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## 1 **Mediterranean Diet and Cognitive Decline in Women with Cardiovascular** 2 **Disease or Risk Factors**

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5 ScD

### 6 7 INTRODUCTION

8       Substantial evidence supports the role of cardiovascular disease (CVD) and coronary risk  
9 factors in both cognitive decline and dementia (1,2). Yet little is known regarding means of  
10 preserving cognitive health in this high-risk group, a group representing as much as 70% of those  
11 aged  $\geq 65$  years in the US (3). Certainly, diet is known to modulate cardiovascular processes (4),  
12 and thus would appear a plausible behavioral approach to also reducing cognitive decline in  
13 those with vascular conditions. While some previous studies have focused on individual nutrients  
14 such as antioxidants, omega 3 fatty acids or B vitamins both in healthy participants and those  
15 with vascular risk, clinical trials of these agents have not shown either major vascular (5-7) or  
16 neuroprotective (8-10) effects in aging. In contrast, there may be additive and interactive effects  
17 between individual dietary components within a dietary pattern, and both randomized trials  
18 (11,12) and cohort studies (13-15) have reported reduced cardiovascular outcomes with a  
19 Mediterranean diet pattern in particular, which is characterized by high intakes of fruits and  
20 vegetables, fish, cereals, legumes, and monounsaturated fat, moderate alcohol, and low amounts  
21 of meat and dairy products (16). Through modulation of vascular processes, Mediterranean diet  
22 may then potentially slow cognitive aging. However, there has been very limited prospective  
23 research on the Mediterranean diet and cognitive health (17-19), and to our knowledge, no data  
24 in those with prevalent vascular disease or risk factors. In fact, even factors which may help  
25 maintain cognition in healthy older persons, may not be equally effective in those with existing  
26 vascular disease, as pathology in the later is likely more severe and potentially less tractable.

27 Thus, the potential effect of Mediterranean diet on cognitive decline was specifically evaluated  
28 in older persons with vascular disease, utilizing data from the cognitive ancillary study among  
29 the oldest participants in the Women's Antioxidant Cardiovascular Study (WACS), a trial of  
30 secondary prevention of CVD.

31

## 32 METHODS

33 The Women's Antioxidant Cardiovascular Study (WACS) began in 1995-1996 ('baseline')  
34 among 8171 American women, as a 2x2x2 randomized placebo-controlled trial of vitamin E,  
35 vitamin C, and beta-carotene supplementation for secondary prevention of CVD (20). Eligible  
36 participants were US female health professionals, aged  $\geq 40$  years, with prevalent CVD or  $\geq 3$   
37 coronary risk factors (i.e., parental history of premature myocardial infarction (MI), diabetes,  
38 hypertension, hyperlipidemia, and body mass index  $\geq 30$  kg/m<sup>2</sup>). Prevalent CVD included MI,  
39 stroke, revascularization procedures (i.e., percutaneous transluminal angioplasty, coronary artery  
40 bypass graft, carotid endarterectomy, or peripheral artery surgery), symptomatic angina pectoris,  
41 or transient cerebral ischemia. In 1998, a fourth arm for B vitamin supplementation (combined  
42 folic acid, vitamin B6, and vitamin B12) was added among 5442 women (21). Participants were  
43 94.0% Caucasian and 3.3% African-American. Until the scheduled end in 2005, they completed  
44 annual questionnaires on compliance, side effects, health, lifestyle and clinical endpoints. This  
45 study was approved by the institutional review board of Brigham and Women's Hospital,  
46 Boston, MA. Each participant gave a written informed consent. None of the supplements were  
47 found to reduce cardiovascular disease recurrence (20,21) or influence cognitive decline (22,23).

48

49 Cognitive subcohort and study population

50 From 1998-2000, cognitive function were assessed using telephone interviews among  
51 participants then aged  $\geq 65$  years. Of the 3170 eligible women, 190 were unreachable, 156  
52 declined participation, and 2824 (95% of contacted women) completed the initial telephone  
53 cognitive assessment. These women received three follow-up assessments at two-year intervals  
54 until 2005; 93% completed at least two cognitive assessments, and 81% completed at least three  
55 among four. For the fourth assessment, 24% of participants were not contacted as only a short  
56 interval had passed between their third interview and the trial end. The mean time from the initial  
57 to the last cognitive assessment was 5.4 years (range 4.1–6.1 years).

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

61

## 62 Cognitive Assessment

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

69 The primary outcome was the rate of change from the initial through the last assessment in  
70 a global composite score, computed as the mean of the z-scores from all cognitive tests. The  
71 secondary outcomes were the changes in TICS score, verbal memory composite score (mean of  
72 the z-scores from the immediate and delayed recalls of both TICS-10 word list and the East

73 Boston Memory Test), and category fluency score. Verbal memory is among the best predictors  
74 of Alzheimer disease (27), and category fluency partly measures executive function, which is  
75 associated with vascular disease. The means of the z-scores from the available relevant tests  
76 were used to derive the composite scores for participants who did not complete all tests (only  
77 0.5% of participants). Extensive evidence supports the face and clinical validity of this telephone  
78 cognitive instrument as previously developed (28).

79

80 Mediterranean diet

81 The Willett semi-quantitative food frequency questionnaire was administered at WACS  
82 baseline. The questionnaire asked about the usual consumption during the past year (nine  
83 possible response categories) of 116 food items with a specified portion size. It has been  
84 extensively studied for validity (29). The mean time from the food frequency questionnaire to the  
85 initial cognitive assessment was 3.5 years (range 3.1-4.4 years). This lag period likely has some  
86 benefits. First, since diet was assessed at somewhat younger ages, it is likely less influenced by  
87 “reverse” causation – that is, changes in diet due to underlying cognitive status. Moreover,  
88 biologically, diet at more remote timepoints is probably more relevant to brain health than more  
89 immediate diet, as cognitive decline develops over many years (27).

90 A widely-used method based on a 0 to 9-point scale was implemented to evaluate the  
91 degree of individual adherence to a Mediterranean diet pattern (30-32), where higher scores  
92 indicated stricter adherence. First, dietary intakes were energy-adjusted using the residual  
93 method. Then, for each of nine major components of the Mediterranean diet (vegetables,  
94 legumes, fruits, cereals, fish, meat, dairy products, ratio of monounsaturated to saturated fat and  
95 alcohol), a value of zero or one was assigned, according to presumed level of health benefit.

96 Specifically, women whose consumption of vegetables, legumes, fruits, cereals, fish, and  
97 monounsaturated to saturated fat ratio was above the median consumption in the study  
98 population were assigned a value of one, and a value of zero otherwise. In contrast, women  
99 whose consumption of meat and dairy products was above the median consumption were  
100 assigned a value of zero and a value of one otherwise. Finally, for alcohol intake, women with  
101 mild-to-moderate alcohol consumption (from 5 to 25 g of alcohol per day) were assigned a value  
102 of one and a value of zero otherwise (31,32). The Mediterranean diet score was generated by  
103 adding all the binary component scores. Its mean was 4.2 (SD, 1.8) and its distribution was  
104 normal. This sum was then divided into three categories (low, middle and high), broadly  
105 corresponding to tertiles: 0-3; 4-5; 6-9. Mean intakes of consumption for the nine diet  
106 components are presented in Table 1.

107 In secondary analysis, an alternate definition for the Mediterranean diet adherence was  
108 considered through a 0-55 point diet score used in a recent study of Mediterranean diet and  
109 cognitive decline (19). This adaptation from the score described by Panagiotakos et al. (33) was  
110 based on reported intakes of alcohol and 10 food groups: seven components consistent with the  
111 Mediterranean diet (nonrefined cereals, potatoes, fruits, vegetables, legumes / nuts / beans, fish,  
112 olive oil) and three 'inconsistent' components (red and processed meats, poultry, full-fat cheese  
113 and other dairy). The scores for each component ranged from 1 to 5 based on the level of  
114 consumption frequency observed at the population level.

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

118

## 119 Covariates

120 Annual questionnaires to WACS participants were used to obtain information on a wide  
121 variety of potential confounders including sociodemographic factors, health, medications and  
122 lifestyle factors plausibly linked with both cognitive decline and dietary habits. Variables  
123 introduced in the models as adjustment variables included: age (years), education (licensed  
124 practical nurse, vocational nurse or associate's degree; registered nurse degree or bachelor's  
125 degree; master's or doctoral degree), energy from diet (quartiles), marital status (married,  
126 divorced, widowed, single), physical activity (quartiles of weekly calories expended from  
127 exercise and climbing the stairs), use of multivitamin supplements (no, yes), smoking status  
128 (never, past, current), body mass index (quartiles), postmenopausal hormone therapy use (never,  
129 past, current), aspirin use exceeding 10 days in the previous month (no, yes), non-steroidal anti-  
130 inflammatory drug use exceeding 10 days in the previous month (no, yes), history of depression  
131 (no, yes), cardiovascular profile at baseline (myocardial infarction, stroke, revascularization  
132 procedures, symptomatic angina pectoris, transient cerebral ischemia, no clinical disease),  
133 diabetes (no, yes), hypertension (no, yes on pharmaceutical treatment, yes without  
134 pharmaceutical treatment), hyperlipidemia (no, yes on pharmaceutical treatment, yes without  
135 pharmaceutical treatment), and randomization assignment for vitamin E (placebo, active),  
136 vitamin C (placebo, active), beta-carotene (placebo, active), and folate (not assigned, placebo,  
137 active). In numerous validation studies in populations similar to WACS, self-reported covariate  
138 data from studies of health professionals have proven to be highly valid.

139

## 140 Statistical Analysis

141 First, participants' age and age-standardized characteristics at dietary assessment were  
142 compared across tertiles of Mediterranean diet score. Homogeneity was tested using p-values  
143 from Chi<sup>2</sup> test or variance analysis depending on the covariate type (categorical or numeric).

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

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

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

164 cardiovascular status (CVD event [n=1882] versus risk factors only [n=622]) and cognitive  
165 status at first assessment (global cognitive score  $\leq$  median [n=1252] versus global cognitive  
166 score  $>$  median [n=1252]).

167

## 168 RESULTS

169 In the study population, mean intakes of vegetables and legumes nearly doubled across  
170 tertiles of Mediterranean diet score and mean intakes of fruit, fish and grains increased by nearly  
171 50% (Table 1). Proportion of mild-to-moderate alcohol consumers was 9% in the first tertile,  
172 17% in the second and 30% in the third tertile of Mediterranean diet score.

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

180

### 181 Mediterranean diet and cognitive change

182 In both the basic-adjusted and multivariable-adjusted models, no significant differences  
183 were observed across the categories of the Mediterranean diet score in the mean annual rate of  
184 cognitive change for the global composite, TICS, verbal memory, or category fluency scores  
185 (Table 3). For example, the mean multivariable-adjusted difference (95% confidence interval  
186 (CI)) in rates of change in the global composite score was 0.01 (-0.01, 0.02) between the second

187 tertile and the first tertile of Mediterranean diet score, and 0.00 (-0.02, 0.01) between the top  
188 tertile and the first tertile (p-value for trend: 0.88).

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

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

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

201

#### 202 Effect modification and stratified analyses

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

208

209

## 210 DISCUSSION

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

217 Of three large studies which have examined the association between Mediterranean diet and  
218 cognitive status in generally healthy participants, the two American studies have reported less  
219 cognitive decline (19) and lower risk of incident mild cognitive impairment (34) and incident  
220 Alzheimer disease (17) with greater adherence to a Mediterranean diet. However, in the French  
221 study (18), higher adherence to the Mediterranean diet was only weakly associated with slower  
222 decline in the MMSE and not consistently with other cognitive tests, and adherence was not  
223 related to risk of dementia. Thus, available results on the potential effect of Mediterranean diet in  
224 cognitive aging come from a limited number of inconsistent studies. What should be particularly  
225 underlined is the great variability across these studies in terms of “absolute” adherence to the  
226 Mediterranean diet : based on a comparison of the reported intakes of the nine components for  
227 the various categories of adherence, reference group in the present study population had higher  
228 intakes of vegetables, cereals and a much higher monounsaturated / saturated fat ratio than the  
229 other studies from the US, and was quite similar to that in the French cohort, which also found  
230 null associations with decline in cognition (except for MMSE) and with dementia. Moreover, it  
231 is possible that prevention is even more challenging in those with prevalent vascular disease or  
232 risk factors, as in WACS.

233           Limitations of this study should be discussed. The WACS dietary data were collected at  
234 trial baseline with a self-administered food frequency questionnaire, which although widely used  
235 in epidemiologic studies (29), is subject to misclassification of exposures. This misclassification  
236 is highly likely to be non-differential because diet was assessed 3.5 years before cognitive  
237 function assessment; such non-differential misclassification would bias results towards the null  
238 and may explain the observed lack of association between Mediterranean diet and cognitive  
239 decline. However, other studies of diet and cognitive decline using this food frequency  
240 questionnaire in populations of health professionals have reported strong relations between diet  
241 and cognition (35,36), indicating that misclassification is likely not a primary factor in the results  
242 here. Moreover, the two studies which have found associations between the Mediterranean diet  
243 and cognitive health (19,37) both used the same food frequency questionnaire to collect their  
244 dietary data. More importantly, the single assessment of dietary habits in late adulthood may not  
245 reflect the long-term dietary intakes of participants (in particular at midlife), which may be more  
246 etiologically relevant. This may be particularly true in this population of women at high  
247 cardiovascular risk, who were likely encouraged to change their diet at some point. To address  
248 this, the analyses were carefully adjusted for participants' cardiovascular profiles at WACS  
249 baseline. Indeed, those with clinical disease rather than only risk factors may be more motivated  
250 to change their diet. Also, subgroup analyses were conducted only among women who reported  
251 at baseline that their diet changed very little in the past five years. All of these approaches  
252 yielded findings very similar to the main analyses. Moreover, long-term dietary change is hard to  
253 achieve even in those with vascular risk (38,39) and no evidence was found in the data that  
254 Mediterranean diet adherence was related to level of clinical cardiovascular disease, suggesting  
255 that adoption of a Mediterranean diet was likely not determined or highly influenced by

256 underlying health. In addition, the study population showed fairly wide ranges in reported intake  
257 of many components in the Mediterranean diet (e.g., a doubling or near doubling in vegetables  
258 and legumes intakes from bottom to top tertile and 50% increase in fruit and grain intake), thus  
259 there was large variability in the Mediterranean diet across participants.

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

270       In summary, in a large sample of community-dwelling women aged  $\geq 65$  years with pre-  
271 existing cardiovascular disease or risk factors, no associations were observed between  
272 Mediterranean diet adherence and 5-year cognitive decline. Given the limited number of studies  
273 of Mediterranean diet and cognitive health, potential effects of Mediterranean diet in brain aging  
274 and dementia requires further evaluation, both in generally healthy participants and in those at  
275 higher risk of cognitive decline. To have a better view in the matter, it would be interesting to  
276 test various approaches for the Mediterranean diet, not only population-dependant approaches of  
277 adherence (such as the 0-9 point scale used here), but also individual ranking based on absolute  
278 dietary intakes.

279

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