannot exclude the possibility of residual confounding.

Cocoa products are particularly rich sources of flavonoids, although this is influenced by the processing during manufacture (19). Due to a high antioxidant capacity, cocoa products have been promoted as having several beneficial properties (mainly cardiovascular). Even very modest consumption of chocolate may significantly contribute to total polyphenol intake (38). However, a recent clinical trial (39) did not find any beneficial effects of short-term (6 wk) dark chocolate and cocoa consumption on cardiovascular outcomes or on neuropsychological tests. In our study, we found that habitual chocolate users performed better in all cognitive tests and had significantly reduced risk for poor test performance in most tests, whereas the mean intake of chocolate among users was as little as <8 g/d. Moreover, a maximum beneficial effect on cognitive performance was gained at a mean intake of chocolate of ~10 g/d. The real effect of polyphenols in chocolate may be even stronger, because not all chocolates are equally good sources of flavonoids and the type of chocolate consumed was not specified in our study. In the US and Europe, milk chocolate is the most popular form, but this contains less cocoa mass than dark chocolate and therefore contains fewer polyphenols (40).

Green tea polyphenols have been promoted as therapeutic agents claimed to alter brain aging processes and as possible neuroprotective agents in progressive neurodegenerative diseases (18). There have been 2 recent studies on the association between tea intake and dementia or cognitive impairment in humans. In a cross-sectional study, Kuriyama et al. (16) found inverse dose-response relations between consumption of green tea and the prevalence of cognitive impairment and a weak relation between consumption of black tea and cognitive impairment. However, a strong inverse relationship was found by Ng et al. (17) between consumption of black tea and both cognitive impairment and cognitive decline. Although the flavonoid content in typical black (31%, wt:wt) and green (33%, wt:wt) tea is similar, there is a significant difference in catechins: ~9% in black tea and ~30% in green tea (41). The

JN THE JOURNAL OF NUTRITION

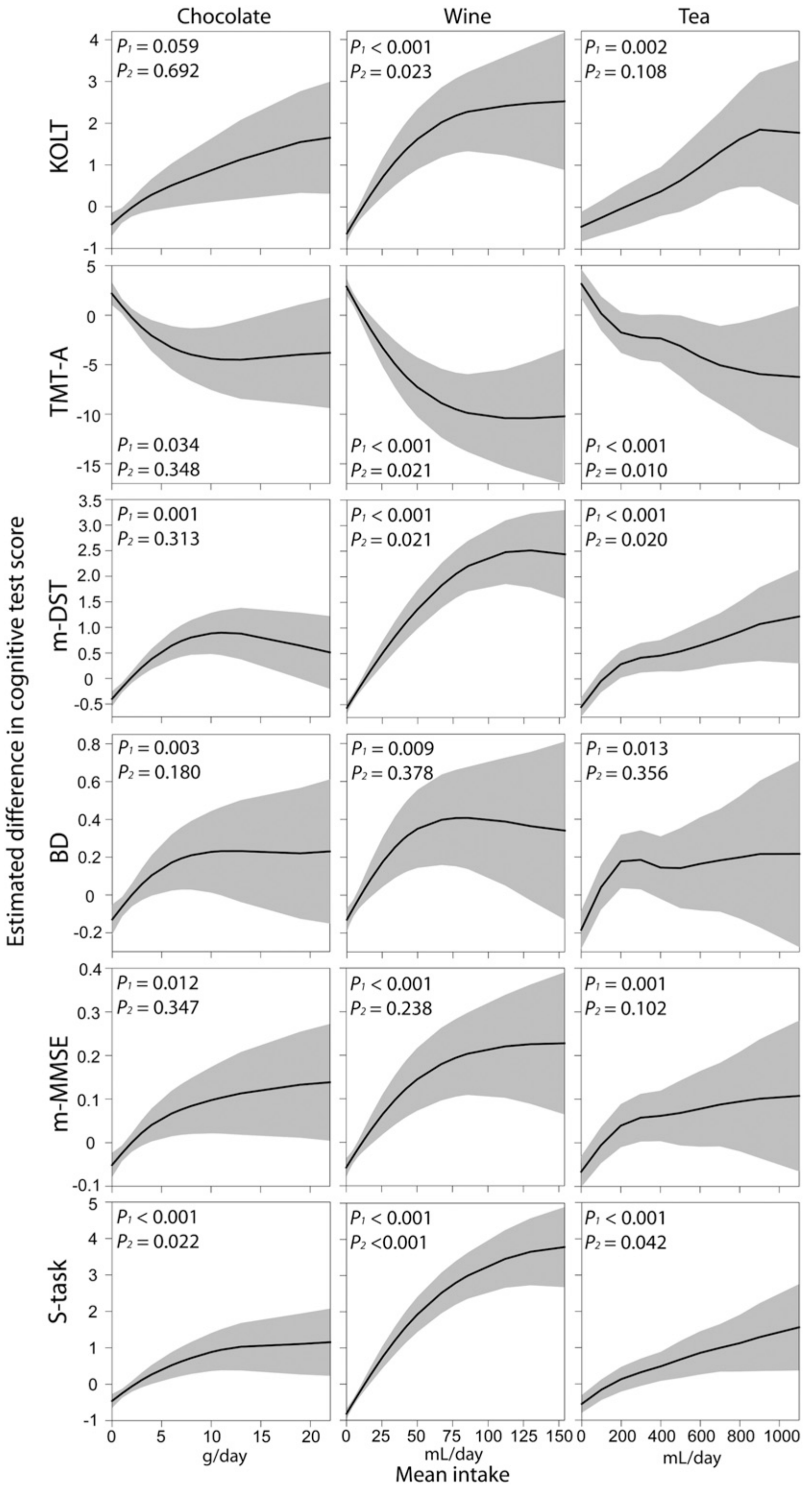

FIGURE 1 Associations between different cognitive tests scores and intake of chocolate, wine, and tea obtained by Gaussian generalized additive regression models. Solid lines are the estimated dose-response curves; shaded areas represent the 95% CI. *P*-values are from corresponding multiple linear regression analyses. P_1-values are adjusted for gender and P_2-values are adjusted for sex, education, vitamin supplement use (multivitamins, folate, and vitamins B, C, D, or E), smoking status, history of CVD, diabetes, and total energy intake. The data for the highest 2.5 percentile of chocolate, wine, and tea intake are not included.

favorable properties ascribed to tea consumption may be due to catechins and their derivatives (18,41,42) that are recognized as multifunctional compounds for neuroprotection. Although we did not record the type of tea consumed, black tea comprised 96% of the total tea imported into Norway in 1999 (43).

Food components are often studied in isolation, but the benefit achieved via food intake may depend not only on the individual component but on the milieu in which it is taken (1). Consistently, we found that the cognitive test scores improved and the risk for poor test performance decreased with the number of different flavonoid-rich items (chocolate, wine, and tea) consumed. Because plateau effects were observed individually for wine and chocolate intake (Fig. 1), the additive effect may reflect confounding by unknown lifestyle factors or it may reflect the presence of other substances that enhance the protective effects of flavonoids.

The strengths of our study include a large population-based sample with 6 different tests to study cognitive performance and the use of a well-validated FFQ. One limitation of dietary studies is error in the estimates of nutrients (4). Thus, it is possible to over- or underestimate true associations with outcomes if the type of certain foods was not specified, i.e. if the person preferred dark chocolate to milk chocolate or red wine to white wine or green tea to black tea. There was also no indication of whether individuals

TABLE 4 Cross-sectional associations in elderly men and women between habitual dietary chocolate, wine, and tea intake (dichotomous variables) during the previous year and poor test performance in different cognitive tests[1]

Cognitive test	Consumers		Nonconsumers			
(cutoff for poor performance)[2]	*n*	Poor test score, *n* (%)	*n*	Poor test score, *n* (%)	OR (95% CI)	*P*
Chocolate						
KOLT (25)	992	86 (8.7)	925	103 (11.1)	0.81 (0.59, 1.11)	0.185
TMT-A (111)	992	65 (6.6)	922	111 (12.0)	0.57 (0.40, 0.79)	0.001
m-DST (5)	990	61 (6.2)	922	93 (10.1)	0.67 (0.47, 0.97)	0.032
m-BD (10)	989	44 (4.4)	920	53 (5.8)	1.03 (0.67, 1.60)	0.887
m-MMSE (10)	986	59 (6.0)	916	104 (11.4)	0.63 (0.44, 0.90)	0.010
S-task (8)	992	76 (7.7)	922	116 (12.6)	0.71 (0.51, 0.98)	0.037
Wine						
KOLT (25)	845	54 (6.4)	1072	135 (12.6)	0.51 (0.36, 0.72)	$<$0.001
TMT-A (111)	844	42 (5.0)	1070	134 (12.5)	0.47 (0.32, 0.68)	$<$0.001
m-DST (5)	843	36 (4.3)	1069	118 (11.0)	0.52 (0.35, 0.77)	0.001
m-BD (10)	843	28 (3.3)	1066	69 (6.5)	0.59 (0.37, 0.95)	0.029
m-MMSE (10)	841	40 (4.8)	1061	123 (11.6)	0.53 (0.36, 0.78)	0.001
S-task (8)	845	49 (5.8)	1069	143 (13.4)	0.54 (0.38, 0.76)	$<$0.001
Tea						
KOLT (25)	1029	81 (7.9)	888	108 (12.2)	0.75 (0.55, 1.03)	0.080
TMT-A (111)	1030	77 (7.5)	884	99 (11.2)	0.72 (0.52, 0.99)	0.045
m-DST (5)	1030	68 (6.6)	882	86 (9.8)	0.77 (0.54, 1.09)	0.133
m-BD (10)	1028	37 (3.6)	881	60 (6.8)	0.64 (0.42, 1.00)	0.048
m-MMSE (10)	1025	77 (7.5)	877	86 (9.8)	0.95 (0.68, 1.33)	0.754
S-task (8)	1029	77 (7.5)	885	115 (13.0)	0.68 (0.49, 0.93)	0.017

[1] Values are adjusted for sex, education, vitamin supplement use (multivitamins, folate, and vitamins B, C, D, or E), smoking status, history of CVD, diabetes, and total energy intake.

[2] Cutoff points for poor test performance were set at about the 10th percentile, except for TMT, where the 90th percentile was used.

preferred weak or strong tea. With regard to alcohol consumption, underreporting by individuals is common and especially the information based on quantity-frequency data has such a tendency (44). Thus, observed relations are, if anything, probably an underestimation of the true effect, if there is one.

Because 77% of the study attendees volunteered for cognitive testing, the possibility of recruitment bias should be considered. Several differences between participants who did and those who did not undergo cognitive testing have been reported earlier (45). For flavonoid-rich food intake, the participants in the cognitive substudy drank more wine and tea than nonparticipants: mean wine intake was 12 [95% CI: 11, 13] vs. 7 [6, 8] mL/d ($P < 0.001$) and mean tea intake was 154 [143, 165] vs. 129 [114, 143] mL/d ($P = 0.007$). The difference in chocolate intake was only 0.5 g/d: 3.8 [3.5, 4.1] g/d vs. 3.3 [2.8, 3.7] g/d, respectively, among participants and nonparticipants ($P = 0.071$). Cognition in the elderly is shaped by long-term exposures (46,47). Thus, a major limitation of our study is the cross-sectional design, even though the questionnaire involved food intake over the previous year. Furthermore, participants with impaired cognition may have altered their diet as a consequence of a change in their cognitive status. In addition, self-reported dietary data collected from participants who are cognitively impaired or demented may be less reliable. However, because the participants in the present study were not seriously impaired, we do not think this had a major impact on our findings. Also, foods are not consumed individually but as part of a diet and therefore confounding by other food items is always an issue in studies using dietary assessments.

In conclusion, in a population-based study, we showed that intake of flavonoid-rich food, including chocolate, wine, and tea, is associated with better performance across several cognitive abilities and that the associations are dose dependent. However, these results should be considered with caution, because they were based on food-based analyses of population data and so we cannot conclude that the observed dietary benefits are truly associated with the flavonoids in chocolate, wine, or tea. We suggest that further studies should directly examine the flavonoid status and take into account other bioactive dietary substances in these foods.

Acknowledgments

We thank Elfrid Blomdal (University of Bergen, Norway), Gunnar Åmlid, and Dr. Kari Solvoll (University of Oslo, Norway) for their excellent support with the literature and the questionnaires.

Literature Cited

1. Van Dyk K, Sano M. The impact of nutrition on cognition in the elderly. Neurochem Res. 2007;32:893–904.
2. Rosenberg IH, Miller JW. Nutritional factors in physical and cognitive functions of elderly people. Am J Clin Nutr. 1992;55:S1237–43.
3. Selhub J, Bagley LC, Miller J, Rosenberg IH. B vitamins, homocysteine, and neurocognitive function in the elderly. Am J Clin Nutr. 2000;71:S614–20.
4. Luchsinger JA, Mayeux R. Dietary factors and Alzheimer's disease. Lancet Neurol. 2004;3:579–87.
5. Frank B, Gupta S. A review of antioxidants and Alzheimer's disease. Ann Clin Psychiatry. 2005;17:269–86.
6. Ancelin ML, Christen Y, Ritchie K. Is antioxidant therapy a viable alternative for mild cognitive impairment? Examination of the evidence. Dement Geriatr Cogn Disord. 2007;24:1–19.
7. Smith AD. The worldwide challenge of the dementias: a role for B vitamins and homocysteine? Food Nutr Bull. 2008;29:S143–72.

8. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. Am J Clin Nutr. 2004;79:727–47.
9. Ramassamy C. Emerging role of polyphenolic compounds in the treatment of neurodegenerative diseases: a review of their intracellular targets. Eur J Pharmacol. 2006;545:51–64.
10. Commenges D, Scotet V, Renaud S, Jacqmin-Gadda H, Barberger-Gateau P, Dartigues JF. Intake of flavonoids and risk of dementia. Eur J Epidemiol. 2000;16:357–63.
11. Letenneur L, Proust-Lima C, Le Gouge A, Dartigues JF, Barberger-Gateau P. Flavonoid intake and cognitive decline over a 10-year period. Am J Epidemiol. 2007;165:1364–71.
12. de Lorimier AA. Alcohol, wine, and health. Am J Surg. 2000;180:357–61.
13. Lindsay J, Laurin D, Verreault R, Hebert R, Helliwell B, Hill GB, McDowell I. Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. Am J Epidemiol. 2002;156:445–53.
14. Larrieu S, Letenneur L, Helmer C, Dartigues JF, Barberger-Gateau P. Nutritional factors and risk of incident dementia in the PAQUID longitudinal cohort. J Nutr Health Aging. 2004;8:150–4.
15. Mehlig K, Skoog I, Guo X, Schutze M, Gustafson D, Waern M, Ostling S, Bjorkelund C, Lissner L. Alcoholic beverages and incidence of dementia: 34-year follow-up of the prospective population study of women in Göteborg. Am J Epidemiol. 2008;167:684–91.
16. Kuriyama S, Hozawa A, Ohmori K, Shimazu T, Matsui T, Ebihara S, Awata S, Nagatomi R, Arai H, et al. Green tea consumption and cognitive function: a cross-sectional study from the Tsurugaya Project 1. Am J Clin Nutr. 2006;83:355–61.
17. Ng TP, Feng L, Niti M, Kua EH, Yap KB. Tea consumption and cognitive impairment and decline in older Chinese adults. Am J Clin Nutr. 2008;88:224–31.
18. Mandel SA, Avramovich-Tirosh Y, Reznichenko L, Zheng H, Weinreb O, Amit T, Youdim MB. Multifunctional activities of green tea catechins in neuroprotection. Modulation of cell survival genes, iron-dependent oxidative stress and PKC signaling pathway. Neurosignals. 2005;14:46–60.
19. Ding EL, Hutfless SM, Ding X, Girotra S. Chocolate and prevention of cardiovascular disease: a systematic review. Nutr Metab (Lond). 2006;3:2.
20. Francis ST, Head K, Morris PG, Macdonald IA. The effect of flavanol-rich cocoa on the fMRI response to a cognitive task in healthy young people. J Cardiovasc Pharmacol. 2006;47 Suppl 2:S215–20.
21. Fisher NDL, Sorond FA, Hollenberg NK. Cocoa flavanols and brain perfusion. J Cardiovasc Pharmacol. 2006;47 Suppl 2:S210–4.
22. HUSK. Recruitment into the cognitive sub-study of the Hordaland Homocysteine Study [cited 2008 May 16]. Available from: www.uib.no/isf/husk/Vedlegg_dokumenter/Cognitive_Sub_study.pdf.
23. Refsum H, Nurk E, Smith AD, Ueland PM, Gjesdal CG, Bjelland I, Tverdal A, Tell GS, Nygard O, et al. The Hordaland Homocysteine Study: a community-based study of homocysteine, its determinants, and associations with disease. J Nutr. 2006;136:S1731–40.
24. Nurk E, Drevon CA, Refsum H, Solvoll K, Vollset SE, Nygard O, Nygaard HA, Engedal K, Tell GS, et al. Cognitive performance among the elderly and dietary fish intake: the Hordaland Health Study. Am J Clin Nutr. 2007;86:1470.
25. Kendrick DC. Kendrick cognitive tests for the elderly. Windsor (UK): NFER-NELSON Publishing Company Ltd; 1985.
26. Reitan RM. Validity of the trail making test as an indicator of organic brain damage. Percept Mot Skills. 1958;8:271–6.
27. Wechsler D. Wechsler Adult Intelligence Scale-revised. New York: Psychological Corporation; 1981.
28. Folstein MF, Folstein SE, McHugh PR. Mini-mental state" A practical method for grading the cognitive state of patients for clinician. J Psychiatr Res. 1975;12:189–98.
29. Benton A, Hamsher K. Multilingual aphasia examination. (IA): AJA Associates; 1989.
30. Nes M, Andersen LF, Solvoll K, Sandstad B, Hustvedt BE, Lovo A, Drevon CA. Accuracy of a quantitative food frequency questionnaire applied in elderly Norwegian women. Eur J Clin Nutr. 1992;46:809–21.
31. Andersen LF, Solvoll K, Drevon CA. Very-long-chain (n-3)fatty acids as biomarkers for intake of fish and (n-3)fatty acid concentrates. Am J Clin Nutr. 1996;64:305–11.
32. Nurk E, Tell GS, Vollset SE, Nygård O, Refsum H, Ueland PM. Plasma total homocysteine and hospitalizations for cardiovascular disease. The Hordaland Homocysteine Study. Arch Intern Med. 2002;162:1374–81.
33. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361–70.
34. Solfrizzi V, D'Introno A, Colacicco AM, Capurso C, Del Parigi A, Baldassarre G, Scapicchio P, Scafato E, Amodio M, et al. Alcohol consumption, mild cognitive impairment, and progression to dementia. Neurology. 2007;68:1790–9.
35. Letenneur L. Risk of dementia and alcohol and wine consumption: a review of recent results. Biol Res. 2004;37:189–93.
36. Stampfer MJ, Kang JH, Chen J, Cherry R, Grodstein F. Effects of moderate alcohol consumption on cognitive function in women. N Engl J Med. 2005;352:245–53.
37. Ruidavets JB, Bataille V, Dallongeville J, Simon C, Bingham A, Amouyel P, Arveiler D, Ducimetiere P, Ferrieres J. Alcohol intake and diet in France, the prominent role of lifestyle. Eur Heart J. 2004;25:1153–62.
38. Scalbert A, Williamson G. Dietary intake and bioavailability of polyphenols. J Nutr. 2000;130:S2073–85.
39. Crews WD Jr, Harrison DW, Wright JW. A double-blind, placebo-controlled, randomized trial of the effects of dark chocolate and cocoa on variables associated with neuropsychological functioning and cardiovascular health: clinical findings from a sample of healthy, cognitively intact older adults. Am J Clin Nutr. 2008;87:872–80.
40. Cooper KA, Donovan JL, Waterhouse AL, Williamson G. Cocoa and health: a decade of research. Br J Nutr. 2008;99:1–11.
41. Wiseman SA, Balentine DA, Frei B. Antioxidants in tea. Crit Rev Food Sci Nutr. 1997;37:705–18.
42. Weinreb O, Mandel S, Amit T, Youdim MBH. Neurological mechanisms of green tea polyphenols in Alzheimer's and Parkinson's diseases. J Nutr Biochem. 2004;15:506–16.
43. Statistics Norway. National economy and external trade. [cited 2008 May 16]. Available from: http://statbank.ssb.no/statistikkbanken/Default_FR.asp?PXSid=0&nvl=true&PLanguage=0&tilside=selectvarval/define.asp&Tabellid=03057.
44. Koppes LLJ, Twisk JWR, Snel J, Kemper HCG. Concurrent validity of alcohol consumption measurement in a 'healthy' population; quantity-frequency questionnaire v. dietary history interview. Br J Nutr. 2002;88:427–34.
45. Nurk E, Refsum H, Tell GS, Engedal K, Vollset SE, Ueland PM, Nygaard HA, Smith AD. Plasma total homocysteine and memory in the elderly: the Hordaland Homocysteine Study. Ann Neurol. 2005;58:847–57.
46. Launer LJ. The epidemiologic study of dementia: a life-long quest? Neurobiol Aging. 2005;26:335–40.
47. Whalley LJ, Dick FD, McNeill G. A life-course approach to the aetiology of late-onset dementias. Lancet Neurol. 2006;5:87–96.