THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2018, Vol. 73, No. 3, 347–354
doi:10.1093/gerona/glx066
Advance Access publication April 29, 2017

OXFORD

Translational Section

The Mediterranean Diet

Research Article

Association Between Adherence to the Mediterranean Diet at Midlife and Healthy Aging in a Cohort of French Adults

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Received: November 13, 2016; Editorial Decision Date: April 1, 2017

Decision Editor: Stephen Kritchevsky, PhD

Abstract

Background: The Mediterranean diet has been suggested as a key element for the prevention of age-related chronic diseases. However, very few studies have examined its relation with multidimensional concepts of healthy aging (HA). Our objective was thus to investigate the association between adherence to the Mediterranean diet at midlife and HA.

Methods: We analyzed data from 3,012 participants of the French *SUpplémentation en Vitamines et Minéraux AntioXydants* (SU.VI.MAX) study aged 45–60 years at baseline (1994–1995) and initially free of major chronic diseases, with available data on HA status in 2007–2009. We defined HA as not developing major chronic disease (cancer, cardiovascular disease, or diabetes), good physical and cognitive functioning (evaluated by validated, standardized tests), independence in instrumental activities of daily living, no depressive symptoms, good social functioning, good self-perceived health, and no function-limiting pain. An index assessing adherence to the Mediterranean diet, the Literature-based Adherence Score to the Mediterranean Diet (LAMD) was calculated using baseline data from repeated 24-hour dietary records.

Results: In 2007–2009, 38% of participants met the HA criteria. Multivariable logistic regression revealed that higher scores on the LAMD ($OR_{\text{Tertile 3}}$ vs $_{\text{Tertile 1}}$: 1.36 [1.12; 1.65]) were associated with higher odds of HA. Supplementary analyses using structural equation modeling revealed a potential mediation of the observed associations by metabolic health-related factors.

Conclusions: Our results suggest a favorable role of a high adherence to the Mediterranean diet at midlife for maintaining good overall health during aging.

Keywords: Nutrition—Successful aging—Epidemiology—Risk factors—Metabolic health

Nutrition is one of the main modifiable factors that have been proposed as key elements of prevention strategies for age-related chronic disease and functional decline (1–3). A recent systematic review has indicated that an overall higher quality of the diet (as measured by different types of "dietary pattern analysis") may play an important role for maintaining a high health-related quality of life and good physical and cognitive functioning during aging (3). Out of various types of dietary patterns, the Mediterranean-style diet is currently considered as particularly promising in terms of disease prevention and the preservation of a good overall health status during aging (1,2).

However, to our knowledge, only one study (4) has investigated a potential beneficial role of adopting a Mediterranean diet with respect to multidimensional concepts of "healthy aging (HA)" or "successful aging," which have been developed to consider the overall health of individuals during aging. In contrast to traditional research, which focuses on specific diseases or functions of the body, multidimensional HA models permit to provide estimates on how different types of exposures are related to overall health during aging. In addition to the possibility to consider different facets of health in a combined manner, multidimensional HA concepts also aim to better reflect what elderly individuals themselves associate with HA—by integrating dimensions such as perceived health, social functioning, and limitations due to pain and to mental health problems.

Multidimensional HA concepts are, for the most part, based on the definition proposed by Rowe and Kahn (5), which includes the absence of disease and disability, good physical and cognitive functioning, and an active engagement with life. The one existing study that has investigated the Mediterranean diet with respect to a multidimensional HA model has found that a high adherence to the Mediterranean diet, defined as being in the 5th quintile of the Alternate Mediterranean Diet Score, was prospectively related to nearly 50% higher odds for HA (4). Thus, the Mediterranean diet may have an important preventive potential with respect to age-related health decline but more studies are needed to confirm the existing findings.

Hence, the objective of our study was to investigate the 13-year association of midlife adherence to a Mediterranean-style diet, measured by the Literature-Based Adherence Score to the Mediterranean Diet (LAMD) (6), with a multidimensional concept of HA in a sample of French adults. A secondary objective was to conduct an investigation of potential mediating factors (biomarkers measured after approximately 8 years of follow-up) and of the interrelations with different socioeconomic and lifestyle factors, using an innovative statistical approach, structural equation modeling (SEM).

Subjects and Methods

Study Design

The SU.VI.MAX (SUpplémentation en Vitamines et Minéraux AntioXydants) study was initially a randomized, double-blind, placebo-controlled primary prevention trial testing the effect of nutritional-dose antioxidant supplementation on the incidence of cancers and cardiovascular disease. The trial was conducted in France between 1994 and 2002 and included 12,741 men aged 45–60 years and women aged 35–60 years. A detailed description of the trial has been published elsewhere (7,8).

In 2007–2009, the SU.VI.MAX participants were invited, on a voluntary basis, to participate in an additional observational follow-up, the SU.VI.MAX 2 study. This follow-up included 6,860 subjects who completed clinical and neuropsychological examinations and a number of questionnaires (9). The SU.VI.MAX and SU.VI.MAX 2 studies were conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Ethics Committee for Studies with Human participants of Paris-Cochin Hospital (CCPPRB n° 706 and n° 2364, respectively) and the Commission Nationale de l'Informatique et des Libertés (CNIL n° 334641 and n° 907094, respectively). Written informed consent was obtained from all subjects.

Baseline Dietary Data (1994–1996)

Dietary data were collected via 24 hours dietary records. Participants were invited to complete one record every 2 months during the SU.VI.MAX study, using computerized questionnaires and an instruction manual including validated photographs of more than 250 foods that allowed them to choose from seven possible portion sizes Dietary records were considered as invalid if energy intake was less than 100 kcal/d or more than 6,000 kcal/d. In addition, to account for energy underreporting, men reporting less than 800 kcal/d and women reporting less than 500 kcal/d across ≥1/3 of records were excluded. Seafood consumption was measured via a frequency questionnaire. Alcohol consumption was estimated via a short, validated, and semiquantitative dietary questionnaire (10). Food and nutrient intakes were computed based on all eligible dietary records during the first 2 years of follow-up. On average, 10.2 records (interquartile range: 8–13) were available per individual. The LAMD score includes six components characterized by food groups that are considered as beneficial (fruits, vegetables, legumes, cereals, fish, and olive oil or the ratio mono-unsaturated fatty acids/saturated fatty acids), two components characterized by food groups that are considered as detrimental (meat and dairy products), and one alcohol-related component that considers moderate intake as beneficial and excessive intake as detrimental. The consumption of each food group is classed into three categories, by using fixed cutoff points that were determined based on an extensive, published review of the literature (6) (Supplementary Table 1).

In a sensitivity analyses, we additionally considered two other dietary indices: the Mediterranean Diet Scale (MDS) (11) and the relative Mediterranean Diet Score rMed (12). The score components are essentially the same as for the LAMD but the cutoffs for point-attribution are based on median-splits for the MDS and on tertiles for the rMed. Further details are provided in Supplementary Online Material 1.

Clinical Indicators at Baseline (1994–1995), in 2001–2002 and in 2007–2009

Weight, height, waist circumference, and hip circumference were measured during a clinical examination performed by trained personnel. Body mass index was calculated as kg/m^2 and waist-to-hip-ratio as the ratio of waist circumference and hip circumference. Systolic and diastolic blood pressure was measured three times with a standard mercury sphygmomanometer after lying down for 10 minutes and mean values were calculated. Moreover, blood samples were collected after a 12-hour fast. The treatment and storage (at −80°C) of these samples, as well as the measurement of serum lipids and glucose has been described previously (7). Medication use (including antidiabetics) was self-reported.

Disease Incidence During Follow-up (1994–2009)

An extensive description of data collection concerning cancer and cardiovascular disease events has been published previously (7,13). Briefly, independent expert committees validated events after review of relevant medical records, while referring to the 10th International World Health Organization (WHO) Classification of Diseases. Diabetes was defined as having fasting blood glucose ≥7 mmol/L, antidiabetic medication use, or self-reported diabetes.

"Healthy aging" Definition

Our HA concept is largely based on the Rowe and Kahn model (4). Thus, HA was defined as follows: (a) the absence of: incident major chronic disease (cancer, cardiovascular disease or diabetes) during follow-up, limitations in instrumental activities of daily living (IADL), function-limiting pain, depressive symptomatology, and health-related limitations in social life; (b) the presence of: good

Table 1. Healthy Aging Definition Developed for the SU.VI.MAX Study

Criterion	Definition in the A Priori-Defined HA Model (components are binary variables)	Definition in the Structural Equation Model (most components are 5-class variables)
Good physical functioning	SPPB ≥ 11/12	Conversion of the score to a 5-level variable (approximate quintiles)
Good cognitive functioning	MMSE ≥ 27/30 and RI-48 ≥ 19/48 and DK-TMT ≥ 5.5	Conversion of the three scores to 5-level variables (quintiles or approximate quintiles). Final composite score = sum of these three variables.
No limitations in IADL	< 1 limitation	Conversion of the score to a 5-level variable (approximate quintiles)
No incident major chronic disease	No incident cancer (ie, cancer of any kind, except for basal cell carcinoma), cardiovascular disease or diabetes during follow-up	Binary variable
No health-related limitations in social life	SF-36 responses: 1–2 to item 6 and 3–5 to item 10	Conversion of the "social functioning" subscore of the SF-36 to a 5-class variable (approximate quintiles)
Good overall self-perceived health	SF-36 responses: 1–3 to item 1	Conversion of the "general health" subscore of the SF-36 to a 5-class variable (quintiles)
No depressive symptoms	CES-D < 16/60	Conversion of the reverse-coded score to a 5-class variable (approximate quintiles)
No function-limiting pain	SF-36 responses: 1–3 to item 7 and 1–2 to item 8	Conversion of the "bodily pain" subscore of the SF-36 to a 5-class variable (quintiles)

Note: Adapted from another article on healthy aging in the SU.VI.MAX study (14). CES-D = Center for Epidemiologic Studies Depression scale (25)—a validated, self-administered questionnaire assessing depressive symptomatology; DK-TMT = Delis–Kaplan Trail-making test—a validated test assessing mental flexibility (26); HA = healthy aging; IADL = Instrumental activities of daily living (27)—a validated self-administered questionnaire assessing independence in activities such as shopping or cooking; MMSE = Mini-Mental State Examination (27)—a validated test of overall cognitive functioning; RI-48 = rappel indicé-48 items (28)—a validated test of episodic memory; SF-36 = Medical Outcome Study Short Form-36 (29)—a validated, self-administered questionnaire assessing various dimensions of health-related quality of life; SPPB = Short Physical Performance Battery (30)—a validated test battery assessing lower extremity function.

physical and cognitive functioning and good overall self-perceived health (see Table 1). HA was defined as a dichotomous variable (meeting all criteria or not). A detailed description has been published elsewhere (14).

Other Baseline Data

Self-administered questionnaires were used to collect data on sex, date of birth, education (primary, secondary, university level), occupation (homemakers, manual workers, intermediate professions, managerial staff/intellectual profession), living arrangement (living alone, living in a couple), smoking status (never smoked, former or current smoker), and physical activity (irregular, <1 hour of walking/d, ≥1 hour of walking/d). In addition, a continuous measure of leisure physical activity at baseline was obtained by a validated, self-administered questionnaire (15).

Study Sample Selection

We selected those participants of the SU.VI.MAX study aged 45–60 years at inclusion (n = 9,867), who were free of diabetes, cardiovascular disease, or cancer at inclusion (n = 9,180) and had available data for the computation of the dietary scores (n = 5,920). After exclusion of subjects with incomplete information on HA status, a final sample of 3,012 individuals (1,578 men and 1,434 women) was obtained.

Statistics

Descriptive statistics

Participant characteristics were compared according to HA status, using Mann–Whitney U- and χ^2 tests. In addition, we compared participants included into our analyses with those excluded due to missing data on HA status, considering the above-mentioned sample of 5,920 participants with complete dietary data as the "source population."

Main analyses

We used logistic regression to evaluate the association of the LAMD, modeled as both tertiles and as a standardized continuous variable, with later HA. Tests for (log-) linear trend consisted in modeling score tertiles as ordinal variables. Model 1 was adjusted for baseline age and gender, and Model 2 for age, gender, follow-up time, supplementation group, occupation, living arrangement, smoking status, educational level, energy intake, number of 24-hour records, and physical activity.

Sensitivity analyses

A first sensitivity analysis consisted of an additional consideration of the MDS and the rMed as dietary indices. Second, we verified whether an additional adjustment for the region of residence would change our results. Finally, in order to partly correct for the selection bias related to the exclusion of individuals with missing data on HA status, we performed inverse probability weighting (16). For each individual of the "source population" (N = 5,920, cf. "*descriptive statistics*"), the probability of inclusion into our study sample was estimated via logistic regression (as a function of baseline variables). The inverse of this probability (multiplied by the sampling proportion $n_{included}/n_{total}$) was then used as weights for our analyses.

Structural equation models

A detailed description of how we applied SEM is described in Supplementary Online Material 2. Briefly, three main latent constructs were created: (a) HA (our outcome variable), using the same variables as those included into our above-described a priori-defined HA model, (b) different biomarkers measured in 2001–2002 (our mediating factor): fasting serum levels of glucose, LDL, HDL, and triglycerides; systolic blood pressure; and waist-to-hip-ratio, and (c) adherence to the Mediterranean diet (our main exposure), modeled on the basis of the LAMD, rMed, and MDS.

All analyses except SEM were performed using SAS software (version 9.3, SAS Institute, Inc.). Missing values for covariables were dealt with by attribution of modal values. For our main analyses (n = 3,012), the number of missing values was: n = 123 for smoking status, n = 100 for living arrangement, n = 76 for occupational category, and n = 22 for physical activity level.

Results

Our study sample's mean age at follow-up was 65.3 (SD = 4.5) years and the mean follow-up time was 13.4 (SD = 0.5) years. The criteria of HA were met by 41% of men and 36% of women. Compared to included participants (n = 3,012), those who were excluded due to missing data on HA (n = 5,920) were younger, less educated, more often smokers, consumed less fruits and vegetables, had lower scores on the tested Mediterranean diet scores, lower physical activity, a higher body mass index, a higher fasting blood glucose, and a higher systolic blood pressure (data not shown).

Descriptive Statistics

Compared to participants not categorized as "healthy agers," "healthily aging" participants were younger, more often men, had higher education, were in a more favored socioprofessional category, more physically active, had a lower body mass index, were more often in the "antioxidant supplementation group" during the SU.VI. MAX trial phase and consumed less protein (Table 2).

Main Analyses

As shown in Table 3, adherence to the Mediterranean diet as measured by the LAMD was related to significantly higher odds of HA: $OR_{Tertile3\ vs\ Tertile1}$ = 1.36; 95% confidence interval (CI) = 1.12–1.65 (p_{trend} = .002). When considering each specific component of the LAMD in an isolated manner, a significant association with HA was observed for fruits and vegetables and associations with $p < .10$ were observed for alcohol and meat (Supplementary Table 1).

Sensitivity Analyses

When using the rMed instead of the LAMD to assess adherence to the Mediterranean diet, similar results were obtained (Supplementary Table 2). When using the MDS, the association with HA did not have a clear linear shape and was not statistically significant when modeling the score as tertiles: $OR_{Tertile3\ vs\ Tertile1}$ = 1.22; 95% CI = 0.98–1.50 (p_{trend} = .08).

An additional adjustment of our main analyses for the region of residence did not substantially change our results (data not shown). Moreover, our sensitivity analyses in which we applied inverse probability weighting yielded essentially the same results as our main analyses, although the observed associations were slightly weaker (Supplementary Table 3)

Structural Equation Models

In the final structural equation model, not all initially tested components of HA were retained (Supplementary Figure 1). The

Table 2. Baseline Characteristics of Participants According to Subsequent Healthy Aging Status

Baseline Characteristics	No Healthy Aging (n = 1,858)	Healthy Aging (n = 1,154)	p
Age, years	65.59 ± 4.57	64.74 ± 4.35	<.001
Men, %	935 (50.3)	643 (55.7)	.004
Intervention group, %	954 (51.3)	641 (55.5)	.02
Educational level, %			<.001
Primary	451 (24.3)	194 (16.8)	
Secondary	745 (40.1)	446 (38.6)	
University level or equivalent	662 (35.6)	514 (44.5)	
Occupational status, %			<.001
Homemaker/inactive	164 (9.0)	73 (6.5)	
Manual worker	123 (6.8)	45 (4.0)	
Employees	1025 (56.5)	585 (52.1)	
Managerial staff/intellectual profession	502 (27.7)	419 (37.3)	
Living arrangement, % living alone	253 (14.0)	134 (12.1)	.13
Smoking habits, %			.19
Never smoker	907 (50.9)	572 (51.7)	
Former smoker	670 (37.6)	430 (38.9)	
Current smoker	206 (11.6)	104 (9.4)	
Physical activity level, %			.004
Irregular or no physical activity	472 (25.6)	234 (20.4)	
< 1 h/d	553 (30.0)	351 (30.7)	
≥ 1 h/d	820 (44.4)	560 (48.9)	
Energy intake, kcal/d	2,178.04 ± 626.43	2,198.60 ± 585.52	.28
Alcohol intake, g/d	20.20 ± 21.29	19.75 ± 19.25	.19
Carbohydrates[a], %	42.04 ± 6.26	42.25 ± 5.87	.54
Lipids[a], %	40.01 ± 5.34	40.06 ± 4.88	.86
Proteins[a], %	17.93 ± 2.75	17.67 ± 2.65	.01
Number of 24-h records	9.99 ± 3.22	10.26 ± 3.04	.03
Body mass index, kg/m^2	24.46 ± 3.48	24.01 ± 2.99	.006

Note: Values are means ± SD or percent. p Values were obtained by Wilcoxon rank-sum tests or χ^2 tests.
[a]Percentage of alcohol-free energy intake.

Table 3. Association Between the Literature-Based Adherence Score to the Mediterranean Diet and Healthy Aging (*N* = 3,012)

	Tertile 1	Tertile 2	Tertile 3	p_{trend}	OR for the Standardized Continuous Score	$p_{continuous}$
Model 1	1 (–)	1.24 (1.03; 1.50)	1.40 (1.16; 1.70)	<.001	1.13 (1.05; 1.22)	<.001
Model 2	1 (–)	1.23 (1.02; 1.49)	1.36 (1.12; 1.65)	.002	1.12 (1.04; 1.21)	.003

Note: Values are OR (95% confidence intervals). Model 1: adjusted for age and gender; Model 2 additionally adjusted for supplementation group, occupation, living arrangement, smoking status, educational level, follow-up time, energy intake, number of 24-h records, and physical activity. OR = odds ratio.

components related to function-limiting pain, health-related limitations in social life, and depressive symptoms critically decreased model fit when entered and were thus excluded from the model.

We observed a significant positive association between the "Mediterranean diet" construct and the latent HA construct. Moreover, there was a significant negative relation between the "Mediterranean diet" and the "intermediate factors" constructs and between the "intermediate factors" and the HA constructs, suggesting a partial mediation of the association between adherence to the Mediterranean diet and HA by a set of biomarkers related to metabolic disorders. The comparative fit index (.92) indicated a satisfactory fit of the final model.

Discussion

Summary of Findings

In this large cohort of French adults, higher adherence to the Mediterranean diet at midlife—as modeled by a score whose design was based on a comprehensive review of the literature—was related to an increased probability to age healthily. Additional analyses in which each component of the score was considered in an isolated manner indicated that the overall association was particularly driven by the components "fruits," "vegetables," "alcohol," and "meat." The favorable role of fruits and vegetables could, among others, be related to the overall elevated content of antioxidant vitamins and minerals, polyphenols, and dietary fiber. These three dietary components have all been related to an increased probability of multidimensional HA in previous studies (14,17,18). However, the consideration of isolated food groups does not take synergic effects into account—which are thought to largely contribute to the overall positive role of adherence to specific dietary patterns such as the Mediterranean diet.

The fact that our sensitivity analyses revealed weaker results when using the MDS instead of the LAMD was probably related to the less refined manner of point attribution. Using the rMed (which is very similar to the MDS but uses a more graduated system of point attribution) yielded results that were largely similar to using the LAMD.

The supplemental analyses performed using structural equation modeling among a reduced study sample indicated a potential mediation of the relation between adherence to the Mediterranean diet and HA by a set of different biomarkers related to various metabolic disorders and adiposity (fasting serum levels of glucose, LDL, HDL, and triglycerides; systolic blood pressure; and waist-to-hip-ratio). Since these biomarkers were measured during a period that was situated between dietary data collection and collection of HA-data, the present study was well-equipped to examine the hypothesis that diet may first affect specific biomarkers/clinical factors and then, partly mediated by these biomarkers, have an impact on age-related diseases and functional decline. The fact that our structural equation model did not fully confirm our a priori concept of HA should, in our view, not be overstated. While this type of complex statistical modeling provides highly interesting insights into the complex interrelations between different sets of variables, latent factors obtained by empirical modeling are strongly dependent on the respective study sample—and thus of more exploratory nature.

Comparison With the Literature

To our knowledge, only one study has investigated the association between adherence to the Mediterranean diet and a multidimensional concept of HA. In that analysis based on the Nurses' Health Study (NHS) (4), HA was defined as survival to ≥70 years, combined with the absence of major chronic disease and of major impairments in cognitive, physical, and mental functioning. The proportion of HA (11%) was much lower than in our study (38%), resulting from a higher mean age of the NHS participants and the use of a different HA definition. Adherence to Mediterranean diet was assessed by the Alternate Mediterranean Diet Score (A-MeDi), which includes seven beneficial components (fruits, vegetables, whole grain, nuts, legumes, fish, and ratio of mono-unsaturated fatty acids to saturated fatty acids), one detrimental component (red and processed meat)), and one "alcohol" component. Being in the 5th quintile of the A-MeDi was associated with 46% higher odds of HA (as compared to being in the 1st quintile).

Despite important methodological differences (population, HA definitions, and diet scores), our study's results clearly confirm the findings obtained in the NHS.

Further studies have investigated HA in relation to measures of the overall diet that tend to share important characteristics with the Mediterranean diet concept. First, two studies have found a prospective association between adherence to national dietary guidelines (more specifically the French (19) and Australian guidelines (20), which promote the consumption of various key components of the Mediterranean diet, such as fruits and vegetables, whole grains, and fish) and HA. Second, two prospective studies have identified an inverse association between a posteriori dietary patterns characterized by a high consumption of meat and fatty foods and HA (21,22). One of these studies has additionally found a positive relation between an a posteriori dietary pattern characterized by a high fruit intake and HA (22). Finally, in an investigation of data from the SU.VI.MAX study, the probability to age healthily was increased among participants who presented both a relatively low energy intakes and high adherence to an a posteriori dietary pattern characterized by a high consumption of key beneficial components of the Mediterranean diet: vegetables, vegetable fat, fruit, whole grains, and fish (23).

The randomized primary prevention trial PREDIMED (24) has found that a Mediterranean-style diet supplemented with extra-virgin olive oil was related to a decreased risk of cardiovascular events and diabetes. Moreover, a favorable impact on biomarkers such as blood pressure, insulin sensitivity, and lipid profiles was observed. This is particularly in agreement with our findings concerning a potential mediating effect of specific biomarkers related to metabolic disorders concerning the association of the Mediterranean diet with HA.

Limitations and Strengths

Our investigation has several limitations. First, no measure of HA status was available at baseline. However, participants were only aged 45–60 years at baseline and free of major chronic disease, thus strengthening our working hypothesis that individuals were initially healthy. Second, our study is prone to self-selection bias.

For instance, individuals with a particularly poor overall diet or health may be underrepresented. Although potential selection bias was addressed by inverse probability weighting, this might have been insufficient to fully counterbalance to differences between excluded and included individuals. Important strengths of our study include the longitudinal study design, the availability of a large set of precise and validated health indicators, and the use of accurate nutritional data, since, on average, 10 dietary records per subject were available.

Conclusion

Our results suggest a favorable role of a high adherence to the Mediterranean diet at midlife for maintaining good overall health during aging. This long-term association may be mediated by clinical indicators related to metabolic disorders. Further studies are needed to confirm these findings.

Supplementary Material

Supplementary data is available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

Funding

The SU.VI.MAX 2 study was funded by the French National Research Agency (n°ANR-05-PNRA-010), the French Ministry of Health, as well as Médéric and MGEN (French health insurance organizations), and Ipsen and Pierre Fabre (pharmaceutical companies). Sodexo, a food catering company, helped organize meetings between researchers and study participants. K.E.A. and M.A. were supported by doctoral fellowships from the University of Paris 13. The funding bodies did not have any involvement in the design/conduct of the research, in data analysis/interpretation, or in writing/approval of the manuscript.

Acknowledgments

The authors thank Younes Esseddik, Paul Flanzy, Yasmina Chelghoum, Than Duong Van, Nathalie Arnault, Véronique Gourlet, Fabien Szabo, Laurent Bourhis, and Stephen Besseau for their technical contribution to the SU.VI.MAX study. The authors also thank Stéphane Raffard and Frédérique Ferrat for their contribution to the SU.VI.MAX 2 neuropsychological evaluation.

Conflict of Interest

None of the authors declare any conflict of interest.

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