

# Adherence to a Mediterranean Diet, Cognitive Decline, and Risk of Dementia

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**T**HE TRADITIONAL MEDITERRANEAN diet is characterized by high consumption of plant foods (vegetables, fruits, legumes, and cereals), high intake of olive oil as the principal source of mono-unsaturated fat but low intake of saturated fat, moderate intake of fish, low to moderate intake of dairy products, low consumption of meat and poultry, and wine consumed in low to moderate amounts, normally with meals.<sup>1</sup> Adherence to a Mediterranean-type diet has been associated with longer survival, reduced risk of cardiovascular or cancer mortality, and reduced risk of neurodegenerative disease.<sup>2,3</sup>

A Mediterranean diet might also have protective effects against cognitive decline in older individuals, because it combines several foods and nutrients potentially protective against cognitive dysfunction or dementia, such as fish, monounsaturated fatty acids, vitamins B<sub>12</sub> and folate, antioxidants (vitamin E, carotenoids, flavonoids), and moderate amounts of alcohol.<sup>4-10</sup> A single study

See also pp 627 and 686 and Patient Page.

**Context** Higher adherence to a Mediterranean-type diet is linked to lower risk for mortality and chronic diseases, but its association with cognitive decline is unclear.

**Objective** To investigate the association of a Mediterranean diet with change in cognitive performance and risk for dementia in elderly French persons.

**Design, Setting, and Participants** Prospective cohort study of 1410 adults ( $\geq 65$  years) from Bordeaux, France, included in the Three-City cohort in 2001-2002 and reexamined at least once over 5 years. Adherence to a Mediterranean diet (scored as 0 to 9) was computed from a food frequency questionnaire and 24-hour recall.

**Main Outcome Measures** Cognitive performance was assessed on 4 neuropsychological tests: the Mini-Mental State Examination (MMSE), Isaacs Set Test (IST), Benton Visual Retention Test (BVRT), and Free and Cued Selective Reminding Test (FCSRT). Incident cases of dementia ( $n=99$ ) were validated by an independent expert committee of neurologists.

**Results** Adjusting for age, sex, education, marital status, energy intake, physical activity, depressive symptomatology, taking 5 medications/d or more, apolipoprotein E genotype, cardiovascular risk factors, and stroke, higher Mediterranean diet score was associated with fewer MMSE errors ( $\beta=-0.006$ ; 95% confidence interval [CI],  $-0.01$  to  $-0.0003$ ;  $P=.04$  for 1 point of the Mediterranean diet score). Performance on the IST, BVRT, or FCSRT over time was not significantly associated with Mediterranean diet adherence. Greater adherence as a categorical variable (score 6-9) was not significantly associated with fewer MMSE errors and better FCSRT scores in the entire cohort, but among individuals who remained free from dementia over 5 years, the association for the highest compared with the lowest group was significant (adjusted for all factors, for MMSE:  $\beta=-0.03$ ; 95% CI,  $-0.05$  to  $-0.001$ ;  $P=.04$ ; for FCSRT:  $\beta=0.21$ ; 95% CI,  $0.008$  to  $0.41$ ;  $P=.04$ ). Mediterranean diet adherence was not associated with the risk for incident dementia (fully adjusted model: hazard ratio,  $1.12$ ; 95% CI,  $0.60$  to  $2.10$ ;  $P=.72$ ), although power to detect a difference was limited.

**Conclusions** Higher adherence to a Mediterranean diet was associated with slower MMSE cognitive decline but not consistently with other cognitive tests. Higher adherence was not associated with risk for incident dementia.

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showed a reduced risk for Alzheimer disease and mild cognitive impairment in participants with greater Mediterranean diet adherence.<sup>11,12</sup> These results were obtained in a non-Mediterranean older population, mainly US Hispanics and blacks (<30% whites), which limits its generalizability.

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The present study examined whether adherence to a Mediterranean diet was associated with change in cognitive performance and with lower risk of all-cause dementia or Alzheimer disease over a 5-year period in a sample of older community dwellers in France.

## METHODS

### Participants

The Three-City (3C) study is a prospective cohort study of vascular risk factors of dementia; the methodology has been described elsewhere.<sup>13</sup> The 3C study protocol was approved by the Consultative Committee for the Protection of Persons participating in Biomedical Research at Kremlin-Bicêtre University Hospital, Paris, France. All participants provided written informed consent.

A sample of 9294 community dwellers 65 years or older was selected in 1999-2000 from the electoral rolls of 3 French cities (Bordeaux, Dijon, and Montpellier). Three follow-up examinations were performed at 2 years (wave 1, 2001-2002), 4 years (wave 2, 2003-2004), and 7 years (wave 3, 2006-2007) after baseline examination. Data collection included sociodemographic information, lifestyle, symptoms and medical complaints, medical history, blood pressure, tobacco use, drug use, anthropometric data, neuropsychological testing, and blood sampling. The present study is based on waves 1, 2, and 3 in Bordeaux, the only center where the standard data collection was completed with a comprehensive dietary survey in 1811 participants (94% of those examined at wave 1). Among these participants, 1712 had no missing dietary data, and 1597 completed the screening procedure for diagnosis of dementia described herein.

We excluded 73 participants with dementia at baseline. The study sample thus comprised the 1410 participants without dementia (92.5%) who had at least 1 follow-up reexamination over 5 years: 1340 were reexamined at wave 2 and 1213 at wave 3. Wave 3 was

closed on December 2007 in the Bordeaux center.

### Dietary Assessment and Mediterranean Diet Score

At wave 1, participants were visited at home by a specifically trained dietician who administered a food frequency questionnaire and a 24-hour dietary recall.<sup>14,15</sup> Data from these questionnaires were validated in an independent 3C subsample.<sup>16</sup> The 24-hour recall was used to estimate nutrient intake (grams per day) and total energy intake (kilocalories per day) and to compute the ratio of monounsaturated fatty acids to saturated fatty acids. Based on the food frequency questionnaire, frequency of consumption of 40 categories of foods and beverages for each of the 3 main meals and 3 between-meals snacks was recorded in 11 classes. The food items were converted into number of servings per week and then aggregated into 20 food and beverage groups, as described elsewhere.<sup>15</sup> We identified the food groups considered to be part of a Mediterranean diet: vegetables; fruits; legumes; cereals including bread, pasta, and rice (whole and refined grains); fish; meat; dairy products; and alcohol.

The number of servings per week for each food group was determined, and the Mediterranean diet score was computed as follows: a value of 0 or 1 was assigned to each food group using sex-specific medians of the population as cutoffs. For beneficial components (vegetables, fruits, legumes, cereals, and fish), individuals whose consumption was below the median were assigned a value of 0, vs 1 for the others. For components presumed to be detrimental (meat and dairy products), individuals whose consumption was below the median were assigned a value of 1, vs 0 for the others.

For alcohol, 1 point was assigned to men if their consumption was within 7 to 14 glasses (10-20 g/d) per week and to women if their consumption was within 1 to 4 glasses (1.4-5.7 g/d) per week. These cutoffs corresponding to the second quartile of distribution of

total alcohol consumption in this population were chosen to represent mild-to-moderate consumption. For the ratio of monounsaturated fatty acids to saturated fatty acids, ratios below the sex-specific median were assigned a value of 0, vs 1 for those above the median.

The Mediterranean diet score was generated by adding the scores (0 or 1 point) for each food category for each participant. Thus, the score could range from 0 to 9, with higher scores indicating greater dietary adherence.<sup>2</sup>

### Evaluation of Cognitive Function and Diagnosis of Dementia

Trained psychologists administered a battery of neuropsychological tests. Four tests were administered at the baseline of our study (wave 1 of the 3C study): (1) The Mini Mental State Examination (MMSE),<sup>17</sup> which is a sum-score evaluating various dimensions of cognition and used as an index of global cognitive performance. Scores range from 0 to 30. (2) The Isaacs Set Test (IST),<sup>18</sup> which evaluates semantic verbal fluency abilities and speed of verbal production. Individuals have to generate a list of words (with a maximum of 10) belonging to a specific semantic category in 15 seconds. Four semantic categories are used successively (cities, fruits, animals, and colors). Scores range from 0 to 40. (3) The Benton Visual Retention Test (BVRT),<sup>19</sup> which evaluates immediate visual memory, consists of presentation for 10 seconds of a stimulus card displaying a geometric figure, after which individuals are asked to identify the initial figure among 4 possibilities. Fifteen figures are successively presented, and scores range from 0 to 15. (4) The Free and Cued Selective Reminding Test (FCSRT),<sup>20</sup> which involves verbal episodic memory, consists of 16 words belonging to 16 semantic categories presented during the encoding phase. Afterward, 3 successive recall trials are performed, each trial starting with a free recall inviting participants to retrieve as many words as possible.

Then, for words not retrieved, the examiner provides a category cue to enhance recall. We considered the total free recall score as corresponding to the sum of the 3 free recalls ranging from 0 to 48.

These cognitive tests were administered at each follow-up except for the FCSRT, which was not administered at wave 2.

The diagnosis of dementia was based on a 2-step procedure following administration of the battery of neuropsychological tests.<sup>13</sup> At each wave, participants suspected of having dementia based on their present neuropsychological performances and decline relative to a previous examination were examined by a neurologist. An independent committee of neurologists then reviewed all potential cases of dementia and analyzed in depth the medical history of each participant to obtain a consensus on the diagnosis and etiology according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition). They confirmed 99 incident cases of dementia (28 at wave 2 and 71 at wave 3) and 66 probable or possible cases of Alzheimer disease (19 at wave 2 and 47 at wave 3) over the 5 years of follow-up.

### Covariates

Sociodemographic information included age, sex, education, income, and marital status. Vascular risk factors included body mass index (BMI) calculated as weight in kilograms divided by height in meters squared, smoking status, history of cardiovascular or cerebrovascular disease, hypertension (blood pressure  $\geq 140/90$  mm Hg or treated), diabetes (glucose level  $\geq 130$  mg/dL [7.2 mmol/L] or treated) and hypercholesterolemia (total cholesterol level  $\geq 240$  mg/dL [6.2 mmol/L]). Moreover, taking 5 medications/d or more was considered an indicator of comorbidity.<sup>13</sup> Apolipoprotein E  $\epsilon 4$  (*ApoE*) genotype was considered dichotomously: presence of at least 1  $\epsilon 4$  allele (only 13 individuals were homozygotic) vs no  $\epsilon 4$  allele. Depressive symptomatology was assessed on the Center for Epide-

miological Studies-Depression Scale (CES-D), used as continuous variable.<sup>21</sup> Practice and intensity of physical exercise were assessed by 2 questions: "Do you practice sports?" (yes/no) and "Do you perspire when you practice sports?" (never/sometimes/most of the time/always). A 3-level variable was computed to describe intensity of physical exercise, as already published.<sup>14</sup>

### Statistical Analyses

All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

Participants were classified according to categories of the Mediterranean diet score. The diet score categories 0-3, 4-5, or 6-9 were defined so as to be nutritionally relevant, close to tertiles of the distribution of the diet score in our sample, and similar to those of the US study.<sup>11</sup> Demographic and clinical characteristics at wave 1 were compared between categories of the diet score using  $\chi^2$  statistics for class variables and analysis of variance, followed by  $2 \times 2$  comparison post hoc tests for continuous variables (2-sided tests with accepted significance at  $P < .05$ ). The characteristics of the 1410 participants with follow-up data were compared with those of individuals who were not reexamined ( $n = 114$ ).

We used mixed models to examine the association between the Mediterranean diet score and the evolution of cognitive performance on each test over time. The outcomes of interest were the repeated measures of individual scores on the 4 cognitive tests. Total scores were modeled for the IST, BVRT, and FCSRT. The square root of the number of errors, calculated as  $(30 - \text{MMSE})^{1/2}$ , was used for the MMSE to approximate a normal distribution as required for linear mixed-model analyses.<sup>22</sup> Thus, an increase in the number of errors on the MMSE score with time indicated cognitive decline. The  $\beta$  coefficient for diet score represented the association of a Mediterranean diet with baseline mean cognitive scores, and the  $\beta$  coefficient for the

diet  $\times$  time interaction (ie, the slope) represented the association of Mediterranean diet effect on the change in the cognitive scores over time. A negative  $\beta$  coefficient for diet  $\times$  time indicates that an increase in the diet score was associated with fewer MMSE errors over time, whereas a positive  $\beta$  coefficient indicates better cognitive performances on the IST, BVRT, and FCSRT, with increasing Mediterranean diet adherence over time. In other exploratory models (sensitivity analyses), we repeated these analyses excluding individuals with incident dementia ( $n = 99$ ).

Cox proportional hazard models with delayed entry and age as a time scale<sup>23</sup> were performed to estimate the risk for incident dementia and Alzheimer disease as a function of baseline Mediterranean diet adherence. Hazard ratios were estimated using Mediterranean diet score as a continuous variable (1-point increase) and as a categorical variable (0-3 as reference, vs 4-5 and 6-9).

We applied the same strategy of selection of covariates for Cox proportional hazard models as well as mixed models. First, model 1 was adjusted for the factors that were significantly different at  $P < .10$  between categories of Mediterranean diet score in univariate analysis: age, sex, education, ApoE genotype, marital status, practice of physical exercise, total energy intake, and taking 5 medications/d or more. Although not significantly different at  $P < .10$ , CES-D score, a potential confounder for age-related cognitive decline or dementia, was also introduced in model 1. Cardiovascular risk factors (tobacco use, BMI, hypertension, hypercholesterolemia, and diabetes) were then entered as additional adjustment variables in model 2. Stroke was added separately as an adjustment variable in model 3. Further control for cardiovascular risk factors and stroke in the same model was also performed (model 4).

We calculated the power of the study to detect incident dementia. Assuming a 26.4% prevalence of a high Mediterranean diet score (6-9), compared with the score 0 to 5 and 99 incident

dementia cases over 5 years, the cohort size of 1410 provides a power of 45% to detect a hazard ratio of 0.6, as found in the US study.<sup>11</sup>

**RESULTS**

The study sample consisted of 1410 individuals (mean age, 75.9 [range, 67.7-94.9] years at wave 1). The median follow-up was 4.1 years between waves 1 and 3. The Mediterranean diet score ranged from 0 to 8, with less than 4% of the total population in the extreme values (0 or 8); 44% participants had a score of 4 or 5. The mean diet score was 4.36 (SD, 1.66), and its distribution was normal.

As expected, greater adherence to a Mediterranean diet was characterized by higher intake of vegetables, fruits, legumes, cereals, and fish and by lower intake of meat and dairy products (TABLE 1).

Greater Mediterranean diet adherence was associated with male sex and being married but not with education, income, or physical activity (TABLE 2). Individuals in the middle or high Mediterranean diet score categories had a lower mean BMI and higher mean energy intake than those in the lowest category. Mean baseline MMSE, BVRT, and FCSRT scores did not differ across diet score categories. However, mean annual decline on the MMSE and FCSRT significantly decreased with increasing Mediterranean diet adherence, with a difference of 0.7 point of MMSE score and 1.1 point of FCSRT score between the lowest and highest diet score categories, over 5 years. Incidence of dementia was not significantly associated with diet score.

The associations between cognitive decline and the Mediterranean diet score as a continuous variable are shown in TABLE 3, and associations with the diet score as a categorical variable are shown in TABLE 4. In longitudinal analyses, each additional unit of diet score was associated with fewer MMSE errors at follow-up (Table 3, model 2). This association was attenuated when stroke was added to the model (model 3). However, in models fully adjusted for car-

diovascular risk factors and stroke, higher diet score was associated with fewer MMSE errors over time (model 4). Conversely, Mediterranean diet adherence analyzed as a categorical variable was not associated with

**Table 1.** Food Consumption, Alcohol Intake, and Fatty Acid Ratio by Categories of Mediterranean Diet Score Among Older Persons Living in Bordeaux—the Three-City Study (2001-2002) (N = 1410)

Characteristic <sup>a</sup>	Mediterranean Diet Score Category		
	Low (0-3) (n = 423)	Middle (4-5) (n = 615) <sup>b</sup>	High (6-9) (n = 372) <sup>b,c</sup>
Food category, mean (SD), servings/wk			
Dairy products	18.4 (7.7)	16.0 (7.2)	14.2 (6.5)
Meat	5.4 (2.6)	4.8 (2.4)	4.2 (2.2)
Vegetables	15.7 (6.2)	19.3 (6.9)	23.3 (6.7)
Fruits	10.8 (6.3)	13.8 (6.7)	16.2 (6.3)
Legumes	0.4 (0.7)	0.6 (0.6)	0.8 (0.6)
Cereal <sup>d</sup>	19.9 (6.4)	22.2 (6.0)	24.5 (5.0)
Fish	2.0 (1.4)	2.9 (1.7)	3.7 (1.7)
Mild to moderate alcohol intake, No. (%) <sup>e</sup>	59 (13.9)	167 (27.1)	174 (46.8)
Ratio of monounsaturated to saturated fatty acids, mean (SD), g/d	0.77 (0.26)	0.87 (0.32)	1.00 (0.31)

<sup>a</sup>All P values <.001 for the analysis of variance or for the  $\chi^2$  test (proportion of mild-to-moderate alcohol consumers) among categories of Mediterranean diet score.  
<sup>b</sup>2 × 2 significant comparisons (P < .05) between categories of Mediterranean diet score, taking the lowest category as reference group.  
<sup>c</sup>2 × 2 significant comparisons (P < .05) between individuals in middle and high categories of Mediterranean diet score.  
<sup>d</sup>Included consumption of cereals, bread and pasta, and rice (whole and refined grains).  
<sup>e</sup>A value of 1 was attributed to individuals whose consumption was mild to moderate, corresponding to the second quartile of distribution of total alcohol intake. One point was given to men if their consumption was within 7 to 14 glasses (10-20 g/d) per week and to women if their consumption was within 1 to 4 glasses (1.4-5.7 g/d) per week.

**Table 2.** Demographic, Clinical, and Dietary Characteristics and Cognitive Performance by Categories of Mediterranean Diet Score Among Older Persons Living in Bordeaux—the Three-City Study, Wave 1 (2001-2002) (N = 1410)

Characteristic	Mediterranean Diet Score Category, No. (%)			P Value <sup>a</sup>
	Low (0-3) (n = 423)	Middle (4-5) (n = 615)	High (6-9) (n = 372)	
Demographic characteristics				
Age, mean (SD), y	76.1 (4.9)	75.9 (4.9)	75.8 (4.6)	.63
Women	288 (60.1)	380 (61.8)	215 (57.8)	.01
Education				
None or primary school	150 (35.5)	184 (30.1)	115 (31.1)	.32
Secondary	113 (26.8)	171 (28.0)	100 (27.0)	
High school	96 (22.8)	132 (21.6)	82 (22.2)	
University	63 (14.9)	124 (20.3)	73 (19.7)	
Monthly income, € <sup>b</sup>				
Refused to answer	25 (5.9)	42 (6.8)	25 (6.7)	.56
<750	40 (9.5)	40 (6.5)	25 (6.7)	
750-1500	153 (36.2)	205 (33.3)	122 (32.8)	
1500-2250	99 (23.4)	155 (25.2)	88 (23.7)	
>2250	106 (25.1)	173 (28.1)	112 (30.1)	
Marital status				
Married	211 (50.0)	343 (56.0)	246 (66.5)	<.001
Divorced/separated	37 (8.8)	45 (7.3)	27 (7.3)	
Widowed	150 (35.5)	183 (29.8)	72 (19.5)	
Single	24 (5.7)	42 (6.9)	25 (6.7)	
Practice of physical exercise				
No	244 (57.7)	318 (51.7)	199 (53.4)	.09
Moderate	69 (16.3)	108 (17.6)	73 (19.6)	
Intensive	20 (4.7)	56 (9.1)	31 (8.3)	
No answer	90 (21.3)	133 (21.6)	69 (18.6)	

(continued)

MMSE performance over time (Table 4), and Mediterranean diet adherence analyzed as a continuous or a categorical variable was not associated with IST, BVRT, or FCSRT performance over time (Tables 3 and 4).

Individuals who developed incident dementia (n=99) or Alzheimer disease (n=66) during the 5 years of follow-up were older (79.4 and 79.1 years, respectively, vs 75.7 years;  $P < .001$ ) at wave 1 than those who remained free from dementia over time. Mediterra-

nean diet adherence, as a continuous or categorical variable, was not associated with risk for incident dementia or Alzheimer disease in multivariate analyses (TABLE 5).

In sensitivity analyses, we assessed the association between cognitive decline and adherence to a Mediterranean diet as a continuous variable (TABLE 6) or as a categorical variable (TABLE 7), excluding individuals with incident dementia (n=99). In longitudinal analyses, each additional unit of Mediterranean diet score was associated with fewer MMSE errors at follow-up when cardiovascular risk factors and stroke were taken into account (Table 6). A similar pattern for the FCSRT was also observed with greater Mediterranean diet adherence. Results were similar although not statistically significant when Mediterranean diet adherence was considered as a categorical variable (Table 7). For example, based on these data a woman with low adherence (score, 0-3) would lose 1.2 point on the MMSE score and 2.6 points on the FCSRT score over 5 years, whereas a comparable woman with high adherence (score, 6-9) would lose 0.75 point and 1.6 points, respectively. There was no association between Mediterranean diet adherence analyzed as a continuous or categorical variable and IST or BVRT performance over time.

**COMMENT**

In this population-based cohort study, higher adherence to a Mediterranean-type diet was associated with slower decline on the MMSE but not other cognitive tests and was not associated with the risk for incident dementia over 5 years of follow-up. This association was independent of energy intake, BMI, depressive symptomatology, cardiovascular risk factors, and stroke, which was partly consistent with the previous study on this topic. In that cohort study of a large community-based population without dementia in New York, higher Mediterranean diet adherence was associated with a reduced risk for

**Table 2.** Demographic, Clinical, and Dietary Characteristics and Cognitive Performance by Categories of Mediterranean Diet Score Among Older Persons Living in Bordeaux—the Three-City Study, Wave 1 (2001-2002) (N = 1410) (continued)

Characteristic	Mediterranean Diet Score Category, No. (%)			P Value <sup>a</sup>
	Low (0-3) (n = 423)	Middle (4-5) (n = 615)	High (6-9) (n = 372)	
<b>Clinical characteristics</b>				
CES-D score	420 (99.3)	612 (99.5)	369 (99.2)	.17
Mean (SD)	8.2 (7.4)	7.5 (7.5)	7.3 (6.8)	
BMI	393 (92.9)	573 (93.2)	346 (93.0)	.03
Mean (SD) <sup>c</sup>	26.1 (4.3)	25.5 (4.0) <sup>d</sup>	25.5 (3.8) <sup>d</sup>	
Total energy intake	423 (100)	615 (100)	372 (100)	<.001
Mean (SD), kcal/d	1544 (502)	1641 (503) <sup>d</sup>	1680 (498) <sup>d</sup>	
Hypertension	213 (50.5)	302 (49.3)	203 (54.6)	.26
Hypercholesterolemia	142 (33.8)	217 (35.5)	150 (40.4)	.13
Diabetes	49 (11.6)	54 (8.8)	31 (8.3)	.22
<b>Smoking status</b>				
Never	270 (63.8)	391 (63.6)	238 (64.0)	.08
Ex-smoker	126 (29.8)	184 (29.9)	124 (33.3)	
Current smoker	27 (6.4)	40 (6.5)	10 (2.7)	
Stroke	10 (2.4)	8 (1.3)	6 (1.6)	.42
>5 Medications/d	228 (53.9)	294 (47.8)	171 (46.0)	.06
ApoE4 carrier	63 (16.8)	105 (18.8)	63 (18.3)	.73
<b>Baseline cognitive performance</b>				
MMSE score	423 (100)	611 (99.3)	372 (100)	.39
Mean (SD)	27.6 (1.9)	27.7 (1.9)	27.6 (2.0)	
IST score	422 (99.8)	602 (97.9)	367 (98.7)	.02
Mean (SD)	31.0 (6.5)	32.1 (6.5) <sup>d</sup>	31.7 (6.4)	
BVRT score	414 (97.9)	598 (97.2)	369 (99.2)	.08
Mean (SD)	11.3 (2.2)	11.6 (2.1)	11.7 (2.1)	
FCSRT score	386 (91.3)	563 (91.5)	347 (93.3)	.19
Mean (SD)	24.1 (6.8)	24.1 (6.7)	24.9 (6.5)	
<b>Annual cognitive decline</b>				
MMSE score	411 (97.2)	597 (97.1)	362 (97.3)	.01
Mean (SD)	-0.20 (0.63)	-0.12 (0.49)	-0.07 (0.62) <sup>d</sup>	
IST score	394 (93.1)	561 (91.2)	343 (92.2)	.54
Mean (SD)	-0.76 (1.44)	-0.81 (1.35)	-0.87 (1.43)	
BVRT score	384 (90.8)	553 (89.9)	342 (91.9)	.61
Mean (SD)	-0.08 (0.57)	-0.05 (0.5)	-0.08 (0.58)	
FCSRT score	283 (66.9)	438 (71.2)	264 (71.0)	.02
Mean (SD)	-0.24 (1.11)	-0.04 (1.13)	0.02 (1.17) <sup>d</sup>	
Incidence of dementia per 100 person-years (95% CI)	2.02 (1.36-2.68)	1.51 (1.0-1.98)	1.45 (0.86-2.04)	.64

Abbreviations: ApoE4, apolipoprotein E ε4; BVRT, Benton Visual Retention Test; BMI, body mass index; CES-D, Center for Epidemiological Studies-Depression Scale; CI, confidence interval; FCSRT, Free and Cued Selective Reminding Test; IST, Isaacs Set Test; MMSE, Mini-Mental State Examination.

<sup>a</sup>P value for the χ<sup>2</sup> test or analysis of variance among categories of Mediterranean diet score.

<sup>b</sup>To convert Euros to US\$, divide by 1.42 (July 21, 2009, exchange rate).

<sup>c</sup>Calculated as weight in kilograms divided by height in meters squared.

<sup>d</sup>2 × 2 significant comparisons ( $P < .05$ ) for means of age, mean baseline cognitive scores, mean annual cognitive decline, BMI, CES-D score, and energy intake between categories of Mediterranean diet score, taking the lowest category as reference group.

mild cognitive impairment and Alzheimer disease.<sup>11,12</sup>

However, 2 important differences between the US study and the present one could explain such discrepancies. First, the length of follow-up differed (range, 0.2-13.9 years or 0.9-16.4 years in US studies vs 1.6-6.1 years in the 3C cohort). Second, country-specific characteristics of the dietary patterns may partly explain the discrepancies observed between the French and US studies,<sup>24</sup> despite similar mean Mediterranean diet scores. For instance, French individuals tend to eat fruits and vegetables more often than individuals in the United States.<sup>25</sup> Therefore, some overlap between

“low” and “high” French and US consumers of fruits and vegetables could occur: the low French consumers may be high US consumers. This may have added misclassification, leading to a decreased chance to observe an association between diet adherence and cognitive decline or incidence of dementia in our study. Moreover, adherence to a Mediterranean diet may reflect specific health concerns and behaviors that may differ between countries, particularly regarding use of supplements or food groups not considered in the diet score computation. For instance, use of dietary supplements is increasingly common in the United States, notably in older persons

(63% of users), whereas in France, use of multivitamins seems largely lower (29%).<sup>26,27</sup> Altogether, this may explain the inconsistent results, since the diet score was computed according to sex-specific medians of consumption of only 9 food groups of each study sample.

Other explanations for such discrepancies are related to cognitive decline in the prodromal phase of dementia. We used 4 tests evaluating different cognitive domains that could be affected in a specific sequence during the time course preceding the clinically defined dementia syndrome.<sup>28</sup> Interestingly, the test related to diet in our study, ie, the MMSE,

**Table 3.** Change in Cognitive Performance per Additional Unit of the Mediterranean Diet Score (0-9) Over 5 Years of Follow-up Among Older Persons Living in Bordeaux—the Three-City Study (2001-2007)<sup>a</sup>

Test	Model 1 <sup>b</sup> (n = 1268)		Model 2 <sup>c</sup> (n = 1180)		Model 3 <sup>d</sup> (n = 1264)		Model 4 <sup>e</sup> (n = 1177)	
	β (95% CI)	P Value	β (95% CI)	P Value	β (95% CI)	P Value	β (95% CI)	P Value
<b>MMSE</b>								
Time	-0.25 (-0.40 to -0.08)	.003	-0.32 (-0.52 to -0.13)	<.001	-0.24 (-0.40 to -0.08)	.004	-0.32 (-0.51 to -0.12)	.001
Diet score (0-9), baseline testing	0.004 (-0.02 to 0.02)	.71	0.008 (-0.01 to 0.03)	.49	0.005 (-0.02 to 0.03)	.60	0.009 (-0.01 to 0.03)	.41
Diet score × time	-0.006 (0.01 to -0.0004)	.05	-0.006 (-0.01 to -0.0004)	.03	-0.005 (-0.01 to 0.0001)	.06	-0.006 (-0.01 to -0.0003)	.04
<b>IST</b>								
Time	0.99 (-0.59 to 2.59)	.22	1.65 (-0.22 to 3.52)	.08	0.98 (-0.62 to 2.58)	.23	1.64 (-0.24 to 3.52)	.09
Diet score (0-9), baseline testing	0.14 (-0.16 to 0.44)	.37	0.07 (-0.24 to 0.39)	.64	0.11 (-0.19 to 0.41)	.46	0.05 (-0.26 to 0.37)	.74
Diet score × time	0.01 (-0.04 to 0.07)	.59	0.03 (-0.03 to 0.08)	.31	0.01 (-0.04 to 0.07)	.60	0.03 (-0.03 to 0.08)	.32
<b>BVRT</b>								
Time	0.57 (0.10 to 1.03)	.02	0.79 (0.24 to 1.33)	.005	0.51 (0.04 to 0.97)	.03	0.72 (0.18 to 1.28)	.01
Diet score (0-9), baseline testing	0.02 (-0.04 to 0.08)	.57	0.0004 (-0.06 to 0.06)	.99	0.02 (-0.04 to 0.08)	.60	-0.001 (-0.06 to 0.06)	.96
Diet score × time	-0.002 (-0.02 to 0.01)	.78	-0.0005 (-0.02 to 0.01)	.95	-0.03 (-0.02 to 0.01)	.74	-0.001 (-0.02 to 0.01)	.90
<b>FCSRT</b>								
Time	0.52 (-0.82 to 1.86)	.45	-0.01 (-1.57 to 1.55)	.98	0.42 (-0.93 to 1.77)	.54	-0.11 (-1.68 to 1.45)	.88
Diet score (0-9), baseline testing	0.12 (-0.09 to 0.33)	.25	0.09 (-0.13 to 0.31)	.42	0.11 (-0.09 to 0.33)	.29	0.08 (-0.14 to 0.30)	.48
Diet score × time	0.04 (-0.01 to 0.08)	.11	0.04 (-0.004 to 0.09)	.07	0.04 (-0.008 to 0.08)	.11	0.04 (-0.004 to 0.09)	.08

Abbreviations: BVRT, Benton Visual Retention Test; CI, confidence interval; FCSRT, Free and Cued Selective Reminding Test; IST, Isaacs Set Test; MMSE, Mini-Mental State Examination.

<sup>a</sup>Linear mixed models: the β coefficient for Mediterranean diet score represents the association of Mediterranean diet with baseline mean cognitive scores; the β coefficient for the Mediterranean diet interaction with time (ie, the slope) represents the association of Mediterranean diet with the change in cognitive scores over time. For MMSE × time, a negative β coefficient indicates that a higher Mediterranean diet score was associated with fewer MMSE errors over time, whereas for IST, BVRT, and FCSRT, a positive β coefficient indicates slower decline in cognitive performance.

<sup>b</sup>Adjusted for age, sex, education, marital status, total energy intake, practice of physical exercise, taking 5 medications/d or more, Center for Epidemiological Studies-Depression Scale score, and apolipoprotein E genotype and their interaction with time.

<sup>c</sup>Adjusted for covariates in model 1 plus additional adjustment for body mass index, hypertension, hypercholesterolemia, diabetes, and tobacco use and their interaction with time.

<sup>d</sup>Adjusted for covariates in model 1 plus additional adjustment for stroke and its interaction with time.

<sup>e</sup>Adjusted for covariates in model 2 plus additional adjustment for stroke and its interaction with time.

assesses global cognitive abilities, considered the hallmark of pathological cognitive aging.<sup>28,29</sup> Results on episodic memory assessed by FCSRT were inconsistent. Conversely, the BVRT involves working memory, a cognitive domain particularly sensitive to normal aging. Therefore, it is possible that a Mediterranean diet may delay decline in cognitive func-

tion specifically involved in pathological brain aging but only at least 5 years before the clinical diagnosis of dementia. The Mediterranean diet would be unable to delay dementia onset or slow cognitive decline in the 5 years preceding the clinical diagnosis.

Taken together, these results suggest that the Mediterranean diet may

have a beneficial effect during the long prodromal phase of dementia<sup>28</sup> rather than in the very last years preceding dementia. There might be a window of opportunity for the beneficial effects, after which it is possible that the pathophysiological processes leading to dementia could not be reversed by diet. During the prodromal phase of dementia, successive

**Table 4.** Change in Cognitive Performance Over 5 Years of Follow-up by Categories of Mediterranean Diet Score Among Older Persons Living in Bordeaux—the Three-City Study (2001-2007)<sup>a</sup>

Test	Model 1 <sup>b</sup> (n = 1268)			Model 2 <sup>c</sup> (n = 1180)			Model 3 <sup>d</sup> (n = 1264)			Model 4 <sup>e</sup> (n = 1177)		
	β (95% CI)	P Value	P Value Overall	β (95% CI)	P Value	P Value Overall	β (95% CI)	P Value	P Value Overall	β (95% CI)	P Value	P Value Overall
<b>MMSE</b>												
Time	-0.26 (-0.42 to -0.10)	.001		-0.34 (-0.53 to 0.15)	<.001		-0.25 (0.41 to -0.09)	.002		-0.33 (-0.52 to 0.14)	.001	
Middle category, baseline testing	-0.03 (-0.11 to 0.05)	.45	.61	0.006 (-0.08 to 0.09)	.88	.94	-0.02 (-0.11 to 0.06)	.55	.63	0.01 (-0.07 to 0.10)	.75	.89
High category, baseline testing	0.01 (-0.09 to 0.10)	.89		0.02 (-0.08 to 0.11)	.74		0.01 (-0.08 to 0.11)	.77		0.02 (-0.07 to 0.12)	.63	
Middle category × time	-0.01 (-0.03 to 0.01)	.35	.18	-0.02 (-0.04 to 0.003)	.10	.13	-0.001 (-0.03 to 0.01)	.37	.19	-0.02 (-0.04 to 0.004)	.11	.13
High category × time	-0.02 (-0.05 to 0.001)	.06		-0.02 (-0.05 to 0.0007)	.06		-0.02 (-0.05 to 0.002)	.07		-0.02 (-0.05 to 0.001)	.06	
<b>IST</b>												
Time	1.09 (-0.48 to 2.67)	.17		1.78 (-0.07 to 3.64)	.06		1.07 (-0.52 to 2.66)	.19		1.76 (-0.09 to 3.63)	.06	
Middle category, baseline testing	1.51 (0.32 to 2.70)	.01	.04	1.32 (0.08 to 2.55)	.04	.10	1.39 (0.20 to 2.58)	.02	.06	1.19 (-0.04 to 2.44)	.06	.14
High category, baseline testing	0.66 (-0.68 to 1.99)	.33		0.51 (-0.89 to 1.90)	.48		0.54 (-0.80 to 1.87)	.43		0.39 (-1.01 to 1.79)	.58	
Middle category × time	-0.07 (-0.28 to 0.14)	.50	.69	-0.01 (-0.22 to 0.21)	.94	.66	-0.07 (-0.29 to 0.14)	.50	.69	-0.01 (-0.23 to 0.21)	.94	.68
High category × time	0.01 (-0.23 to 0.25)	.93		0.09 (-0.16 to 0.33)	.48		0.01 (-0.23 to 0.25)	.93		0.09 (-0.16 to 0.33)	.49	
<b>BVRT</b>												
Time	0.53 (0.07 to 0.99)	.02		0.75 (0.21 to 1.29)	.007		0.47 (0.01 to 0.94)	.04		0.69 (0.15 to 1.24)	.01	
Middle category, baseline testing	0.08 (-0.16 to 0.33)	.50	.78	0.02 (-0.22 to 0.27)	.84	.98	0.08 (-0.16 to -0.32)	.51	.80	0.02 (-0.23 to 0.27)	.88	.99
High category, baseline testing	0.07 (-0.20 to 0.34)	.60		0.01 (-0.27 to 0.29)	.94		0.07 (0.20 to 0.34)	.62		0.005 (-0.27 to 0.28)	.97	
Middle category × time	0.04 (-0.02 to 0.10)	.25	.50	0.04 (-0.02 to 0.10)	.18	.41	0.03 (-0.03 to 0.09)	.29	.55	0.04 (-0.02 to 0.10)	.21	.46
High category × time	0.02 (-0.05 to 0.08)	.65		0.03 (-0.04 to 0.10)	.44		0.01 (-0.06 to 0.08)	.71		0.02 (-0.05 to 0.10)	.50	
<b>FCSRT</b>												
Time	0.58 (-0.75 to 1.91)	.39		0.08 (-1.47 to 1.62)	.92		0.49 (-0.84 to 1.83)	.47		-0.02 (-1.57 to 1.54)	.98	
Middle category, baseline testing	-0.30 (-1.13 to 0.52)	.47	.12	-0.49 (-1.35 to 0.37)	.26	.28	-0.34 (-1.17 to 0.49)	.42	.32	-0.54 (-1.40 to 0.32)	.22	.15
High category, baseline testing	0.58 (-0.35 to 1.50)	.22		0.49 (-0.47 to 1.46)	.32		0.54 (-0.38 to 1.47)	.25		0.45 (-0.52 to 1.41)	.36	
Middle category × time	0.15 (-0.003 to 0.32)	.10	.13	0.13 (-0.04 to 0.31)	.14	.15	0.14 (-0.03 to 0.32)	.11	.14	0.13 (-0.05 to 0.31)	.14	.08
High category × time	0.19 (-0.008 to 0.38)	.06		0.19 (-0.007 to 0.39)	.06		0.19 (-0.01 to 0.38)	.06		0.19 (-0.01 to 0.39)	.06	

Abbreviations: BVRT, Benton Visual Retention Test; CI, confidence interval; FCSRT, Free and Cued Selective Reminding Test; IST, Isaacs Set Test; MMSE, Mini-Mental State Examination.

<sup>a</sup>For explanation of footnotes, see footnotes "a" through "e" in Table 3. For footnote "a" in this table, the lowest category of Mediterranean diet score was chosen as referent. For all analyses, middle category indicates scores of 4 through 5; high category, scores of 6 through 9.

emergence of cognitive deficits on IST and BVRT appear more than 10 years before the diagnosis of dementia.<sup>28</sup>

The clinical implications of these results may seem modest but could be sizeable with longer follow-up.

The biological basis for the apparent health benefits of a Mediterranean diet involve a decrease in oxi-

**Table 5.** Mediterranean Diet Adherence and Age-Adjusted Risk for Dementia and Alzheimer Disease Among Older Persons Living in Bordeaux—the Three-City Study, Wave 1 (2001-2002)<sup>a</sup>

Category	Model 1 <sup>b</sup>			Model 2 <sup>c</sup>			Model 3 <sup>d</sup>			Model 4 <sup>e</sup>		
	HR (95% CI)	P Value	P Value Overall	HR (95% CI)	P Value	P Value Overall	HR (95% CI)	P Value	P Value Overall	HR (95% CI)	P Value	P Value Overall
<b>Risk for Dementia With An Increase of 1 Point of Mediterranean Diet Score or Compared With the Low Score Category</b>												
Diet score (0-9)	0.99 (0.87-1.13)	.90		1.04 (0.91-1.20)	.53		0.99 (0.87-1.14)	.97		1.06 (0.92-1.21)	.43	
Middle category	0.92 (0.56-1.52)	.75	.70	1.02 (0.59-1.76)	.94	.86	0.97 (0.58-1.63)	.92	.80	1.11 (0.63-1.94)	.71	.72
High category	0.89 (0.50-1.59)	.70		1.06 (0.57-1.96)	.86		0.92 (0.51-1.66)	.78		1.12 (0.60-2.10)	.72	
<b>Risk for Alzheimer Disease With An Increase of 1 Point of Mediterranean Diet Score or Compared With the Low Score Category</b>												
Diet score (0-9)	0.92 (0.78-1.08)	.92		0.99 (0.83-1.17)	.88		0.93 (0.79-1.09)	.37		1.00 (0.85-1.19)	.96	
Middle category	0.76 (0.42-1.39)	.38	.26	0.93 (0.48-1.79)	.82	.59	0.80 (0.43-1.46)	.46	.31	0.99 (0.51-1.94)	.98	.72
High category	0.67 (0.33-1.37)	.28		0.81 (0.37-1.75)	.59		0.70 (0.34-1.43)	.33		0.86 (0.39-1.88)	.71	

Abbreviations: CI, confidence interval; HR, hazard ratio.  
<sup>a</sup>P values from Cox proportional hazard models with delayed entry and age as a time scale. There were 99 incident cases of dementia and 66 incident cases of Alzheimer disease. Middle category indicates scores of 4 through 5; high category, scores of 6 through 9.  
<sup>b</sup>Adjusted for sex, education, marital status, total energy intake, practice of physical exercise, taking 5 medications/d or more, Center for Epidemiological Studies-Depression Scale score, and apolipoprotein E genotype. N=86 for dementia and 58 for Alzheimer disease.  
<sup>c</sup>Adjusted for covariates in model 1 plus additional adjustment for body mass index, hypertension, hypercholesterolemia, diabetes, and tobacco use. N=76 for dementia and 51 for Alzheimer disease.  
<sup>d</sup>Adjusted for covariates in model 1 plus additional adjustment for stroke. N=84 for dementia and 57 for Alzheimer disease.  
<sup>e</sup>Adjusted for covariates in model 2 plus additional adjustment for stroke. N=74 for dementia and 50 for Alzheimer disease.

**Table 6.** Change in Cognitive Performance Over 5 Years of Follow-up for Each Additional Unit of the Mediterranean Diet Score (0-9) Among Older Persons, Excluding Those Who Developed Incident Dementia, Living in Bordeaux—the Three-City Study (2001-2007)<sup>a</sup>

Test	Model 1 <sup>b</sup> (n = 1182)		Model 2 <sup>c</sup> (n = 1104)		Model 3 <sup>d</sup> (n = 1180)		Model 4 <sup>e</sup> (n = 1103)	
	β (95% CI)	P Value	β (95% CI)	P Value	β (95% CI)	P Value	β (95% CI)	P Value
<b>MMSE</b>								
Time	-0.11 (-0.27 to 0.05)	.19	-0.14 (-0.33 to 0.05)	.14	-0.10 (-0.26 to 0.06)	.22	-0.13 (-0.32 to 0.05)	.16
Diet score (0-9), baseline testing	0.009 (-0.01 to 0.03)	.40	0.01 (-0.01 to 0.03)	.25	0.01 (-0.01 to 0.03)	.36	0.01 (-0.01 to 0.04)	.22
Diet score × time	-0.005 (-0.01 to 0.0003)	.06	-0.006 (-0.01 to 0.0007)	.03	-0.005 (-0.01 to 0.0003)	.06	-0.006 (-0.011 to -0.007)	.03
<b>IST</b>								
Time	0.16 (-1.45 to 1.76)	.85	0.39 (-1.52 to 2.30)	.69	0.11 (-1.50 to 1.72)	.89	0.35 (-1.56 to 2.26)	.72
Diet score (0-9), baseline testing	0.05 (-0.26 to 0.37)	.74	0.01 (-0.32 to 0.34)	.93	0.03 (-0.28 to 0.35)	.82	0.004 (-0.32 to 0.33)	.98
Diet score × time	0.02 (-0.03 to 0.08)	.42	0.04 (-0.02 to 0.09)	.18	0.02 (-0.03 to 0.08)	.43	0.04 (-0.02 to 0.09)	.18
<b>BVRT</b>								
Time	0.47 (-0.004 to 0.94)	.05	0.62 (0.06 to 1.18)	.03	0.45 (-0.02 to 0.93)	.06	0.61 (0.05 to 1.17)	.03
Diet score (0-9), baseline testing	0.01 (-0.05 to 0.07)	.67	0.004 (-0.06 to 0.07)	.90	0.01 (-0.05 to 0.07)	.66	0.004 (-0.06 to 0.07)	.90
Diet score × time	-0.004 (-0.02 to 0.01)	.65	-0.002 (-0.02 to 0.01)	.83	-0.003 (-0.02 to 0.01)	.63	-0.002 (-0.02 to 0.01)	.81
<b>FCSRT</b>								
Time	0.49 (-0.84 to 1.82)	.47	-0.09 (-1.63 to 1.46)	.91	0.46 (-0.87 to 1.80)	.50	-0.09 (-1.64 to 1.46)	.90
Diet score (0-9), baseline testing	0.07 (-0.14 to 0.28)	.52	0.03 (-0.19 to 0.25)	.78	0.07 (-0.14 to 0.28)	.50	0.03 (-0.19 to 0.25)	.76
Diet score × time	0.04 (-0.0007 to 0.09)	.05	0.05 (0.006 to 0.10)	.03	0.04 (-0.001 to 0.09)	.06	0.05 (0.005 to 0.010)	.03

Abbreviations: BVRT, Benton Visual Retention Test; CI, confidence interval; FCSRT, Free and Cued Selective Reminding Test; IST, Isaacs Set Test; MMSE, Mini-Mental State Examination.  
<sup>a</sup>For explanation of footnotes, see footnotes "a" through "e" in Table 3.

dative stress, inflammation, and vascular disease, which also participate in the pathophysiology of neurodegenerative disease.<sup>30,31</sup> Individuals with higher adherence to a Mediterranean diet have been shown to have higher plasma concentrations of some presumed beneficial biomarkers.<sup>32-34</sup> The strong evidence relating a Mediterranean diet to lower risk of vascular disease is sup-

ported in part by our results, which indicate that the association between a Mediterranean diet and cognitive decline was not attenuated when adjusting for stroke and cardiovascular risk factors in general. More research is needed to better understand the biological mechanisms involved in the association between a Mediterranean diet and cognitive decline.

Our results should be interpreted with caution because of some potential methodological limitations. The Mediterranean diet score is based on a traditional Mediterranean reference pattern defined a priori, which does not consider the overall correlation between foods.<sup>35</sup> Dietary patterns derived by a priori<sup>36</sup> or a posteriori<sup>15</sup> methods were already associated with a significantly re-

**Table 7.** Change in Cognitive Performance Over 5 Years of Follow-up by Categories of Mediterranean Diet Score Among Older Persons, Excluding Those Who Developed Incident Dementia, Living in Bordeaux—the Three-City Study (2001-2007)<sup>a</sup>

Test	Model 1 <sup>b</sup> (n = 1182)			Model 2 <sup>c</sup> (n = 1104)			Model 3 <sup>d</sup> (n = 1180)			Model 4 <sup>e</sup> (n = 1103)		
	β (95% CI)	P Value	P Value Overall	β (95% CI)	P Value	P Value Overall	β (95% CI)	P Value	P Value Overall	β (95% CI)	P Value	P Value Overall
<b>MMSE</b>												
Time	-0.12 (-0.28 to -0.04)	.14		-0.16 (-0.35 to 0.03)	.10		-0.11 (-0.27 to 0.05)	.16		-0.15 (-0.34 to 0.03)	.11	
Middle category, baseline testing	-0.02 (-0.11 to 0.06)	.59	.54	0.01 (-0.07 to 0.10)	.72	.75	-0.02 (-0.10 to 0.06)	.65	.52	0.02 (-0.06 to 0.11)	.66	.70
High category, baseline testing	0.02 (-0.07 to 0.12)	.60		0.04 (-0.06 to 0.14)	.45		0.03 (-0.06 to 0.12)	.53		0.04 (-0.05 to 0.14)	.40	
Middle category × time	-0.01 (-0.03 to 0.009)	.27	.19	-0.02 (-0.04 to 0.0007)	.06	.08	-0.01 (-0.06 to 0.001)	.27	.18	-0.02 (-0.04 to 0.0003)	.05	.08
High category × time	-0.02 (-0.04 to 0.002)	.07		-0.02 (-0.05 to -0.0007)	.04		-0.02 (-0.05 to 0.001)	.06		-0.03 (-0.05 to 0.001)	.04	
<b>IST</b>												
Time	0.27 (-1.31 to 1.86)	.73		0.56 (-1.33 to 2.44)	.56		0.22 (-1.37 to 1.82)	.78		.051 (-1.37 to 2.40)	.59	
Middle category, baseline testing	1.42 (0.20 to 2.65)	.02	.05	1.22 (-0.06 to 2.50)	.06	.13	1.34 (0.11 to 2.57)	.03	.06	1.14 (-0.14 to 2.42)	.08	.15
High category, baseline testing	0.36 (-1.01 to 1.74)	.60		0.26 (-1.19 to 1.70)	.72		0.27 (-1.10 to 1.65)	.70		0.19 (-1.26 to 1.63)	.80	
Middle category × time	-0.05 (-0.26 to 0.16)	.62	.79	0.01 (-0.20 to 0.24)	.89	.69	-0.05 (-0.27 to 0.16)	.62	.79	0.02 (-0.20 to 0.24)	.89	.71
High category × time	0.02 (-0.22 to 0.25)	.89		0.10 (-0.15 to 0.35)	.43		0.01 (-0.22 to 0.26)	.90		0.09 (-0.15 to 0.34)	.45	
<b>BVRT</b>												
Time	0.43 (-0.04 to 0.90)	.07		0.62 (0.05 to 1.19)	.03		0.42 (-0.05 to 0.89)	.08		0.58 (0.02 to 1.13)	.04	
Middle category, baseline testing	0.04 (-0.19 to 0.29)	.71	.90	-0.002 (-0.25 to 0.25)	.98	.98	0.05 (-0.19 to 0.29)	.70	.89	-0.002 (-0.25 to 0.25)	.98	.99
High category, baseline testing	0.06 (-0.21 to 0.33)	.66		0.02 (-0.26 to 0.30)	.91		0.06 (-0.21 to 0.33)	.65		0.02 (-0.26 to 0.30)	.91	
Middle category × time	0.03 (-0.03 to 0.10)	.30	.48	0.042 (-0.02 to 0.11)	.20	.41	0.03 (-0.03 to 0.09)	.31	.50	0.04 (-0.02 to 0.11)	.20	.41
High category × time	0.002 (-0.07 to 0.07)	.94		0.017 (-0.06 to 0.09)	.65		0.002 (-0.07 to 0.07)	.95		0.02 (-0.06 to 0.09)	.66	
<b>FCSRT</b>												
Time	0.58 (-0.74 to 1.90)	.39		0.04 (-1.49 to 1.57)	.96		0.55 (-0.77 to 1.87)	.41		0.03 (-1.51 to 1.57)	.97	
Middle category, baseline testing	-0.34 (-1.17 to 0.49)	.42	.25	-0.51 (-1.37 to 0.35)	.25	.18	-0.33 (-1.16 to 0.50)	.44	.25	-0.49 (-1.36 to 0.36)	.26	.19
High category, baseline testing	0.37 (-0.56 to 1.29)	.44		0.27 (-0.70 to 1.23)	.59		0.38 (-0.55 to 1.31)	.42		0.28 (-0.69 to 1.25)	.57	
Middle category × time	0.18 (0.006 to 0.35)	.04	.07	0.17 (-0.007 to 0.35)	.06	.08	0.18 (0.002 to 0.35)	.048	.08	0.17 (-0.009 to 0.35)	.06	.08
High category × time	0.19 (0.001 to 0.39)	.048		0.21 (0.01 to 0.41)	.04		0.19 (-0.003 to 0.39)	.05		0.21 (0.008 to 0.41)	.04	

Abbreviations: BVRT, Benton Visual Retention Test; CI, confidence interval; FCSRT, Free and Cued Selective Reminding Test; IST, Isaacs Set Test; MeDi, Mediterranean diet; MMSE, Mini-Mental State Examination.

<sup>a</sup>For explanation of footnotes, see footnotes "a" through "e" in Table 3. For all analyses, middle category indicates scores of 4 through 5; high category, scores of 6 through 9.

duced risk for Alzheimer disease and fewer cognitive symptoms in the 3C cohort. The use of sex-specific cutoff points to develop the Mediterranean diet score does not measure adherence to a universal traditional Mediterranean diet pattern but rather to a specific pattern.<sup>37</sup> The hallmark of the traditional Mediterranean diet is a high consumption of olive oil, leading to a high ratio of monounsaturated fatty acids to saturated fatty acids.<sup>38</sup> As already reported in a non-Mediterranean population,<sup>11,12</sup> we found a relatively low ratio, but we verified that consumption of olive oil was positively correlated with the diet score and with the ratio (data available on request).

A relatively short follow-up could also introduce a bias attributable to changes in dietary habits in the phase preceding dementia. In sensitivity analyses excluding incident dementia cases over 5 years, the significant association between greater Mediterranean diet adherence and slower cognitive decline tends to confirm such a potential bias. Another interpretation of these results might be that a Mediterranean diet is no longer protective when the neurodegenerative process of dementia is too advanced to be reversed by diet.

Moreover, a selection bias cannot be dismissed. Participants with missing follow-up data (n=114), compared with those with available follow-up data, were older, had a lower mean BMI, higher mean CES-D score, higher mean daily use of medications, and lower cognitive performance on each test. Individuals with missing follow-up data also had a slightly lower mean diet score (4.09 vs 4.36,  $P=.09$ ) than those with follow-up data.

Another limitation concerning cognitive tests was their potential ceiling or floor effects. Moreover, our study lacked the power to definitively detect an association with incident dementia; our cohort size provided an a posteriori power of less than 10% to detect a hazard ratio of 0.9 for incident dementia, as ob-

served in our study. Lastly, we cannot rule out the possibility of residual confounding by unknown risk factors, such as a general healthier lifestyle of individuals adhering to a Mediterranean diet.

Despite these limitations, the strengths of the present study are its size, the population-based design, and control for several potential confounders. In particular, we controlled for depressive symptomatology, because links between cognitive impairment and depression are well documented.<sup>28,39</sup>

This study shows that higher Mediterranean diet adherence is associated with slightly slower MMSE decline but not with other measures of cognitive decline in older persons, especially in those who remained free from dementia over 5 years. The Mediterranean diet pattern probably does not fully explain the better health of persons who adhere to it, but it may contribute directly. A Mediterranean diet also may indirectly constitute an indicator of a complex set of favorable social and lifestyle factors that contribute to better health. Further research is needed to allow the generalization of these results to other populations and to establish whether a Mediterranean diet slows cognitive decline or reduces incident dementia in addition to its cardiovascular benefits.

**Author Contributions:** Dr Féart had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Portet, Dartigues, Scarmeas, Barberger-Gateau.

**Acquisition of data:** Féart, Barberger-Gateau.

**Analysis and interpretation of data:** Féart, Samieri, Rondeau, Amieva, Scarmeas, Barberger-Gateau.

**Drafting of the manuscript:** Féart.

**Critical revision of the manuscript for important intellectual content:** Samieri, Rondeau, Amieva, Portet, Dartigues, Scarmeas, Barberger-Gateau.

**Statistical analysis:** Féart, Samieri, Rondeau, Scarmeas.

**Obtained funding:** Dartigues, Barberger-Gateau.

**Administrative, technical, or material support:** Portet.

**Study supervision:** Scarmeas, Barberger-Gateau.

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