Mediterranean diet and cognitive function: a French study1–4

Emmanuelle Kesse-Guyot, Valentina A Andreeva, Camille Lassale, Monique Ferry, Claude Jeandel, Serge Hercberg, Pilar Galan, and the SU.VI.MAX 2 Research Group

ABSTRACT
Background: Evidence on the association between Mediterranean diet (MedDiet) adherence and cognition is presently inconsistent.
Objectives: The aims of this study were to investigate the association between midlife MedDiet adherence and cognitive performance assessed 13 y later among participants in the SU.VI.MAX (Supplementation with Vitamins and Mineral Antioxidants) study and to test the hypothesis of effect modification by occupation and educational status as cognitive reserve markers.
Design: A Mediterranean Diet Score (MDS) and a Mediterranean-Style Dietary Pattern Score (MSDPS) were estimated by using repeated 24-h dietary records (1994–1996) from 3083 middle-aged subjects. Cognitive performance was assessed in 2007–2009 by using 6 neuropsychological tests, and a composite score was built. Subgroup analyses were performed according to occupational and educational status. Mean differences and 95% CIs were estimated through covariance analyses.
Results: After potential confounders were accounted for, no association between MDS or MSDPS and cognitive scores was detected except for a lower phonemic fluency score with decreasing MSDPS (P = 0.048) and a lower backward digit span score with decreasing MDS (P = 0.03). In turn, a low MDS was related to a lower composite cognitive score in the small subsample of manual workers (n = 178, P-interaction = 0.04) who could be hypothesized to have low cognitive reserve. MedDiet adherence did not interact with educational level in relation to cognitive function.
Conclusion: This study did not find support for a beneficial effect of MedDiet adherence on cognitive function, irrespective of educational level, which is the strongest indicator of cognitive reserve. This trial was registered at clinicaltrials.gov as NCT00272428. Am J Clin Nutr 2013;97:369–76.

INTRODUCTION
As a consequence of an increasing life expectancy, the prevalence of pathological cognitive decline leading to dementia and other age-related diseases has been rising dramatically. Because, at present, dementia is not curable and current treatments have limited effectiveness in postponing or slowing down cognitive decline, prevention through modifiable factors, such as diet, emerges as the only effective short-term strategy to counteract age-related cognitive disorders (1).

The Mediterranean diet (MedDiet)5 is characterized by a limited intake of animal-derived and processed foods and the consumption of a variety of plant-based foods (fruit, vegetables, breads, and other whole-grain cereals, pulses, nuts, and seeds), wine, and olive oil (as the main source of lipids). Adherence to a MedDiet has been associated with a reduced risk of chronic disease morbidity (2, 3). The MedDiet constitutes a promising approach in the prevention of cognitive decline or risk of dementia due to its direct and/or indirect impact on brain aging through its nutritional constituents, which may enhance neuronal plasticity, counteract inflammation and oxidative stress, and improve vascular variables (4, 5). However, the inconsistency of epidemiologic data precludes the possibility of drawing firm conclusions (6–12). Some studies have in fact failed to find any associations between the MedDiet and cognitive decline/dementia among women at increased cardiovascular risk (8) or among healthy elderly individuals (8, 11).

In turn, many epidemiologic studies that investigated potential preventive factors of cognitive aging have focused mainly on old or very old population samples, which prevents the possibility of examining middle-aged, preclinical exposure. There are, however, established scientific arguments that support the critical role of midlife factors in terms of preventive action (5, 13). The... 

1 From the Université Paris 13, Sorbonne Paris Cité, UREN (Nutritional Epidemiology Research Unit), INSERM (U557), Institut National de la Recherche Agronomique (U1125), and Conservatoire National des Arts et Métiers, Bobigny, France (EK-G, VAA, CL, MF, SH, and PG); the Département de Santé Publique, Hôpital Avicenne, Bobigny, France (SH); and the Centre de Gériatricie, Clinique Antonin Balmes, CHU Montpellier, Université Montpellier I, Montpellier, France (CJ).
2 A full list of SU.VI.MAX 2 Research Group members is available as supplemental material under “Supplemental data” in the online issue.
3 Supported by the Agence Nationale de la Recherche (no. ANR-05-PNRA-010), Direction Générale de la Santé (Ministry of Health), Médecine, Sodexo, Ipsen, Mutuelle Générale de l’Éducation Nationale (MGEN), and Pierre Fabre. Mederic and MGEN are French health insurance organizations complementary to the national health insurance system. Ipsen and Pierre Fabre are private pharmaceutical companies; they financially supported the overall implementation of the research project. Sodexo is a food-catering company that sponsored events with researchers and study participants. Sponsors were not involved in the analyses or interpretation of findings. CL was supported by a doctoral dissertation fellowship from Region Île de France.
4 Address correspondence to E Kesse-Guyot, UREN, SMBH Paris 13, 74 rue Marcel Cachin, 93017 Bobigny Cedex, France. E-mail: e.kesse@uren.smbh.univ-paris13.fr.
5 Abbreviations used: AD, Alzheimer disease; MDS, Mediterranean Diet Score; MedDiet, Mediterranean diet; MSDPS, Mediterranean-Style Dietary Pattern Score; SU.VI.MAX, Supplementation with Vitamins and Mineral Antioxidants; WHICAP, Washington Heights-Inwood Columbia Aging Project.

Received July 23, 2012. Accepted for publication November 15, 2012. First published online January 2, 2013; doi: 10.3945/ajcn.112.047993.
cognitive reserve hypothesis, for example, holds that some individual factors (eg, intelligence quotient, education, and, to a lesser extent, occupation) may provide supplementary capacities to cope with or compensate for neuropathological damage, thus delaying the clinical expression of cognitive impairment (14–16). The cognitive reserve concept has been supported by some epidemiologic research (14–16). We hypothesized that cognitive reserve markers might act as effect modifiers of the putative link between a MedDiet and cognition, because the potentially harmful effect of a low adherence to a MedDiet could be masked by a compensatory phenomenon among subjects with high cognitive reserve. We aimed to assess the influence of cognitive reserve on the association between a MedDiet and cognitive function by evaluating statistical interactions between MedDiet adherence and occupation and educational level, respectively, in relation to cognitive test performance. Indeed, if such interactions exist, they could help reconcile the extant findings, suggesting that MedDiet adherence may benefit cognitive function only when cognitive reserve is low.

**SUBJECTS AND METHODS**

**Population**

The Supplementation with Vitamins and Mineral Antioxidants (SU.VI.MAX) study (1994–2002; n = 12,741) was a randomized, double-blind, placebo-controlled primary prevention trial initially designed to evaluate the effect of daily supplementation with antioxidant vitamins (vitamin E, vitamin C, and β-carotene) and minerals (selenium and zinc) at nutritional doses on the incidence of cancer and ischemic heart disease (17, 18). At the end of the trial (2002), a total of 6850 subjects who had agreed to participate in a postsupplementation observational follow-up were included in the SU.VI.MAX 2 study.

The SU.VI.MAX and SU.VI.MAX 2 studies were conducted according to the Declaration of Helsinki guidelines and were approved by the Ethics Committee for Studies with Human Subjects of the Paris-Cochin Hospital (CCPRB no. 706 and no. 2364, respectively) and the Comité National Informatique et Liberté (CNIL no. 334641 and no. 907094, respectively). Written informed consent was obtained from all participants.

**Inclusion and exclusion criteria**

For this study, we retained participants with available exposure (assessed during 1994–1996) and outcome (assessed during 2007–2009) data. Thus, from the 6850 participants in the SU.VI.MAX 2 study, we excluded those with missing neuropsychological test scores (n = 1136), those with <3 dietary records during the first 2 y of follow-up (n = 1085), those younger than 45 y at baseline (n = 1267), or those with missing data on one or more of the covariates (n = 279), leaving a total sample of 3083 participants.

**Dietary data assessment and MedDiet score computation**

During the SU.VI.MAX study, subjects were invited to provide a 24-h dietary record every 2 mo for a total of 6 records per year. For each subject, the days of the week for these records were selected at random so that each day of the week and all seasons were covered. Information was collected via computerized questionnaires. Participants were assisted by an instruction manual that included validated photographs of >250 generic foods represented in 3 main portion sizes. Participants could also choose from 2 intermediate or 2 extreme portions, for a total of 7 different portion sizes (19). A French food-composition table was used to estimate nutrient intake (20). In the present study, all food and nutrient intakes refer to the average consumption based on the 24-h dietary records provided during the first 2 y of follow-up.

We computed the Mediterranean Diet Score (MDS) by using an established algorithm (21). Briefly, sex-specific medians of food group intake were calculated. For putative favorable components, such as vegetables, fruit, grains, fish, nuts, legumes, and the ratio of MUFA$s$ to SFA$s$, 1 point was attributed if consumption was at or above the sex-specific median value. For putative detrimental components, such as meat and dairy products, 1 point was given if consumption was below the sex-specific median value. For alcohol consumption, 1 point was given when the reported ethanol consumption was 5–25 g/d for women and 10–50 g/d for men. Thus, the maximum value of the MDS was 9 points, and higher scores indicate better adherence.

In addition, we computed the Mediterranean-Style Dietary Pattern Score (MSDPS), which was recently developed in the United States (22). The MSDPS estimates adherence to recommended intakes of 13 different food groups included in the MedDiet pyramid (23) with a maximum score of 100 points after standardization. Except for olive oil, each component was scored from 0 to 10 according to the level of adherence. Lower scores were attributed proportionally on both sides of each recommended value. Exclusive olive oil use yielded 10 points, whereas no use yielded 0 points. The use of olive oil as well as other added fat yielded 5 points. Finally, because the MedDiet pyramid does not account for consumption of certain foods (eg, refined cereal), the MSDPS was weighted by a factor ranging from 0 to 1, reflecting the proportion of energy intake provided by foods actually included in the MedDiet pyramid. For example, if a subject consumed 70% of energy from foods included in the MedDiet pyramid, the calculated weight was 0.7.

For descriptive purposes, nutrient intake was energy-adjusted by using the residual method defined by Willett and Stampfer (24). Finally, the 2 scores that showed the level of adherence to a MedDiet were split into categories. For MSDPS, tertiles of adherence were calculated. However, given the limited value ranges of the MDS (which prevented the calculation of actual tertiles), that score was split into low (<4), medium (4–5), and high (≥5) adherence.

**Cognitive assessment and scoring**

During 2007–2009, all participants were invited to undergo a medical examination as part of the observational SU.VI.MAX 2 study, which included an overall clinical examination and a neuropsychological evaluation carried out by trained neuropsychologists. Episodic memory was evaluated by using the RI-48 [Rappel indiqué (cued recall)-48 items] which is based on a list of 48 words belonging to 12 different categories. The score was the number of words retrieved (maximum score of 48) (25). Lexical-semantic memory was assessed by verbal fluency tasks including a semantic fluency task, which consisted of naming as many animals as possible, and a phonemic fluency task consisting of citing words beginning with the letter P. The score was the number of correct words produced during a 2-min period for each task (26). Short-term and working memory was assessed...
with the forward and backward digit span task. Subjects were asked to repeat 2 sequences of digits, forward or backward. The number of digits increased by 1 unit after each repetition, until the participant failed 2 consecutive trials of the same digit span. One point was assigned for each sequence repeated correctly, with a maximum score of 14 points for digit span forward as well as backward (27). Mental flexibility was assessed with the Delis-Kaplan trail-making test, which consists of connecting numbers and letters that alternate between the 2 series. The score was the time (in s) needed to complete the task (28), implying that a lower value indicated better performance. For our analyses, we used the inverse of the trail-making test score; thus, a higher score corresponded to better performance. The inverse of the trail-making test score was log-transformed to improve normality.

Individual cognitive test scores were converted into T scores (mean = 50, SD = 10) (29). Thus, a 1-point difference in the test score corresponded to one-tenth of an SD difference. A composite cognitive score defined as the mean of the standardized individual test scores was rescaled to SD = 10.

Covariates

Sex, date of birth, education (primary, secondary, or university level), occupation (homemaker, manual worker, or blue- or white-collar worker), geographic region (north, south), smoking status (never smoked or former or current smoker), physical activity (irregular, <1 h of walking/d, ≥1 h of walking/d), memory troubles (yes or no), and medication use were collected at baseline through self-administered questionnaires. The 4 occupational categories referred to homemakers (ie, individuals staying at home), manual workers (eg, farmers and manual laborers), blue-collar workers (eg, craftspeople, retailers, technicians, administrative staff), and white-collar workers (eg, managerial/professional staff). The occupational category of retired and unemployed people was determined according to the last job held. Anthropometric and clinical measurements were collected at the initial clinical examination (1995–1996), as previously described (30). BMI was calculated as the ratio of weight to squared height (kg/m²). Fasting blood samples were obtained at baseline and at the end of the follow-up, and all biochemical measurements were centralized. Fasting blood glucose was measured by using an enzymatic method (Advia 1650; Bayer Diagnostics). In case of suspected cardiovascular disease during the follow-up period, relevant medical data (clinical, biochemical, histologic, and radiologic reports) were requested from participants, physicians, and/or hospitals. All reported cardiovascular events were reviewed and validated by an independent expert committee.

In SU.VLMAX 2, depressive symptoms were assessed by using the French self-administered version of the Center for Epidemiologic Studies Depression Scale, and the total score was used as a covariate (31).

Statistical analyses

Descriptive baseline characteristics are reported as means ± SDs or percentages across categories of the MDS and MSDPS. Reported P values refer to tests for linear contrast or to the Mantel-Haenszel chi-square trend tests, as appropriate. ANCOVA was used to estimate the association between categories of MedDiet adherence and cognitive scores (ie, the composite score and the individual test scores). P values for the continuous MedDiet score are reported. In the initial analyses, the models were adjusted for age, sex, education, follow-up time between baseline and cognitive evaluation, supplementation group during the trial phase, and number of 24-h dietary records. In the second set of models, analyses were additionally adjusted for energy intake, BMI, occupational status, tobacco use status, physical activity, memory difficulties at baseline, depressive symptoms concomitant with the cognitive function assessment, and incidence of diabetes, hypertension, or cardiovascular disease during follow-up.

In addition, effect modifications by sex, educational level, and occupation were tested. For these tests, a product term [MDS in 3 categories × effect modifier (2 categories for sex, 3 categories for education, 4 categories for occupation)] was added in the model.

Sensitivity analyses were also performed by using 2 modified MDSs where the MUFA:SFA ratio was replaced by a ratio of olive oil to other added fats or by replacing alcohol intake with alcohol from wine.

Statistical tests were 2-sided, with type I error set at <0.05. All analyses were performed by using SAS software (release 9.1; SAS Institute Inc).

RESULTS

Sample description

A total of 3083 participants (1655 men and 1428 women) were included in the present analysis. At baseline, mean (±SD) age was 52.0 ± 4.6 y, and at the time of the cognitive evaluation mean age was 65.4 ± 4.6 y. Mean composite cognitive scores by educational level were 44.01 ± 8.91, 49.62 ± 9.38, and 52.61 ± 9.67 among participants attaining primary, secondary, and university level, respectively. Across occupations, mean composite cognitive scores were 48.11 ± 10.11, 43.45 ± 10.04, 49.26 ± 9.62, and 52.91 ± 9.72 among homemakers, manual workers, blue-collar workers, and white-collar workers, respectively.

Age, BMI, education, occupation, tobacco use, physical activity, supplementation group, baseline self-reported memory difficulties, history of hypertension/diabetes/cardiovascular diseases, energy intake, number of 24-h records, and depressive symptoms were all associated with performance on at least one cognitive test. All covariates except for history of diabetes, history of cardiovascular disease, and number of 24-h records were associated with the composite cognitive performance score (data not shown).

Included and excluded participants

A comparison of cognitive performance between included and excluded participants did not show any significant differences except for slightly lower scores on forward and backward digit span among excluded participants with available data: a mean forward digit span score of 6.9 ± 2.0 compared with 7.1 ± 2.0 (P = 0.01) and a mean backward digit span score of 6.2 ± 2.1 compared with 6.3 ± 2.1 (P = 0.04), respectively. Excluded participants (with available data) also showed slightly lower adherence to a MedDiet than did their included counterparts:
4.4 ± 1.6 compared with 4.6 ± 1.6 (P = 0.003) for MDS and 22.4 ± 5.7 compared with 22.8 ± 5.8 (P = 0.04) for MSDPS.

Characteristics according to the MDS

Baseline characteristics of the participants are presented across categories of the MDS (Table 1). Compared with those with a low MDS (<4), participants with a high MDS (>5) were more often men, older, better educated, more physically active, and nonsmokers; were less likely to report depressive symptoms; and had higher total energy intake. A higher MDS was associated with higher energy intake from carbohydrates and a lower energy intake from lipids and proteins. In addition, the MDS was positively correlated with intakes of MUFAs, n−3 and total PUFAs, β-carotene, folic acid, vitamin C, vitamin E, and fiber.

### Table 1

Baseline characteristics of the population across categories of the MDS and MSDPS (n = 3083)

<table>
<thead>
<tr>
<th>Variable</th>
<th>MDS</th>
<th>MSDPS</th>
<th>P²</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS/MSDPS cutoff</td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>n</td>
<td>833</td>
<td>1407</td>
<td>843</td>
</tr>
<tr>
<td>Male (%)</td>
<td>51</td>
<td>54</td>
<td>57</td>
</tr>
<tr>
<td>Intervention group (%)</td>
<td>50</td>
<td>54</td>
<td>55</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.5 ± 3.5</td>
<td>24.4 ± 3.3</td>
<td>24.1 ± 3.2</td>
</tr>
<tr>
<td>Age at cognitive evaluation (y)</td>
<td>64.9 ± 4.3</td>
<td>65.4 ± 4.6</td>
<td>66.0 ± 4.6</td>
</tr>
<tr>
<td>CES-D score at cognitive evaluation</td>
<td>9.2 ± 7.5</td>
<td>8.7 ± 7.5</td>
<td>8.3 ± 7.2</td>
</tr>
<tr>
<td>No. of 24-h records</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Energy intake (kcal/d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteins (%)</td>
<td>16.5 ± 2.9</td>
<td>17.9 ± 2.8</td>
<td>17.2 ± 2.4</td>
</tr>
<tr>
<td>Carbohydrates (%)</td>
<td>40.7 ± 6.3</td>
<td>42.0 ± 6.1</td>
<td>43.5 ± 5.8</td>
</tr>
<tr>
<td>MUFAs (g/d)</td>
<td>34.1 ± 4.9</td>
<td>34.4 ± 5.4</td>
<td>34.9 ± 5.7</td>
</tr>
<tr>
<td>PUFAs (g/d)</td>
<td>12.7 ± 3.1</td>
<td>13.7 ± 3.4</td>
<td>14.9 ± 3.7</td>
</tr>
<tr>
<td>n−3 PUFAs (g/d)</td>
<td>11.1 ± 2.9</td>
<td>12.0 ± 3.2</td>
<td>13.2 ± 3.5</td>
</tr>
<tr>
<td>SFAs (g/d)</td>
<td>39.7 ± 6.1</td>
<td>37.9 ± 6.3</td>
<td>35.1 ± 6.3</td>
</tr>
<tr>
<td>Folic acid (µg/d)</td>
<td>292.8 ± 67.9</td>
<td>326.2 ± 72.9</td>
<td>356.4 ± 76.3</td>
</tr>
<tr>
<td>β-Carotene (mg/d)</td>
<td>3299.8 ± 1882.7</td>
<td>4062.7 ± 2390.7</td>
<td>4873.1 ± 2510.0</td>
</tr>
<tr>
<td>Vitamin C (mg/d)</td>
<td>82.4 ± 38.0</td>
<td>97.9 ± 41.4</td>
<td>113.6 ± 44.8</td>
</tr>
<tr>
<td>Vitamin E (mg/d)</td>
<td>11.4 ± 3.2</td>
<td>12.8 ± 3.7</td>
<td>14.8 ± 4.4</td>
</tr>
<tr>
<td>Fiber (g/d)</td>
<td>17.1 ± 4.0</td>
<td>20.0 ± 4.8</td>
<td>23.3 ± 5.7</td>
</tr>
<tr>
<td>Education (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>26</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Secondary</td>
<td>28</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>University level</td>
<td>46</td>
<td>53</td>
<td>56</td>
</tr>
<tr>
<td>Geographic region (%)</td>
<td>20</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>Residence (%)</td>
<td>14</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Physical activity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irregular</td>
<td>25</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>≤1 h walking/d</td>
<td>30</td>
<td>30</td>
<td>29</td>
</tr>
<tr>
<td>≥1 h walking/d</td>
<td>45</td>
<td>46</td>
<td>51</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>51</td>
<td>50</td>
<td>52</td>
</tr>
<tr>
<td>Former smoker</td>
<td>37</td>
<td>39</td>
<td>40</td>
</tr>
<tr>
<td>Current smoker</td>
<td>12</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Occupational status (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homemaker</td>
<td>10</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Manual worker</td>
<td>7</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Blue-collar worker</td>
<td>55</td>
<td>54</td>
<td>55</td>
</tr>
<tr>
<td>White-collar worker</td>
<td>28</td>
<td>34</td>
<td>32</td>
</tr>
<tr>
<td>Memory difficulties (%)</td>
<td>35</td>
<td>35</td>
<td>37</td>
</tr>
</tbody>
</table>

1 Values are baseline values except when otherwise specified. CES-D, Center for Epidemiologic Studies Depression Scale; MDS, Mediterranean Diet Score; MSDPS, Mediterranean-Style Dietary Pattern Score.
2 P values are based on linear contrast or Mantel-Haenszel chi-square trend test.
3 Mean ± SD (all such values).
4 Values are percentages of total daily energy intake (without alcohol).
5 Values were adjusted for energy.
Characteristics according to the MSDPS

Baseline characteristics of the participants are also presented across categories of the MSDPS (Table 1). Compared with those with a low MSDPS (first tertile), participants with a high MSDPS (third tertile) were more often older, better educated, and less likely to reside in rural areas. A higher MSDPS was associated with a higher energy intake from lipids and proteins and a lower energy intake from carbohydrates. The MSDPS was positively correlated with intake of MUFAs, n-3 and total PUFAs, β-carotene, folic acid, vitamin C, vitamin E, and fiber.

Pearson and Spearman correlation coefficients between the MDS and the MSDPS were $r = 0.30$ and $r_s = 0.29$, respectively.

Association between MedDiet and cognitive function

No interaction between adherence to a MedDiet and sex with regard to cognitive performance was detected (all $P > 0.20$). Longitudinal associations between MedDiet adherence estimated through the MDS and MSDPS and cognitive performance are presented in Table 2. In the first model, a higher MDS was associated with better performance on the backward digit span task. In turn, a higher MSDPS was associated with a better composite cognitive score as well as with better performance on the phonemic and semantic fluency tasks. In the fully adjusted model, most associations did not remain significant except for a link between a lower MDS and poorer backward digit span performance and a link between a lower MSDPS and poorer phonemic fluency performance.

In sensitivity analysis, after replacement of the MUFA:SFA ratio with the ratio of olive oil to other added fats or after replacement of alcohol intake with alcohol from wine, the findings were similar (data not shown).

Differential association between MedDiet and cognitive function according to educational level and occupation

Only in the subsample of manual laborers ($n = 178$), poorer adherence to a MedDiet assessed through the MDS was related to a lower composite cognitive score (mean difference $= -5.14; 95\%\ CI: -9.18, -1.11; P$-trend $= 0.01, P$-interaction $= 0.04$). No similar interaction was detected when adherence to a MedDiet was assessed with the MSDPS ($P$-interaction $= 0.07$). No interaction between educational level and adherence to a MedDiet with regard to cognitive function was detected (data not shown).

DISCUSSION

In this French population of adults, midlife adherence to a MedDiet was not associated with global cognitive performance assessed 13 y later, after major confounders including lifestyle behaviors, sociodemographic factors, and health events were accounted for. Some specific associations between MedDiet and individual cognitive test scores were observed.

A few epidemiologic studies have reported associations between a MedDiet and cognitive outcomes (7, 8, 11, 12, 32–37). Among them, some have found lower cognitive decline or lower risk of Alzheimer disease (AD) with increasing MedDiet adherence (12, 34–37), whereas others have not found such benefits (8, 11, 32, 33), which is consistent with the present results. Nonetheless, it should be noted that approximately half of the published findings are based on a single data set from the Washington Heights-Inwood Columbia Aging Project (WHICAP) study (34–37). Indeed, the first study reporting such a promising beneficial effect of MedDiet adherence was conducted in WHICAP participants aged $\geq 65$ y. A 40% reduction in risk of AD over a 4-y follow-up period was observed among participants with high compared with low adherence to a MedDiet estimated by using the MDS (35). On the contrary, another study conducted in a French cohort of healthy elderly individuals (the Three-City Study) did not find any associations between compliance with a MedDiet and AD risk (32).

Such inconsistencies may be due to methodologic issues. For example, dietary data are heterogeneous across studies in terms of assessment methods and accuracy of intake estimation. In addition, in most of these studies follow-up was relatively short, yet, as recently highlighted, AD is preceded by a relatively long prodromal period and cognitive decline is initiated several years before diagnosis (38, 39). Thus, changes in dietary habits may have occurred before the follow-up as a consequence of cognitive modification. Given the long prodromal period leading up to AD, the age of the studied population is also of major importance (40) and argues for identifying midlife factors associated with cognitive aging (13, 41). However, WHICAP included participants aged $\geq 65$ y. Thus, dietary data in WHICAP reflected exposure among elderly individuals, whereas the mean age of the SU.VI.MAX participants at the time of the dietary data assessment was 52 y, allowing an investigation of midlife exposure. Furthermore, the MDS computation is based on median values in the given population, which prevents a direct comparison across studies.

In our study, occupational status, which is one of the markers of cognitive reserve, exhibited an effect modification of the long-term association between midlife adherence to a MedDiet and cognitive function. This finding might suggest that the potentially harmful effect of nonadherence to a MedDiet on cognitive function in the context of aging could be overridden among participants with a higher cognitive reserve. However, we did not observe similar findings when education, which has been established as a better indicator of cognitive reserve (42), was modeled as a potential effect modifier, advocating for an alternative explanation. In fact, the significant association between cognitive function and MDS (but not MSDPS) observed among manual workers might be due to residual confounding in this specific stratum, to an artifact, to an outlier impact, or to chance.

The absence of convincing effect modification of cognitive reserve markers with regard to the relation between MedDiet adherence and cognitive outcome is in concordance with the findings of 2 recent studies (8, 12).

Other nutrition scores or dietary patterns identified through principal components analysis have been significantly associated with cognitive function in the same population (30, 43). Contrary to the present findings, we have previously reported a positive association between a healthy dietary pattern and cognitive function (30). The discrepancy between the results could be explained in terms of the respective methodology. In fact, dietary pattern analysis and analyses based on a priori–derived scores (such as the MDS) are conceptually and computationally different, even though the MedDiet and a healthy dietary pattern...
share some characteristics (44). Another explanation for the null results in the present study pertains to the sample homogeneity with regard to adherence to a MedDiet in our population. This is shown by the lack of differences in the level of adherence to the MedDiet across geographic area, the north compared with the south of France.

Some limitations of our study should be noted. First, cognitive performance was not measured at baseline; thus, baseline differences...
in cognitive performance according to MedDiet adherence cannot be ruled out, which prevents an inference of causality. However, the relatively young age of our population and their ability to follow the protocol (completing many questionnaires over a long period of time) argue for the likely absence of cognitive impairment at baseline. Nonetheless, despite an adjustment for baseline memory troubles, the lack of baseline cognitive assessment is a major limitation, which also prevents the assessment of cognitive decline over time. Second, a priori indexes show some limitations, including the arbitrary selection of components (nutrients, food groups, and their constituents), the definition of cutoffs, and scoring methods (45). However, the strength of the MedDiet scores has been shown via significant associations with various outcomes, in various populations and countries (2, 3), including prior evidence from the SU.VI.MAX study (46). The differential findings according to the score of choice (MDS or MSDDS) show the importance of considering several exposure measurements when using scores, because they do not measure exactly the same dietary pattern. For instance, in our population, the MSDDS was less strongly correlated with intake of MUFA s, antioxidants, folic acid, and fiber than was the MDS (data not shown). Third, the external validity of our findings might be limited. Indeed, the present analysis was based on a selected subsample of SU.VI.MAX participants. Finally, residual confounding cannot be excluded even though it is likely minimized due to extensive adjustment for confounders.

In turn, our study also exhibits several strengths and other original aspects, including its large sample of community-dwelling subjects, its longitudinal design, and the use of highly accurate dietary data that reflect midlife exposure. Computing different MedDiet scores allowed us to test the robustness of the findings and thus limit subjectivity related to score computation.

In conclusion, our study does not support the hypothesis of a significant neuroprotective effect of a MedDiet on cognitive function. Specifically, MedDiet adherence was not associated with cognitive performance overall. Moreover, no compelling effect modification by cognitive reserve markers was observed.

We especially thank Stéphane Raffard (neuropsychologist), who was responsible for standardization of the cognitive evaluation; Nathalie Arnault (statistician), who coordinated data management; Frédéric Ferrat, who coordinated the logistic aspects of the neuropsychological evaluation; and Gwenaël Monot (computer scientist), who coordinated the computing aspects. The authors’ responsibilities were as follows—EK-G: carried out data checking and analyses and was responsible for drafting the manuscript; CL, VAA, CJ, MF, SH, and PG: were involved in interpreting results and editing the manuscript; and EK-G, PG, and SH: were responsible for developing the design and protocol of the study. All authors read and approved the final version of the manuscript. The authors declared no conflicts of interest.

REFERENCES

4. Frisardi V, Panza F, Seripa D, Imbimbo BP, Vendemiale G, Pilotto A, Solfrizzi V. Nutraceutical properties of Mediterranean diet and cognit-