Caffeine and cognitive decline in elderly women at high vascular risk.

Marie-Noël Vercambre, Claudine Berr, Karen Ritchie, Jae Kang

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Marie-Noël Vercambre[1*], PhD   (mvercambre@mgen.fr)

Claudine Berr[2,3], MD PhD   (claudine.berr@inserm.fr)

Karen Ritchie[2,3], PhD   (karen.ritchie@inserm.fr)

Jae H. Kang[4], ScD   (nhjhk@channing.harvard.edu)

[1] From the MGEN Foundation for Public Health, Paris, France

[2] From Inserm, U1061, Montpellier, France

[3] From the University of Montpellier 1, Montpellier, France

[4] From the Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

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*Corresponding author: Marie-Noël Vercambre

Phone: +33 (0)1 40 47 20 43; Fax: +33 (0)1 40 47 21 91.

MGEN Foundation for Public Health, 3 square Max-Hymans, 75748 Paris Cedex 15

ABSTRACT

Background: Persons with vascular disorders are at higher risk of cognitive decline.

Objective: To determine whether caffeine may be associated with cognitive decline reduction in elderly at high vascular risk.

Methods: We included 2475 women aged 65+ years in the Women's Antioxidant Cardiovascular Study, a randomized trial of antioxidants and B vitamins for cardiovascular disease secondary prevention. We ascertained regular caffeine intake at baseline (1995-1996) using a validated 116 item-food frequency questionnaire. From 1998-2000 to 2005-2006, we administered four telephone cognitive assessments at two-year intervals evaluating global cognition, verbal memory and category fluency. The primary outcome was the change in global cognitive score, which was the average of the z-scores of all tests. We used generalized linear models for repeated measures that were adjusted for various sociodemographic, health and lifestyle factors to evaluate the difference in cognitive decline rates across quintiles of caffeine intake.

Results: We observed significantly slower rates of cognitive decline with increasing caffeine intake (p-trend=0.02). The rate difference between the highest and lowest quintiles of usual caffeine intake (> 371 versus < 30 mg/day) was equivalent to that observed between those who were 7 years apart in age (p=0.006). Consumption of caffeinated coffee was significantly related to slower cognitive decline (p-trend=0.05), but not other caffeinated products (e.g., decaf, tea, cola, chocolate). We conducted interaction analyses and observed stronger associations in women assigned to vitamin B supplementation (p-interaction = 0.02).

Conclusions: Caffeine intake was related to moderately better cognitive maintenance over 5 years in older women with vascular disorders.

Keywords: Cognition; Aging; Caffeine; Cohort studies; Risk factors; Epidemiology

INTRODUCTION

Caffeine has well known acute effects on alertness, mood, attention and energy [1]; caffeine may also have more long-term positive effects [2], including maintaining cognitive function into old age [3-6]. However, data are still lacking on whether caffeine may show beneficial associations with cognitive function among individuals suffering from pathologies already known to accelerate cognitive decline, notably cardiovascular disease [7]. In western countries, coffee is the major dietary source of caffeine in adults, with the highest consumption in adults over 30 years of age [8, 9], a point in the life-span at which rates of cardiovascular disorders with their associated risk of later-life cognitive impairment [10] also increase rapidly. Given the growing number of studies suggesting caffeine may have a vascular protective effect [11-13] and the lack of major adverse outcomes associated with caffeine consumption among groups at high cardiovascular risk [14], caffeine intake/coffee consumption is a promising exposure to evaluate in persons at high risk of cognitive impairment due to vascular risk factors. Thus, we examined the association between caffeine intake and cognitive decline over 5 years among 2475 elderly participants of the Women's Antioxidant Cardiovascular Study (WACS), a cohort of women with vascular disease or coronary risk factors. Our hypothesis was that moderate to high caffeine intake would be associated with greater cognitive stability in a dose-dependent manner.

MATERIALS AND METHODS

The WACS began in 1995-1996 (baseline) and included 8171 women, as a 2x2x2 randomized placebo-controlled trial of vitamin E, vitamin C, and beta-carotene supplementation for the secondary prevention of cardiovascular disease (CVD) [15]. Eligible participants were female health professionals, aged ≥ 40 years, with prevalent CVD or ≥ 3 coronary risk factors (i.e., parental history of premature myocardial infarction (MI), diabetes, hypertension,

hyperlipidemia, and body mass index ≥ 30 kg/m^2). Prevalent CVD included MI, stroke, revascularization procedures, symptomatic angina pectoris, or transient cerebral ischemia. In 1998, a fourth arm for B vitamin supplementation (combined folic acid, vitamin B6, and vitamin B12) was added among 5442 women [16]. Until the scheduled end in 2005, participants completed annual questionnaires on compliance, side effects, health, lifestyle and clinical endpoints. None of the supplements were found to reduce cardiovascular disease recurrence [15, 16] or influence cognitive decline [17, 18].

Cognitive sub-cohort

From 1998-2000, we assessed cognitive function through telephone interviews among participants aged ≥ 65 years. Of the 3170 eligible women, 190 were unreachable, 156 declined participation, and 2824 (95% of contacted women) completed the initial telephone cognitive assessment. These women received three further follow-up assessments at two-year intervals until 2005; 93% completed at least two cognitive assessments, and 81% completed at least three among four. For the fourth assessment, 24% of participants were not contacted as only a short interval had passed between their third interview and the end of the trial. The mean time from the initial to the last cognitive assessment was 5.4 years (range 4.1–6.1 years). The cognitive WACS sub-study was approved by the institutional review board of the Brigham and Women's Hospital, Boston, MA.

Cognitive Assessment

The telephone interview consisted of five cognitive tests, whose validity has already been described in detail previously [19, 20]. Global cognition was evaluated with the Telephone Interview of Cognitive Status (TICS) [21], a telephone adaptation of the Mini-Mental State Examination (range 0 to 41 points). Verbal memory was assessed with the TICS 10-word list

(immediate and delayed recall) and the East Boston Memory Test (immediate and delayed recall) [22]. A test of category fluency [23], in which women were asked to name as many animals as possible in one minute, was also administered.

Our primary outcome was the annual rate of change from the initial through the last assessment in a global composite score, computed as the mean of the z-scores from all cognitive tests ("global cognitive score"). As secondary outcomes, we considered the changes in TICS score, verbal memory composite score (mean of the z-scores from the immediate and delayed recalls of both TICS-10 word list and the East Boston Memory Test: "verbal memory score"), and category fluency score. Verbal memory is among the best predictors of Alzheimer disease [24]. Category fluency task activate a complex neural network encompassing frontal, parietal and angular regions, as well as the superior temporal gyri and the cerebellum [25]. This task is highly sensitive to vascular disorders in many cortical and sub-cortical areas of the brain, notably frontal-subcortical connections [26].

To derive the composite scores for participants who did not complete all tests (only 0.5% of the interviewed persons), we used the means of the z-scores from the available relevant tests.

Caffeine intake

The Willett semi-quantitative food frequency questionnaire was administered at WACS baseline. This dietary questionnaire, which has been extensively validated [27], asked about usual consumption during the past year of 116 food/beverage items, including "coffee with caffeine", "decaffeinated coffee", "tea, not herbal tea", "Coke, Pepsi, or other cola with sugar", "low-calorie cola, e.g, diet coke with caffeine" and "chocolate (e.g. Hershey's, M & M's)". Respondents had to choose among nine possible response categories with a specified portion size (1 glass, bottle or can; 1 cup; 1 bar or packet; etc.). The reports of coffee consumption has been found to show high validity in a study with similar participants [28].

For each food/beverage item, the reported amount consumed daily (calculated taking into account the consumption frequency together with the portion size) was multiplied by its caffeine content from the US Department of Agriculture National Nutrient Database for Standard Reference (http://www.ars.usda.gov/nutrientdata). Usual daily caffeine intake was computed as a sum across all food/beverage sources. Caffeine intake was first energy-adjusted using the residual method [29] and then categorized into quintiles.

We also considered the usual consumption of the main contributors of caffeine: caffeinated coffee, decaffeinated coffee, caffeinated cola, caffeinated diet cola, tea, and chocolate.

The mean time from the food frequency questionnaire to the initial cognitive assessment was 3.5 years (range 3.1-4.7 years). This lag period likely has some benefits. First, because diet was assessed at somewhat younger ages, the possibility of reverse causation (i.e. changes in diet due to underlying cognitive status leading to spurious associations) is minimized. Second, biologically, diet at more remote timepoints is probably more relevant to brain health than more immediate diet, as cognitive decline develops over a long period of time [24]. To further evaluate caffeine intake that represents stable intake over the long-run and to assess the robustness of our results to recent changes in diet, we conducted subgroup analyses only among women who reported at WACS baseline that their diet changed very little in the past five years.

For this study on diet and cognitive decline, 349 participants among the 2824 with initial cognitive assessment were excluded because of incomplete dietary information. Excluded women showed slightly lower cognitive scores than included women. There was no difference in caffeine intake between eligible women participating and not participating in the cognitive subcohort. In the end, the analysis sample for the present study included 2475 women.

Covariates

We obtained information on numerous potential confounders including sociodemographic status, medical conditions, medications and lifestyle factors plausibly linked with both cognitive decline and dietary habits. Basic models included age at initial cognitive assessment, education and energy from diet. In full multivariable models, we further adjusted for the WACS randomization assignments, as well as lifestyle and health variables (described in the footnote of Table 2). In secondary analyses, we further adjusted for incident vascular events during follow-up.

Statistical Analysis

We used general linear models for repeated measures with random intercepts and slopes to estimate the association of caffeine intake level with the annual rate of cognitive change. The longitudinal correlation in scores within subject was incorporated into the models using an unstructured covariance matrix. To help interpret the mean differences in annual rate of cognitive decline, we compared the effect estimate we found for caffeine and cognitive decline to that for age and cognitive decline, thus using the effect of age on cognitive decline as a "benchmark" for interpreting the mean differences in rates.

We tested for linear trends across quintiles of caffeine intake by assigning the median intake to each of the five categories as a continuous ordinal variable. We used Wald tests for statistical testing. All models were fitted by maximum likelihood method using the SAS software (SAS release 9.1, SAS Institute Inc., Cary, NC).

Considering the possibility that caffeine intake patterns or associations with cognitive decline may differ according to age, hypertension, diabetes, overall cardiovascular profile at baseline (prevalent CVD vs. vascular risk factors only), alcohol, smoking status, and trial assignment, we evaluated the interaction terms between caffeine intake and each of these factors and

conducted stratified analyses by potential effect modifiers (p-interaction <0.10). We also conducted analyses only among women with intact cognitive function at initial assessment (in the top 90th percentile of global cognitive score).

RESULTS

The mean score in our population at first cognitive assessment was 34.3 on TICS and 16.4 on category fluency test.

Higher caffeine intake was associated with lower age, greater alcohol consumption, lower level of physical activity and current smoking (Table 1). Concerning cardiovascular conditions/risk factors, higher caffeine intake was related to modestly lower prevalence of a history of hypertension and hyperlipidemia, but was not associated with the prevalence of a history of clinical MI, stroke, revascularization surgery, angina, transient ischemic attack, or diabetes.

Caffeine intake and cognitive change

In the multivariable-adjusted models, higher caffeine intake was related to rates of decline that were significantly slower in the global cognitive score (p-trend=0.02) and verbal memory score (p-trend=0.05) (Table 2). Higher caffeine intake was also inversely but not significantly associated with decline in the TICS (p-trend=0.07) and category fluency score (p-trend=0.08). In particular, women in the highest quintile of daily caffeine intake had significantly slower global cognitive decline than those in the bottom quintile (p<0.01); the caffeine in the highest quintile is equivalent to the amount of caffeine in approximately 4 cups of coffee (>371 mg/day). Dividing the effect estimate we found for caffeine and cognitive decline (0.028 standard unit/year slower rate of decline between the top and first quintile) by that for age and cognitive decline (0.004 standard unit/year slower rate of decline for every year of being

younger), we observed that the mean difference in rates of cognitive change between the fifth

and first quintiles of caffeine intake was equivalent to the mean differences found for women

7 years apart in age. Results were not substantially altered when we controlled for incident

major cardiovascular events during follow-up.

In multivariable models of cognitive change, we also evaluated the consumption of the main

contributors to caffeine intake as exposure variables (data not shown in table). We detected a

significant association between increasing caffeinated coffee consumption and slower

cognitive decline (the difference in rate for global score change for ≥ 4 cups / day vs. none

was 0.02 (95% Confidence Intervals (CI) = 0.00, 0.05); p-trend=0.05) but we observed no

associations with decaffeinated coffee (the difference in rate for ≥ 2 cups/day vs. none was -

0.01 (95% CI = -0.03, 0.01); p-trend=0.09). Similarly no associations were observed with the

other caffeinated products (tea, cola with caffeine, diet cola with caffeine, chocolate).

Secondary analyses

Among the subset of 840 women who declared a stable diet over the previous 5 years at

baseline, we observed similar (and somewhat stronger) associations between caffeine and

cognitive maintenance (Table 3).

Models limited to women in the top 90th percentile of global score at first cognitive interview

(i.e., with preserved cognitive function) yielded similar significant results as the primary

analyses (Table 3).

We observed no significant interaction with age, alcohol, smoking status, overall

cardiovascular profile at baseline (prevalent CVD vs. vascular risk factors only), diabetes,

hypertension or assignment to vitamin C, E or beta-carotene. However, when we examined

whether the association differed by trial assignment to vitamin B (active [n=890] vs. not

participating [n=700] or placebo [n=885]), we found that the protective association between

higher caffeine intake and cognitive decline was more pronounced among those assigned to vitamin B supplementation (p for interaction=0.02) (Table 4).

DISCUSSION

In our prospective study of over 2400 women with vascular conditions, those with higher caffeine intake (approximately 4 cups of coffee per day) showed significantly less 5-year decline in global cognitive functioning and in verbal memory compared to low- or non-consumers of caffeinated products.

Our results are consistent with previous studies [3-6, 30], and support the notion of a long-term protective effect of caffeine in cognitive decline. A unique contribution of our study has been to demonstrate that this protective effect is also evident in women with CVD or cardiovascular risk factors, who are at increased risk of cognitive impairment. Also, in this population of women whose baseline caffeine intake was not clearly related to cardiovascular health status, we observed an association between caffeine and cognitive maintenance, which was significant even when cardiovascular factors were controlled for, suggesting a direct neuroprotective effect of caffeine, independent of its putative indirect effect on cognition through cardiovascular risk modulation. The causal relationship is further supported by our observation of a dose-effect and well-known biological effects of caffeine on brain function [31], including modulation of white matter lesions and/or microvascular ischemic lesions [32]. A potential mechanism for the long-term neuroprotective effect of caffeine may involve blockade of adenosine A2A receptors [1], which may attenuate damage caused by beta-amyloid, the toxic peptide that accumulates in the brain of patients with Alzheimer disease (AD) [33]. Indeed, both acute or long-term caffeine administration were shown to reduce brain amyloid-beta levels in AD transgenic mice [34, 35] and memory restoration and reversal of AD pathology in mice with preexisting beta-amyloid burden [36]. Another neuroprotective

mechanism for caffeine would involve improving insulin sensitivity [37] and reducing the risk of diabetes [11], which is a strong risk factor for cognitive decline; this pathway would be particularly more relevant in populations with CVD or cardiovascular risk factors such as ours. More generally, protective effects of caffeine in cognitive aging could also be mediated through benefits on psychological factors, as caffeine may improve depressive symptoms [38], which, in turn, may protect against decline in cognitive functioning [39].

We further observed that the protective association with higher caffeine intake was stronger among women who were supplemented with B vitamins (folic acid, B6 and B12). Although this may be a chance finding, this result has some biological plausibility. An adverse effect of high coffee intake is the elevation of homocysteine [40], which is neurotoxic [41], and it has previously been reported that the cytogenetic damage induced by folate deficiency in mice was enhanced by large amounts of caffeine [42]. It is possible that in those with vitamin B supplementation, higher caffeine intake would not cause neurotoxic elevations in homocysteine, while still exerting other neuroprotective effects. This finding warrants further investigation.

Major strengths of the study included its large sample size, longitudinal design, the use of a validated cognitive test battery and the opportunity to adjust for several potential confounders such as smoking, physical activity and depression. Also, we implemented generalized linear models for repeated measures that took into account the within-person intra-correlation of assessments and that allows for data with incomplete follow-up, thus limiting attrition bias. Furthermore, the use of repeated cognitive assessment reduces the measurement error in the longitudinal analyses.

Regarding the limitations of this study, caffeinated product consumption was assessed using a self-administered questionnaire, which, although validated, fails to differentiate coffee bean type or method of preparation. Also, self-administered food frequency questionnaire could

have induced some differential misclassification. Caffeine intake might have been under-estimated in cognitively impaired persons who also had more frequent missing information and might be more likely to experiment decline. However, results were unchanged in the stratified analysis among persons with preserved cognitive function at initial cognitive assessment (top 90th percentile of global score). Also, the intake may not reflect long-term use as it was based on just the baseline assessment. However, recent data suggest that caffeinated beverage drinking habits are relatively stable over time [4], even in those with CVD events [14]. Moreover, our results were similar (and somewhat stronger) among women reporting a stable diet over the past 5 years. Thus, our results support the idea that for maintenance of cognitive health into old age, habitual long-term caffeine intake may be of importance. Although we were able to adjust for a large number of covariates, residual confounding remains a possibility (e.g., unmeasured beneficial lifestyle or social factors associated with coffee drinking). Because our study included only women, we are not able to generalize our findings to men. Results from previous studies suggest that women may be more sensitive than men to the positive effects of caffeine against both cardiovascular risk [12] and cognitive aging [31]. This differential effect of caffeine by sex should be examined in further studies. Finally, among the various constituents of coffee, we were able to directly measure the intake of caffeine; however, studies have shown that other constituents in coffee (e.g. polyphenols) may also have direct neuroprotective effects [43]. In this study, we were unable to evaluate other non-caffeine components in coffee and their relation to cognition. Although the results of our analysis (associations with caffeine and an associations with caffeinated but not de-caffeinated coffee consumption) are consistent with putative caffeine effects, further studies, including randomized clinical trials of caffeine, would be needed to isolate the effects of caffeine versus the effect of other coffee components on cognition.

CONCLUSION

In our cohort of over 2400 elderly women with vascular conditions, higher caffeine intake was associated with lesser cognitive decline over a 5-year period. Given the global population aging and related increasing prevalence of both cardiovascular and cognitive pathologies, and because the modifiable lifestyle habit of caffeinated products consumption is particularly common and socially well-integrated, our results could have major public health implications. However, as a psychoactive stimulant molecule with potentially detrimental effects associated with excessive intake (withdrawal, sleep deprivation, etc), further confirmatory studies, including short-term clinical trials, evaluating different dosages and timing of caffeine intake on cognition are warranted.

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The authors report no conflicts of interest.

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Table 1. Characteristics[a] of the WACS cognitive cohort participants by quintile of caffeine intake (n=2475)

	Quintile of caffeine intake					
	Q1	Q2	Q3	Q4	Q5	*p* value[c]
Age at initial cognitive assessment (y)	72.9(4.6)	72.6(4.2)	72.4(4.2)	72.3(4.1)	71.9(3.6)	***
Master's or a doctoral degree (%)	12	10	12	12	10	*ns*
Married (%)	60	62	61	58	59	*ns*
Alcohol intake (g/d)	2.8(6.9)	3.4(7.8)	3.7(8.4)	5.1(10.4)	3.9(7.9)	***
Physical activity[b] (kcal/wk)	1053(1377)	960(1220)	891(1340)	817(1011)	830(975)	*
Use of multivitamin supplements (%)	32	30	29	31	26	*ns*
Current smoker (%)	5	6	7	13	18	***
Body Mass Index (kg/m^2)	28.9(5.6)	28.7(5.5)	28.9(6.0)	28.7(5.7)	27.9(5.4)	*ns*
History of depression (%)	13	17	16	16	14	*ns*
History of myocardial infarction (%)	25	19	20	20	20	*ns*
History of stroke (%)	9	7	10	9	7	*ns*
History of revascularization surgery (%)	21	20	19	21	22	*ns*
History of angina (%)	43	50	46	43	44	*ns*
History of transient ischemic attack (%)	15	16	16	16	15	*ns*
History of diabetes (%)	21	18	17	18	14	*ns*
History of hypertension (%)	80	81	78	75	74	*
History of hyperlipidemia (%)	77	79	74	69	75	**

[a] Values are means (standard deviation) or percentages and are standardized to the age distribution of the study population (except for the age variable); those with missing information were not included for the tabulation

[b] Weekly calories expended from exercise and climbing the stairs

[c] From chi-squared tests or analysis of variance depending on the type of variable (categorical or numeric): *ns* = non-significant, * = $p<0.05$, ** = $p<0.01$, *** = $p<0.001$

Table 2. Adjusted mean differences (95% confidence intervals) in annual rates of cognitive change by quintiles of caffeine intake, WACS cognitive cohort (n=2475)

	Quintile of caffeine intake					
	Q1	Q2	Q3	Q4	Q5	
Median intake (mg/day)	10	57	152	296	495	
Range	<30	30-111	112-203	204-371	>371	*p* Trend
Global cognitive score[a]						
Basic-adjusted model[b]	0 (Reference)	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)	0.00 (-0.02, 0.02)	0.02 (0.00, 0.04)	0.066
Multivariable-adjusted model[c]	0 (Reference)	0.01 (-0.01, 0.03)	0.02 (0.00, 0.04)	0.00 (-0.02, 0.02)	0.03 (0.01, 0.05)	0.020
TICS						
Basic-adjusted model[b]	0 (Reference)	-0.02 (-0.12, 0.07)	-0.01 (-0.10, 0.09)	-0.02 (-0.12, 0.07)	0.06 (-0.03, 0.15)	0.151
Multivariable-adjusted model[c]	0 (Reference)	0.00 (-0.09, 0.10)	0.03 (-0.07, 0.12)	0.00 (-0.09, 0.09)	0.09 (-0.01, 0.18)	0.074
Verbal memory[a]						
Basic-adjusted model[b]	0 (Reference)	0.00 (-0.02, 0.02)	0.01 (-0.01, 0.03)	0.00 (-0.02, 0.02)	0.02 (0.00, 0.04)	0.110
Multivariable-adjusted model[c]	0 (Reference)	0.00 (-0.02, 0.03)	0.01 (-0.01, 0.04)	0.00 (-0.02, 0.03)	0.02 (0.00, 0.05)	0.048

Category fluency

Basic-adjusted model[b]	0 (Reference)	0.06 (-0.07, 0.19)	0.06 (-0.07, 0.19)	0.07 (-0.07, 0.20)	0.12 (-0.01, 0.25)	0.115
Multivariable-adjusted model[c]	0 (Reference)	0.04 (-0.09, 0.18)	0.05 (-0.08, 0.18)	0.06 (-0.07, 0.20)	0.13 (-0.01, 0.26)	0.077

TICS: Telephone Interview of Cognitive Status

[a] Global cognitive score is a composite score of the z-scores of the TICS, immediate and delayed recalls of the East Boston Memory Test, category fluency, and delayed recall of the TICS 10-word list; verbal memory score is a composite score of the z-scores of the immediate and delayed recalls of both the TICS 10-word and the East Boston Memory Test

[b] Adjusted for age (years), education (licensed practical nurse, vocational nurse or associate's degree; registered nurse degree or bachelor's degree; master's or doctoral degree) and energy from diet (tertiles)

[c] Further adjusted for marital status (married, divorced, widowed, single), alcohol intake (abstainer, 0.1-0.9g/day, ≥10g/day), physical activity (quartiles of weekly calories expended from exercise and climbing the stairs), use of multivitamin supplements (no, yes), smoking status (never, past, current), body mass index (quartiles), postmenopausal hormone therapy use (never, past, current), aspirin use exceeding 10 days in the previous month (no, yes), non-steroidal anti-inflammatory drug use exceeding 10 days in the previous month (no, yes), history of depression (no, yes), cardiovascular profile at baseline (myocardial infarction, stroke, revascularization procedures, symptomatic angina pectoris, transient cerebral ischemia, no clinical disease), diabetes (no, yes), hypertension (no, yes on pharmaceutical treatment, yes without pharmaceutical

treatment), hyperlipidemia (no, yes on pharmaceutical treatment, yes without pharmaceutical treatment), dietary intakes of vitamin C (tertiles),

vitamin E (tertiles), carotene (tertiles), vitamin B6 (tertiles), vitamin B12 (tertiles) and folates (tertiles), and randomization assignment for

vitamin E (placebo, active), vitamin C (placebo, active), beta-carotene (placebo, active), and folate (not assigned, placebo, active)

Table 3. Adjusted[a] mean differences (95% confidence intervals) in annual rates of cognitive change by quintiles of caffeine intake in two different strata, WACS cognitive cohort

	Q1	Q2	Q3	Q4	Q5	*p* Trend
			Quintile of caffeine intake			
Among the subset of women who reported a stable diet at baseline (no major change in diet over the prior 5 years) (N=840)						
Global cognitive score[b]	0 (reference)	0.03 (-0.01, 0.06)	0.05 (0.01, 0.08)	0.03 (-0.01, 0.06)	0.06 (0.03, 0.10)	0.004
TICS	0 (reference)	0.04 (-0.13, 0.21)	0.06 (-0.11, 0.23)	0.08 (-0.10, 0.25)	0.20 (0.02, 0.37)	0.022
Verbal memory[b]	0 (reference)	0.02 (-0.02, 0.05)	0.04 (0.01, 0.08)	0.03 (-0.01, 0.06)	0.06 (0.02, 0.09)	0.008
Category fluency	0 (reference)	0.16 (-0.07, 0.39)	0.22 (-0.01, 0.44)	0.11 (-0.13, 0.35)	0.31 (0.08, 0.55)	0.036
Among the subset of women in the top 90th percentile of global score at first cognitive interview (N=2227)						
Global cognitive score[b]	0 (reference)	0.00 (-0.02, 0.02)	0.01 (-0.01, 0.03)	0.00 (-0.02, 0.02)	0.02 (0.00, 0.04)	0.015
TICS	0 (reference)	-0.02 (-0.11, 0.07)	-0.01 (-0.10, 0.07)	-0.01 (-0.10, 0.08)	0.08 (-0.01, 0.18)	0.036
Verbal memory[b]	0 (reference)	0.00 (-0.02, 0.02)	0.01 (-0.01, 0.03)	0.00 (-0.02, 0.03)	0.02 (0.00, 0.04)	0.040
Category fluency	0 (reference)	0.02 (-0.12, 0.17)	0.02 (-0.12, 0.16)	0.04 (-0.10, 0.18)	0.09 (-0.05, 0.24)	0.177

TICS: Telephone Interview of Cognitive Status

[a] All models are multivariable-adjusted (covariates listed in footnotes b and c of Table 2)

[b] Global cognitive score is a composite score of the z-scores of the TICS, immediate and delayed recalls of the East Boston Memory Test, category fluency, and delayed recall of the TICS 10-word list; verbal memory score is a composite score of the z-scores of the immediate and delayed recalls of both the TICS 10-word and the East Boston Memory Test

Table 4. Adjusted[a] mean differences (95% confidence intervals) in annual rates of global cognitive change[b] by quintiles of caffeine intake, stratified by trial assignment to vitamin B supplementation, WACS cognitive cohort

Assignment to vitamin B supplementation	Quintile of caffeine intake					p Trend	p Interaction[a]
	Q1	Q2	Q3	Q4	Q5		
Active (N=890)	0 (reference)	0.02 (-0.01, 0.05)	0.04 (0.00, 0.07)	0.02 (-0.01, 0.05)	0.06 (0.03, 0.09)	0.002	
Not participant[c] or placebo (N=1585)	0 (reference)	-0.01 (-0.03, 0.02)	0.00 (-0.02, 0.03)	-0.01 (-0.04, 0.02)	0.01 (-0.02, 0.03)	0.468	0.022

[a] All models are multivariable-adjusted (covariates listed in footnotes b and c of Table 2)

[b] Change in the global cognitive score, which is a composite score of the z-scores of the TICS, immediate and delayed recalls of the East Boston Memory Test, category fluency, and delayed recall of the TICS 10-word list

[c] 28% of the whole sample did not participate to the Vitamin B supplementation arm of the trial