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Mediterranean diet and cognitive decline in women with cardiovascular disease or risk factors

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Abstract

Background—Cardiovascular disease and vascular risk factors increase rates of cognitive impairment, but very little is known regarding prevention in this high-risk group. The heart-healthy Mediterranean-type dietary pattern may beneficially influence both vascular and cognitive outcomes.

Objectives—We examined the association between Mediterranean-style diet and cognitive decline in women with prevalent vascular disease or ≥3 coronary risk factors.

Design / Participants / Setting—Prospective cohort study among 2504 women participants of the Women's Antioxidant Cardiovascular Study (WACS), a cohort of female health professionals Adherence to the Mediterranean diet was determined at WACS baseline (1995–1996) using a zero-to-nine-point scale with higher scores indicating higher adherence. In 1998–2000, participants aged ≥ 65 years underwent a telephone cognitive battery including five tests of global cognition, verbal memory, and category fluency. Tests were administered three additional times over 5.4 years.

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Statistical analyses performed—We used multivariable-adjusted generalized linear models for repeated measures to compare the annual rates of cognitive score changes across tertiles of Mediterranean diet score, as assessed at WACS baseline.

Results—In both basic- and multivariable-adjusted models, Mediterranean diet was not related to cognitive decline. No effect modification was detected by age, education, depression, cardiovascular disease severity at WACS baseline, or level of cognition at initial assessment.

Conclusions—In women at higher risk of cognitive decline due to vascular disease or risk factors, adherence to the Mediterranean diet was not associated with subsequent 5-year cognitive change.

Keywords

cognitive decline; vascular disease; hypertension; Mediterranean diet; longitudinal study

INTRODUCTION

Substantial evidence supports the role of cardiovascular disease (CVD) and coronary risk factors in both cognitive decline and dementia[1, 2]. Yet little is known regarding means of preserving cognitive health in this high-risk group, a group representing as much as 70% of those aged ≥ 65 years in the US[3]. Certainly, diet is known to modulate cardiovascular processes[4], and thus would appear a plausible behavioral approach to also reducing cognitive decline in those with vascular conditions. While some previous studies have focused on individual nutrients such as antioxidants, omega 3 fatty acids or B vitamins both in healthy participants and those with vascular risk, clinical trials of these agents have not shown either major vascular[5–7] or neuroprotective[8–10] effects in aging. In contrast, there may be additive and interactive effects between individual dietary components within a dietary pattern, and both randomized trials[11, 12] and cohort studies[13–15] have reported reduced cardiovascular outcomes with a Mediterranean diet pattern in particular, which is characterized by high intakes of fruits and vegetables, fish, cereals, legumes, and monounsaturated fat, moderate alcohol, and low amounts of meat and dairy products[16]. Through modulation of vascular processes, Mediterranean diet may potentially slow cognitive aging. However, there has been very limited prospective research on the Mediterranean diet and cognitive health[17–19], particularly in those with prevalent vascular disease or risk factors. In addition, even factors which may help maintain cognition in healthy older persons, may not be equally effective in those with existing vascular disease, as the pathology in the latter is likely more severe and potentially less tractable. Thus, the hypothesis that was tested was that a Mediterranean diet may be beneficial against cognitive decline in older persons with vascular disease; this study utilized data from the cognitive ancillary study among the oldest participants in the Women's Antioxidant Cardiovascular Study (WACS), a trial of secondary prevention of CVD.

METHODS

The Women's Antioxidant Cardiovascular Study (WACS) began in 1995–1996 ('baseline') among 8171 women across the United States, as a 2×2×2 randomized placebo-controlled trial of vitamin E, vitamin C, and beta-carotene supplementation for secondary prevention of CVD[20]. 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 (i.e., percutaneous transluminal angioplasty, coronary artery bypass graft, carotid endarterectomy, or peripheral artery surgery), 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[21]. Participants were 94.0% Caucasian and 3.3% African-American. Until the scheduled end in 2005, they completed annual questionnaires on compliance, side effects, health, lifestyle and clinical endpoints. All trial participants provided a written informed consent, and this study was approved by the institutional review board of Brigham and Women's Hospital, Boston, MA. None of the supplements were found to reduce cardiovascular disease recurrence[20, 21] or influence cognitive decline[22, 23].

Cognitive subcohort and study population

Among participants aged ≥ 65 years in 1998–2000, cognitive function was assessed using telephone interviews. 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 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 trial end. The mean time from the initial to the last cognitive assessment was 5.4 years (range 4.1–6.1 years).

For this study on diet and cognitive decline, 320 participants among the 2824 with initial cognitive assessment were excluded because of incomplete dietary information. Thus, the analysis sample for the present study was comprised of 2504 women.

Cognitive Assessment

The telephone interview consisted of five cognitive tests. Global cognition was evaluated with the Telephone Interview of Cognitive Status (TICS)[24] (range 0 to 41 points), a telephone adaptation of the Mini-Mental State Examination (MMSE). Verbal memory was assessed with the TICS 10-word list (immediate and delayed recalls) and the East Boston Memory Test (immediate and delayed recalls)[25]. A test of category fluency[26], in which women were asked to name as many animals as possible in one minute, was also administered.

The primary outcome was the 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. The secondary outcomes were 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), and category fluency score. Verbal memory is among the best predictors of Alzheimer disease[27], and category fluency partly measures executive function, which is associated with vascular disease. The means of the z-scores from the available relevant tests were used to derive the composite scores for participants who did not complete all tests (only 0.5% of participants). The derived composite scores were normally distributed. Extensive evidence supports the face and clinical validity of this telephone cognitive instrument as previously developed[28].

Mediterranean diet

The Willett semi-quantitative food frequency questionnaire was administered at WACS baseline. The questionnaire asked about the usual consumption during the past year (nine possible response categories) of 116 food items with a specified portion size. It has been extensively studied for validity[29]. The mean time from the food frequency questionnaire to the initial cognitive assessment was 3.5 years (range 3.1–4.4 years). This lag period likely has some benefits. First, because diet was assessed at somewhat younger ages, it is likely less influenced by "reverse" causation – that is, changes in diet due to underlying changes in cognitive status. Moreover, biologically, diet at more remote timepoints is probably more

relevant to brain health than more immediate diet, as cognitive decline develops over many years[27].

A widely-used method based on a 0 to 9-point scale was implemented to evaluate the degree of individual adherence to a Mediterranean diet pattern[30–32], where higher scores indicated stricter adherence. First, dietary intakes were energy-adjusted using the residual method, and 1600 kcal was added to the residuals for interpretability.[33] Then, for each of the nine major components of the Mediterranean diet (vegetables, legumes, fruits, cereals, fish, meat, dairy products, ratio of monounsaturated to saturated fat and alcohol), a value of zero or one was assigned, according to presumed level of health benefit. Specifically, women whose consumption of vegetables, legumes, fruits, cereals, fish, and monounsaturated to saturated fat ratio was above the median consumption in the study population were assigned a value of one, and a value of zero otherwise. In contrast, women whose consumption of meat and dairy products was above the median consumption were assigned a value of zero and a value of one otherwise. Finally, for alcohol intake, women with mild-to-moderate alcohol consumption (from 5 to 25 g of alcohol per day) were assigned a value of one and a value of zero otherwise[31, 32]. The Mediterranean diet score was generated by adding all the binary component scores. Its mean was 4.2 (SD, 1.8), and its distribution was normal. This sum was then divided into three categories (low, middle and high), broadly corresponding to tertiles: 0–3; 4–5; 6–9. Mean intakes of consumption for the nine diet components are presented in Table 1.

In secondary analysis, an alternate definition for the Mediterranean diet adherence was considered through using a 0–55 point diet score utilized in a recent study of Mediterranean diet and cognitive decline[19]. This adaptation from the score described by Panagiotakos et al.[34] was based on reported intakes of alcohol and 10 food groups: seven components consistent with the Mediterranean diet (nonrefined cereals, potatoes, fruits, vegetables, legumes / nuts / beans, fish, olive oil) and three ‘inconsistent’ components (red and processed meats, poultry, full-fat cheese and other dairy). The scores for each component ranged from 1 to 5 based on the level of consumption frequency observed at the population level.

To further assess the robustness of the results and susceptibility to recent changes in diet, subgroup analyses were conducted only among women who reported at WACS baseline that their diet changed very little in the past five years (n=847).

Covariates

Annual questionnaires to WACS participants were used to obtain information on a wide variety of potential confounders including sociodemographic factors, health, medications and lifestyle factors plausibly linked with both cognitive decline and dietary habits. Variables included in the models as adjustment variables are as follows: age (years), education (licensed practical nurse, vocational nurse or associate’s degree; registered nurse degree or bachelor’s degree; master’s or doctoral degree), energy from diet (quartiles), marital status (married, divorced, widowed, single), 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 (kg/m^2, 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), and randomization assignment for vitamin E (placebo, active), vitamin C (placebo, active), beta-carotene (placebo, active), and folate (not assigned, placebo, active). In numerous validation studies in populations similar to WACS, self-reported covariate data from studies of health professionals have proven to be highly valid.

Statistical Analysis

First, participants' characteristics at dietary assessment were compared across tertiles of Mediterranean diet score, using chi-squared tests (categorical variables) or analysis of variance (continuous variables).

Then, general linear models for repeated measures with random intercepts and slopes were used to estimate the association of Mediterranean diet score with the annual rate of cognitive change. The longitudinal correlation in scores within subject was incorporated into the models using an unstructured covariance matrix. Linear trends across level of Mediterranean diet adherence were tested by assigning the median value to each of the three categories of the Mediterranean diet score as a continuous ordinal variable. Wald tests were used for statistical testing. All models were fitted by maximum likelihood method using the SAS software (SAS release 9.1, SAS Institute Inc., Cary, NC).

Basic models included adjustment for age at initial cognitive assessment, educational attainment, and energy from diet. Full multivariable models further adjusted for WACS randomization assignments, and numerous lifestyle and health variables (as described above). Secondary analysis also adjusted for incident vascular events during follow-up.

Given the possibility that age, education, depression, cardiovascular profile at baseline or cognitive status at initial assessment could modify the association between Mediterranean diet and cognitive decline, interaction terms for these variables and Mediterranean diet score were evaluated, and stratified analyses by these variables were conducted as well. Potential effect modifiers were defined as follows: age at first cognitive assessment (age 65 – 72 [n=1261] versus age 73 – 91 [n=1243]); highest attained education (licensed practical nurse, vocational nurse, associate's or registered nurse degree [n=1802] versus bachelor's or master's or doctoral degree [n=702]); history of depression at baseline (no [n=2128] versus yes |n=376]); baseline cardiovascular status (CVD event [n=1882] versus risk factors only [n=622]) and cognitive status at first assessment (global cognitive score ≤ median [n=1252] versus global cognitive score > median [n=1252]).

RESULTS

The mean intakes of vegetables and legumes nearly doubled across tertiles of Mediterranean diet score, and mean intakes of fruit, fish and grains increased by nearly 50% (Table 1). The proportion of consumers of 5–25g of alcohol was 9% in the first tertile, 17% in the second and 30% in the third tertile of Mediterranean diet score.

As expected, stricter adherence to the Mediterranean diet was linked with higher education, lower body mass index and generally healthier behaviors (e.g., greater physical activity, less smoking) (Table 2). Importantly, adherence to Mediterranean diet was not clearly associated with cardiovascular profile at WACS baseline (i.e., history of clinical MI, stroke, revascularization surgery, angina, or transient ischemic attack; history of diabetes; history of hypertension), suggesting that the severity of cardiovascular disease at baseline was not a major confounder in the present study.

Mediterranean diet and cognitive change

In both the basic-adjusted and multivariable-adjusted models, no significant differences were observed across the categories of the Mediterranean diet score in the mean annual rate of cognitive change for the global composite, TICS, verbal memory, or category fluency scores (Table 3). For example, the mean multivariable-adjusted difference (95% confidence interval (CI)) in rates of change in the global composite score was 0.01 (−0.01, 0.02) between the second tertile and the first tertile of Mediterranean diet score, and 0.00 (−0.02, 0.01) between the top tertile and the first tertile (p-value for trend: 0.88).

Results were not substantially altered when models were controlled for incident major cardiovascular events during follow-up. In addition, results were consistently null when the Mediterranean diet score was considered as a continuous variable (e.g., for the global composite score, mean difference per additional score point was −0.001 (p-value for trend=0.40).

Also, no relations were observed with the alternate Mediterranean diet score: p-values for trend in cognitive change across tertiles were 0.58 for the global composite score, 0.25 for the TICS, 0.39 for the verbal memory score and 0.52 for the category fluency score.

In the 847 women who reported stable diets (34% of the whole sample), effect estimates were virtually identical to those from the entire cohort, and there were no statistically significant associations between Mediterranean diet score and cognitive decline (e.g., for global composite score, mean difference (95% CI) between top and bottom tertiles of Mediterranean diet score was 0.00 (−0.03, 0.03), p-value for trend: 0.95).

Effect modification and stratified analyses

When investigating whether the associations with Mediterranean diet on cognitive decline may differ by baseline age, education, depression history at baseline, cardiovascular profile at baseline or cognitive score at first assessment, no significant interactions were found. Similarly, stratified analyses revealed no quantitative or qualitative differences between associations across strata of any of these variables (data not shown in table).

DISCUSSION

In this large prospective study of older women with vascular disease or at high vascular risk, no association was observed between adherence to the Mediterranean diet and cognitive decline over 5 years of follow-up. The absence of association was consistent across various cognitive outcomes, different definitions of Mediterranean diet scores and various strata of the population. There was no suggestion of an association among women who reported that their diet had been stable for at least the past 5 years.

Of three large studies which have examined the association between Mediterranean diet and cognitive status in generally healthy participants, the two American studies have reported less cognitive decline[19] and lower risk of incident mild cognitive impairment[35] and incident Alzheimer disease[36] with greater adherence to a Mediterranean diet. However, in the French study[18], higher adherence to the Mediterranean diet was only weakly associated with slower decline in the MMSE and not consistently with other cognitive tests, and adherence was not related to risk of dementia. Thus, available results on the potential effect of Mediterranean diet in cognitive aging come from a limited number of inconsistent studies. The differences in absolute intakes of Mediterranean diet components across studies might explain some inconsistencies in the literature: the reference groups for the various components (based on median intakes) in the present study population had higher intakes of vegetables, cereals and a much higher monounsaturated / saturated fat ratio than the other studies from the US and

were quite similar to that in the French cohort, which also found null associations with decline in cognition (except for MMSE) and with dementia. Studies that test alternative approaches for quantifying adherence to the Mediterranean diet using individual rankings based on absolute dietary intakes may be informative, as would more studies from Mediterranean countries, where greater variability in Mediterranean diet adherence is to be expected. Finally, it is possible that prevention is even more challenging in those with prevalent vascular disease or risk factors, as in WACS.

Limitations of this study should be discussed. The WACS dietary data were collected at trial baseline with a self-administered food frequency questionnaire, which although widely used in epidemiologic studies[29], is subject to misclassification of exposures. This misclassification is likely to be non-differential because diet was assessed 3.5 years before cognitive function assessment; such non-differential misclassification would bias results towards the null and may explain the observed lack of association between Mediterranean diet and cognitive decline. However, other studies of diet and cognitive decline using this food frequency questionnaire in populations of health professionals have reported strong relations between diet and cognition[37, 38], indicating that misclassification is likely not a primary factor explaining the results. Moreover, the two studies which have found associations between the Mediterranean diet and cognitive health[19, 36] both used the same food frequency questionnaire to collect their dietary data. More importantly, the single assessment of dietary habits in late adulthood may not reflect the long-term dietary intakes of participants (particularly at midlife), which may be more etiologically relevant. This may be particularly true in this population of women at high cardiovascular risk, who were likely encouraged to change their diet at some point. To address this, the analyses were carefully adjusted for participants' cardiovascular profiles at WACS baseline as those with clinical disease rather than only risk factors may be more motivated to change their diet. Also, subgroup analyses were conducted only among women who reported at baseline that their diet changed very little in the past five years. All of these approaches yielded findings very similar to the main analyses. Moreover, long-term dietary change is hard to achieve even in those with vascular risk[39, 40], and no evidence was found in the data that Mediterranean diet adherence was related to level of clinical cardiovascular disease, suggesting that adoption of a Mediterranean diet was likely not determined or highly influenced by underlying health. In addition, the study population showed fairly wide ranges in reported intake of many components in the Mediterranean diet (e.g., a doubling or near doubling in vegetables and legumes intakes from bottom to top tertile and 50% increase in fruit and grain intake), thus there was large variability in the Mediterranean diet across participants.

Concerning the cognitive evaluation, a telephone assessment might lack validity. However, both reliability and validity studies of the telephone instrument (compared to in-person interviews) have provided convincing evidence of its utility to evaluate cognitive function in epidemiologic settings. Moreover, using the same or a similar telephone battery, significant associations with cognitive aging have been found with a large number of risk factors, including dietary variables establishing that the telephone instrument validly identifies risk factors for cognitive decline[37, 41]. Another limitation is that participants were mostly Caucasian, which precludes extending the findings to other ethnic minorities. Finally, residual confounding is always a possibility in observational studies, although the analyses were carefully adjusted on various potential confounders for the association between diet and cognitive change.

In summary, in a large sample of community-dwelling women aged ≥ 65 years with preexisting cardiovascular disease or risk factors, no associations were observed between Mediterranean diet adherence and 5-year cognitive decline. Given the limited number of studies of Mediterranean diet and cognitive health, potential effects of Mediterranean diet in

brain aging and dementia requires further evaluation, both in generally healthy participants and in those at higher risk of cognitive decline.

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Table 1

The nine Mediterranean diet components by tertile of Mediterranean diet score in the WACS Cognitive Cohort (n=2504)

	Mediterranean diet score			
Age-adjusted mean or percentage	**Low [0–3] n=889**	**Middle [4–5] n=1012**	**High [6–9] n=603**	**p-value***
Monounsaturated / saturated fat ratio	1.0	1.1	1.2	<0.001
Vegetable (serving/day)	2.6	3.8	4.7	<0.001
Fruit (serving/day)	1.9	2.5	3.0	<0.001
Legumes (serving/day)	0.3	0.5	0.6	<0.001
Fish (serving/day)	0.2	0.3	0.3	<0.001
Grain (serving/day)	1.5	2.0	2.3	<0.001
Meat (serving/day)	1.3	1.2	1.0	<0.001
Dairy (serving/day)	4.0	3.1	2.3	<0.001
Alcohol intake (% consumers 5–25g/day)	9%	17%	30%	<0.001

* From chi-squared tests or analysis of variance depending on the type of variable (categorical or continuous)

Table 2

Age and age-adjusted characteristics of WACS Cognitive Cohort by tertile of Mediterranean diet score (n=2504)

	Mediterranean diet score			
	Low [0–3]	**Middle [4–5]**	**High [6–9]**	**p-value***
Age at initial cognitive assessment (y): Mean+/−SD (range)	71.9+/−3.9 (66.1–91.2)	72.5+/−4.3 (66.1–90.5)	72.6+/−4.0 (66.1–90.1)	0.002
Cognitive score at initial cognitive assessment: Mean (SD)				
Global cognitive score† (standard unit)	0.005 (0.6)	−0.026 (0.7)	0.025 (0.7)	0.34
TICS (point)	34.4 (3.0)	34.3 (3.3)	34.6 (3.2)	0.14
Verbal memory† (standard unit)	0.002 (0.7)	−0.022 (0.7)	0.039 (0.7)	0.44
Category fluency (point)	16.5 (4.8)	16.4 (4.9)	16.7 (4.9)	0.56
Health and lifestyle characteristics: Mean or %				
Master's or a doctoral degree (%)	8%	10%	15%	<0.001
Married (%)	58%	61%	64%	0.09
Physical activity‡ (mean kcal/wk)	707	949	1138	<0.001
Use of multivitamin supplements (%)	29%	28%	32%	0.33
Current smoker (%)	13%	10%	5%	<0.001
Body Mass Index (mean kg/m^2)	29.1	28.8	27.6	<0.001
History of depression (%)	16%	16%	12%	0.04
History of myocardial Infarction (%)	20%	22%	21%	0.52
History of stroke (%)	8%	8%	9%	0.69
History of revascularization surgery (%)	20%	20%	24%	0.18
History of angina (%)	43%	46%	47%	0.23
History of transient ischemic attack (%)	15%	15%	14%	0.94
History of diabetes (%)	17%	18%	16%	0.54
History of hypertension (%)	78%	78%	75%	0.35
History of hyperlipidemia (%)	72%	76%	79%	0.005

SD: standard deviation; TICS: Telephone Interview of Cognitive Status

*From chi-squared tests or analysis of variance depending on the type of variable (categorical or continuous)

†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

‡Weekly calories expended from exercise and climbing the stairs

Table 3

Adjusted mean differences (95% confidence intervals) in annual rates of cognitive decline by tertiles of Mediterranean Diet score (n=2504)

	Mediterranean Diet score			
	Low [0–3]	**Middle [4–5]**	**High [6–9]**	**p-value for trend**
Global cognitive score (n=2504)*				
Basic-adjusted model†	0 (Reference)	0.01 (0.00, 0.02)	0.00 (−0.01, 0.02)	0.67
Multivariable-adjusted model‡	0 (Reference)	0.01 (−0.01, 0.02)	0.00 (−0.02, 0.01)	0.88
TICS (n=2504)				
Basic-adjusted model†	0 (Reference)	0.03 (−0.04, 0.10)	−0.01 (−0.09, 0.06)	0.81
Multivariable-adjusted model‡	0 (Reference)	0.02 (−0.05, 0.08)	−0.03 (−0.11, 0.05)	0.53
Verbal memory (n=2504)*				
Basic-adjusted model†	0 (Reference)	0.01 (−0.01, 0.02)	0.00 (−0.01, 0.02)	0.54
Multivariable-adjusted model‡	0 (Reference)	0.00 (−0.01, 0.02)	0.00 (−0.02, 0.02)	0.97
Category fluency (n=2499)				
Basic-adjusted model†	0 (Reference)	0.01 (−0.08, 0.11)	−0.03 (−0.14, 0.08)	0.67
Multivariable-adjusted model‡	0 (Reference)	0.01 (−0.08, 0.11)	−0.03 (−0.14, 0.08)	0.64

TICS: Telephone Interview of Cognitive Status

* 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

† 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 (quartiles)

‡ Further adjusted for marital status (married, divorced, widowed, single), 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 (kg/m^2, 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), and randomization assignment for vitamin E (placebo, active), vitamin C (placebo, active), beta-carotene (placebo, active), and folate (not assigned, placebo, active)