8-19-2019

Adherence to a Mediterranean diet is associated with cognitive function in an older non- Mediterranean sample: findings from the Maine- Syracuse Longitudinal Study

Alexandra T. Wade

Merril F. Elias

Karen J. Murphy

Adherence to a Mediterranean diet is associated with cognitive function in an older non-Mediterranean sample: findings from the Maine-Syracuse Longitudinal Study

Alexandra T. Wade, Merrill F. Elias & Karen J. Murphy

KEYWORDS: Mediterranean diet, cognitive function, ageing, nutrition, cross-sectional, longitudinal, U.S., adults, risk-reduction

ABSTRACT

Background: Adherence to a Mediterranean diet is associated with higher cognitive function and reduced risk of dementia in Mediterranean populations. However, few studies have investigated the association between Mediterranean diet adherence and cognition in populations outside of the Mediterranean basin. Furthermore, it is currently unknown whether the association between Mediterranean diet adherence and cognitive function differs between middle-aged and older individuals.

Methods: Cross-sectional (n = 894) and longitudinal (n = 530) multivariable analyses were undertaken using data from community-dwelling adults from the Maine-Syracuse Longitudinal Study (MSLS). Mediterranean diet adherence was measured by applying a literature-based Mediterranean diet score to food frequency questionnaire data. Cognitive function was assessed with a battery of tests and composites scores were computed for global cognitive function, Visual-Spatial Organization and Memory, verbal memory, working memory, scanning, and tracking and abstract reasoning.

Results: No cross-sectional associations between Mediterranean diet adherence and cognitive function were detected. Over a period of five years, higher adherence to a Mediterranean diet was associated with improvements in Global Cognitive Function, Visual-Spatial Organization and Memory and scanning and tracking in participants ≥70 years. No significant longitudinal associations were observed for participants <70 years.

Conclusion: Our findings suggest that higher adherence to a Mediterranean diet is associated with better cognitive performance, and therefore less cognitive decline, in older but not middle-aged individuals.

Introduction

Dementia is one of the leading causes of death and disability worldwide [1,2]. Due to population ageing, the global prevalence of dementia is predicted to double every 20 years, with rates increasing from 47 million in 2015 to over 130 million by 2050 [3]. In the absence of a cure, preventative measures and interventions are imperative to reducing the risk and impact of dementia worldwide.

Historically, Mediterranean countries have experienced lower rates of dementia mortality when compared to Western countries like the United States [4]. It has been proposed that the positive health outcomes observed in Mediterranean populations are due to lifestyle factors and, in particular, the benefits of the Mediterranean diet [5].

The Mediterranean diet is characterized by the high consumption of extra virgin olive oil, vegetables, fruits, legumes, cereals, nuts and seeds; moderate consumption of fish, dairy, eggs and red wine; and low consumption of red meat and processed foods [6]. The key ingredients of the Mediterranean diet

contain a range of bioactive nutrients which may be beneficial to cognitive health. For example, monounsaturated fatty acids found in EVOO, and polyunsaturated fatty acids found in nuts and fish, have anti-inflammatory effects which could improve cerebral blood vessel functioning [7,8]. Furthermore, omega-3 fatty acids are a vital component of neural cell membranes but are unable to be synthesized by the body [9]. Dietary intake of omega-3s is therefore crucial to maintain neuronal cell structure and integrity.

Observational studies conducted in Mediterranean populations indicate that adherence to a Mediterranean diet is associated with improved cognitive function and reduced risk of dementia and Alzheimer's disease [10–13]. The cognitive benefits of the Mediterranean diet have been further supported by the PREDIMED study, a large-scale randomized intervention trial conducted in Spain [14,15]. After a median follow-up of 4.1 years, a Mediterranean diet supplemented with extra virgin olive oil or nuts led to higher scores in tests of cognitive function and reduced cognitive decline compared to a low-fat control diet [15].

Relatively few studies have examined the relationship between adherence to a Mediterranean diet and cognitive function in non-Mediterranean countries, and findings have been inconsistent. In a cohort of older adults from the Nurses' Health Study, Mediterranean diet adherence was cross-sectionally associated with global cognitive status, but not with longitudinal cognitive decline [11]. In contrast, Mediterranean diet adherence was not associated with cognitive status or trajectories of cognitive change in the Women's Health Study [11,16]. However, investigators from the Washington Heights Inwood and Columbia Aging Project (WHICAP) reported that higher adherence to a Mediterranean diet was associated with a lower risk of developing mild cognitive impairment and Alzheimer's disease [17,18].

Inconsistencies across studies may be due to the method of measuring Mediterranean diet adherence. Traditional Mediterranean diet adherence scores, as used in the WHS and the NHS, are based on the median consumption of the study sample [19]. However, the median intake of Mediterranean dietary components is likely lower in non-Mediterranean populations. Therefore, the median cut-off score in a US sample is not likely to reflect true adherence to the Mediterranean diet. Alternate scoring systems based on predetermined intake ranges, such as that proposed by Sofi et al. (2013), may be more appropriate [20].

The Mediterranean diet may be a suitable lifestyle intervention for reducing dementia risk. However, it is unclear whether the association between Mediterranean diet adherence and cognitive function persists in populations outside of the Mediterranean basin. Accordingly, the current study aimed to examine the relationship between adherence to a Mediterranean diet and cognitive function over time using data collected from participants of the Maine-Syracuse Longitudinal Study (MSLS), living in Central New York, U.S.A.

In the current study, we also aimed to examine whether the association between Mediterranean diet adherence differs between middle-aged and older individuals. Cognitive functions including memory, executive function and processing speed follow a trajectory of decline over the life-span, with steeper declines and more pronounced impairment observed from the age of 65 [21]. The majority of literature concerning the Mediterranean diet and cognitive function has therefore focused on older adults [10,12,20,22]. Specifically, studies have observed significant associations between Mediterranean diet adherence and cognitive function in samples with a mean age ≥70 years [11,12,17]. While the

Mediterranean diet may have neuroprotective effects across all ages, detection of associations is likely difficult before cognitive decline begins [21]. Based on previous studies, we hypothesized that higher Mediterranean diet adherence would be associated with improvements in cognitive function in persons aged ≥70 years over a five-year period. Moreover, we hypothesized that Mediterranean diet adherence would not be associated with change in cognitive function in persons aged <70 years.

Methods

Participants

This investigation and the MSLS study were approved by the University of Maine Institutional Review Board. Written informed consent was obtained from all participants.

The MSLS was a multi-wave longitudinal cohort study of cardiovascular and cognitive function. Data were collected from community-dwelling adults living in Central New York every five years from 1975 (Wave 1) to 2010 (Wave 7). Data from the current investigation were drawn from Wave 6 (2001–2006) and Wave 7 (2006–2010) of the MSLS, as Wave 6 marked the beginning of collection of data on nutrition.

Participants with complete nutrition, health and cognitive data at Wave 6 and Wave 7 were included in the current study. Exclusion criteria included: missing data for nutrition or health variables (n = 134), acute stroke (n = 28), probable dementia (n = 8), renal dialysis treatment (n = 5), inability to read English (n = 1), and prior alcohol abuse (n = 1). Stroke was defined as an acute onset focal neurological deficit persisting for more than 24 h and was based on self-report confirmed by hospitalization, medical records confirmed by record review, or both. Clinical diagnoses of dementia were determined from cognitive data, medical records, and data on activities of daily living. As in the Framingham Dementia Study, dementia was assessed according to National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [23], and confirmed using the more recent International Classification of Diseases (ICD-10) guidelines [24]. On the basis of these data and criteria, a dementia review was conducted by a neuropsychologist and social psychologist, and confirmed by a geriatric physician with extensive experience in dementia studies.

Complete data were available for 872 participants at Wave 6 (cross-sectional analysis). Of these, 807 were invited to return at Wave 7 (longitudinal analysis) and 530 completed testing. Sixty-five participants were not invited back to Wave 7 due to a driving distance more than 100 miles one-way between the laboratory and home.

Procedure

Assessment of dietary intake and Mediterranean diet adherence

Dietary intake data were collected at Wave 6 using the Nutrition and Health Questionnaire (NHQ). The NHQ asks participants to indicate how frequently they consume particular foods, including fruit, vegetables, meat, fish, eggs, breads, cereals, rice and pasta, legumes, dairy foods, nuts, other snack-type foods, and beverages including alcohol. For each food participants answered whether their habitual consumption was never, seldom, once per week, 2–4 times per week, 5–6 times per week and once or more per day. Average weekly and daily food intakes were estimated by converting response options to the median score. For example, 2–4 times per week was estimated as 3 times per week.

To address the challenge of measuring Mediterranean diet adherence in a non-Mediterranean population, the current study employed a Mediterranean diet adherence score with predetermined cut-offs for each Mediterranean food group based on empirical evidence and traditional Mediterranean dietary guidelines [20]. The adherence score developed by Sofi et al. (2013) allocates a score of 0, 1 or 2 for 9 food categories associated with the Mediterranean diet: (1) Fruit, (2) Vegetables, (3) Legumes, (4) Cereals, (5) Fish, (6) Meat and meat products, (7) Dairy products, (8) Red wine, and (9) Olive oil. For food categories associated with positive health outcomes (fruit, vegetables, legumes, cereals, fish and olive oil) higher intake is awarded a higher score. For foods which are typically low on the Mediterranean diet (meat and meat products and dairy) higher intake is awarded a lower score. For red wine less than one serving per day is awarded a score of 1, between 1 and 2 serves per day is awarded a score of 2 and more than 2 servings per day is awarded a score of 0. The adherence score ranges from 0 to 18, with a high total score indicative of higher adherence, and a low total score indicative of lower adherence. Intake ranges for each category in the Mediterranean diet adherence score are provided in Supplemental Table 1.

Assessment of cognitive function

The MSLS neuropsychological test battery has been described in detail previously [25]. In brief, subtests from the Weschler Adult Intelligence Scale and the Halstead-Reitan Neuropsychological Test Battery were administered to participants at Wave 6 and Wave 7 of the MSLS. Cognitive domains were identified through factor analysis. Raw scores from each subtest were converted to Z scores and combined into the following cognitive domain composite scores: Visual Spatial Organization and Memory, Verbal Episodic Memory, Scanning and Tracking, Working Memory and Abstract Reasoning. A Global Composite Score was calculated to reflect cognitive function across all cognitive domains. The tests and subtests comprising each cognitive domain are presented in Table 1.

Design and statistical analysis

Data were analyzed using IBM SPSS Statistics (Version 24, Chicago, IL, U.S.A.). Based on the findings of previous Mediterranean diet studies, participants were stratified into two age groups: ≥70 years and <70 years [11,12,17]. Multivariable linear regression analyses (described below) were performed within these groups following preliminary analyses.

Preliminary analysis

Independent-samples t-tests were used to compare differences between participants >70 years and ≤70 years for continuous variables. Chi-square tests of independence were used to detect differences between groups for dichotomous variables. Independent t-tests and chisquare tests of independence were also conducted to compare characteristics of individuals who returned at Wave 7 with those who did not. Outliers were inspected for coding errors across demographic, cognitive and dietary variables. None were found and thus no participants were removed from the sample.

Primary analysis

As categorization of Mediterranean diet adherence into groups may ignore variance of scores within groups and misrepresent associations, the continuous distribution of Mediterranean diet adherence scores was used as the predictor variable. Multivariable linear regressions were then performed to examine the association between Mediterranean diet adherence scores and cognitive function for each

age group. Initial inspection of the data revealed both linear and quadratic trends. Linear and quadratic trend analyses were therefore performed, with each controlled statistically for the other.

Covariates were employed to statistically adjust for demographic, cardiovascular and lifestyle factors likely to influence cognitive function. Covariates were based on previous MSLS analyses [26,27] and cognitive Mediterranean diet investigations [11,18] and were included in the model if they were significantly correlated with both the predictor and outcome variable. Covariates were organized into two models:

(1) Basic model: age, gender and education, ethnicity (African American/Non-African American) and

(2) Extended model: Basic model + systolic blood pressure (mmHg), total cholesterol (mg/dL), physical activity (MET hours per week), smoking (yes/no), total serves of food per day

For longitudinal analyses of cognitive function, the corresponding baseline score from Wave 6 was included in each model. This allowed adjustment for baseline cognitive performance, to obtain the predictive value of Mediterranean diet adherence on cognitive change between Wave 6 and Wave 7. This is a widely used alternative to repeated measures analysis and has been described previously by Hand et al. (1987) [28,29]. A positive slope indicates increasing cognitive function over time, controlling for prior cognitive performance. A two-tailed alpha of $p < .05$ was considered statistically significant.

Results

Demographic, lifestyle and health characteristics stratified by age group are reported in Table 2. Across the whole sample, Mediterranean diet adherence scores ranged from 3 to 16 out of 18. Older participants reported significantly higher adherence to the Mediterranean diet and consumed more energy each day. Furthermore, older adults had significantly higher mean systolic blood pressure and BMI, were more likely to have cardiovascular disease but were less likely to smoke than middle aged adults. No other significant differences were detected between groups.

Cross-sectional analysis

A total of 894 participants had complete diet and cognition data at Wave 6. As reported in Supplemental Table 2 (a–c), no significant cross-sectional associations were observed between Mediterranean diet adherence and domains of cognitive function for participants within the two age groups, or for the overall sample.

Longitudinal analysis

Tables 3 and 4 present linear and quadratic trend components for the longitudinal associations between Mediterranean diet adherence and cognitive function for participants ≥70 years and <70 years respectively.

Statistically significant linear and quadratic trends were observed between Mediterranean diet adherence score and Global Composite Score (linear: b = 0.26, 95% CI 0.07–0.45, p = .01), Visual-Spatial Organization and Memory (linear: b = 0.28, 95% CI 0.04–0.53, p = .02), and Scanning and Tracking (linear: b = 0.23, 95% CI 0.03–0.44, p = .02), for participants ≥70 years. No significant associations were observed for participants <70 years. Figures 1–3 illustrate the nature of the linear and quadratic trends observed as scatterplots relating Mediterranean diet adherence scores to standardized regression coefficients of

Global Cognitive Function, Visual-Spatial Organization and Memory, and Scanning and Tracking respectively in participants ≥70 years. All scores are adjusted for covariates in Model 2.

Attrition analysis

Differences between participants who returned (n = 530) and did not return (n = 277; excluding those not invited back) are presented in Table 5. Returners had significantly lower systolic and diastolic blood pressure were less likely to have cardiovascular disease and had significantly higher performance across all cognitive outcomes at Wave 6. The same finding was observed when those who were not invited back were counted as non-responders at Wave 7.

To examine the effect of attrition on findings, cross-sectional analyses were repeated for participants who returned at Wave 7 only. As in the primary analysis, no cross-sectional associations were detected for the two age groups or for the whole sample (n = 530).

Discussion

We examined the cross-sectional and longitudinal associations between Mediterranean diet adherence and cognitive function over different age groups in a sample of participants from Central New York, U.S.A. Multivariable linear regression analysis did not detect cross-sectional associations between Mediterranean diet adherence and cognitive function controlling for demographic, lifestyle, and cardiovascular risk factors. However, longitudinal analyses revealed significant curvilinear associations between Mediterranean diet adherence and Global Cognitive Function, Visual-Spatial Organization and Memory, and Scanning and Tracking for study participants ≥70 years. No longitudinal associations were found for participants <70 years of age.

The curvilinear longitudinal association is of particular interest. Our findings demonstrate that lower adherence to the Mediterranean diet is associated with greater cognitive decline over a period of five years in older adults. In comparison, moderate to higher adherence is associated with better performance and therefore less decline. However, a slight declining trend was observed between moderate and higher levels of adherence. Similar curvilinear associations have been reported in previous studies, suggesting that higher adherence to a

Mediterranean diet may not be as beneficial as moderate adherence [10,11]. It is possible that this effect is the result of consuming elements of both a Mediterranean diet and a Western diet concurrently. Due to the limitations of most Mediterranean diet adherence scores, not all dietary intake is captured. For example, processed foods high in sugar and saturated fat are neither included in the median-based adherence score developed by Trichopoulou et al., nor in the literature-based score developed by Sofi et al. Therefore, some participants may have been consuming high levels of saturated fat or refined foods in addition to foods typical of a Mediterranean diet. Notably, diets high in saturated fat and refined sugars have been associated with increased levels of inflammation in the brain [30], as well as reductions in brain function [31]. Alternatively, the curvilinear association may be related to the length of time individuals followed the diet. For example, participants may have changed their eating habits between Wave 6 and Wave 7. Unfortunately, based on the data collected, the length of dietary adherence is unknown. It is also possible that the limited sample size of the current study influenced the relationship. Mediterranean diet adherence scores did not exceed 15 out of a possible 18 points in participants ≥70 years. Furthermore, only 10 of the 139 participants aged 70 years and older achieved a score above 13.

Our significant linear findings support the notion of a neuroprotective effect of the Mediterranean diet in older individuals [32,33]. Previous studies have shown that the Mediterranean diet adherence is associated with improvements in cardiovascular risk factors that have been related to cognitive decline [34–36]. Furthermore, bioactive components of the diet, such as omega-3 fatty acids, may have direct effects on neuronal synthesis and repair [37]. These mechanisms may facilitate cognitive function and attenuate decline. However, the association between Mediterranean diet adherence and cognitive function may not become evident until individuals reach older age and changes associated with cognitive decline begin.

Our study also adds to the literature with respect to the cognitive domains associated with improvement over time as a function of the Mediterranean diet. In the current study, the Global Cognitive Function score was a composite of performance across all cognitive domains. The significant positive association detected for Global Cognitive Function is therefore reflective of trends observed across Visual-Spatial Organization, Verbal Memory, Working Memory and Scanning and Tracking. Significant associations were found between Mediterranean diet adherence and Visual Memory and Organization, and Scanning and Tracking. Associations for Verbal and Working Memory followed the same linear and quadratics trend but did not reach statistical significance. Both Visual Memory and Organization and Scanning and Tracking contain measures of executive function, also known as fluid cognitive ability or novel problem-solving. Our results therefore suggest that executive functioning is positively influenced by Mediterranean diet adherence. Notably, executive function tasks are among the most difficult in the test battery. Furthermore, these domains are more vulnerable to the effects of ageing [38–40] compared with tests of verbal knowledge included in Abstract Reasoning [41].

Our study did not find evidence of a cross-sectional association between Mediterranean diet adherence and cognitive function. This contradicts previous research conducted in Mediterranean populations [12,42] and suggests that, at Wave 6, participants may not have been exposed to the Mediterranean diet for a sufficient period of time to shown beneficial effects. However, our longitudinal analyses show that higher Mediterranean diet adherence at baseline may be capable of influencing cognitive function over time.

It is important to note that the current study was conducted in a U.S. sample. To date, the majority of Mediterranean diet investigations have been conducted in populations surrounding the Mediterranean basin [10,12,43]. Relatively few studies have assessed the association between Mediterranean diet adherence and cognitive function in non-Mediterranean populations. Furthermore, the studies that have been conducted yield mixed results [11,16,44]. Inconsistent findings among previous studies may be a function of cognitive testing methodologies. For example, the NHS and WHS employed MMSE as a test of global cognitive function [16]. The MMSE has a low ceiling and is appropriate for detecting cognitive deficits leading to the examination of possible dementia. However, it is not a sensitive test of cognitive function in relatively well-performing individuals. In contrast, the current study employed a battery of cognitive assessments with demonstrated sensitivity to capturing changes across more than one cognitive domain.

Another possible explanation for inconsistencies across studies in non-Mediterranean populations is the classification of Mediterranean diet adherence. To more accurately assess adherence, the current study utilized a literature-based score with predetermined ranges of consumption that reflect traditional intake of each Mediterranean diet components [20].

Limitations

The findings of the current study should be interpreted taking into account the following limitations. Firstly, our method of dietary data collection through food frequencies questionnaires relies on accuracy and honesty of participant responses. Furthermore, in questions regarding food quantity, participants were asked 'how often' foods were eaten, but not 'how much' of each food was consumed. As portion and serving sizes are likely to vary between individuals, this limits the accuracy of estimate intakes and final Mediterranean diet score. Secondly, dietary data was only collected at Wave 6. We were therefore unable to assess or adjust for any change in diet between the two cognitive testing time points. Thirdly, the NHQ did not allow us to determine how long participants had been exposed to the Mediterranean diet at Wave 6. Finally, our sample was limited with regard to size and diversity. With very few participants achieving high adherence to the Mediterranean diet outliers were more likely to influence our longitudinal results. Furthermore, limited diversity in demographic characteristics like education, and health characteristics such as blood pressure, cholesterol and BMI, suggest that our sample may not be representative of the general population, limiting generalizability. Moreover, due to the associations between Mediterranean diet adherence, cardiovascular health and cognitive function, our sample may have been less likely to demonstrate change compared to one with greater variance in cardiovascular health.

Strengths

On the other hand, the study has a number of strengths. The current study is one of the first to apply a true Mediterranean diet adherence score to a non-Mediterranean population. Our analyses employed a longitudinal design and found evidence of cognitive change over time associated with Mediterranean diet adherence. Furthermore, we examined Mediterranean diet adherence as a continuous variable, which enabled detection of both linear and quadratic trends. We compared associations for older and middle-aged cohorts, finding that benefits may not be observed until age-related cognitive decline begins. Finally, we controlled for cardiovascular risk factors with the potential to confound associations between Mediterranean diet adherence and cognitive function.

Conclusions

We report significant longitudinal associations between Mediterranean diet adherence and cognitive functions in adults aged ≥70 years. Furthermore, we detected evidence of both linear and quadratic trends for Global Cognitive Function as well as measures of executive function, indicating less cognitive decline in older individuals who achieve moderate adherence to the Mediterranean diet. Our findings lead us to conclude that the Mediterranean diet may be beneficial to older non-Mediterranean populations. This research is specifically relevant to non-Mediterranean populations like the United States and Australia, who do not typically follow a Mediterranean diet. Larger observational studies are now needed to replicate these findings.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

The Maine-Syracuse Longitudinal Study was supported by grants R01HL067358, and R01HL081290 from the National Heart, Lung and Blood Institute, National Institutes of Health (U.S.A.), and research grant R01AG03055 from the National Institute on Aging, National Institutes of Health (U.S.A.). A.T.W. is supported by an Australian Government Research Training Program Scholarship. The funding sources had no involvement in the study design, data collection, writing or decision to submit for publication.

References

[1] Alzheimer's Disease International. World Alzheimer report 2015 the global impact of dementia. London; 2015.

[2] Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. Lancet. 2017;390(10113):2673–2734.

[3] Alzheimer's Association. Changing the trajectory of Alzheimer's disease: how a treatment by 2025 saves lives and dollars. New York: Alzheimer's Association; 2015. p. 16–16.

[4] Alonso A, Jacobs DR, Menotti A, Nissinen A, Dontas A, Kafatos A, et al. Cardiovascular risk factors and dementia mortality: 40 years of follow-up in the seven countries study. J Neurological Sci. 2009;280(1–2):79–83.

[5] Trichopoulou A, Vasilopoulou E, Georga K, Soukara S, Dilis V. Traditional foods: Why and how to sustain them. Trends Food Sci Technol. 2006;17(9):498–504.

[6] Davis CR, Bryan J, Hodgson J, Murphy K. Definition of the Mediterranean diet: a literature review. Nutrients. 2015;7(11):9139–9153.

[7] Calder PC. Omega-3 fatty acids and inflammatory processes. Nutrients. 2010;2(3):355–74.

[8] Creegan R, Hunt W, McManus A, Rainey-Smith SR. Diet, nutrients and metabolism: cogs in the wheel driving Alzheimer's disease pathology? Br J Nutr. 2015;113 (10):1499–1517.

[9] Crawford MA, Bloom M, Broadhurst CL, Schmidt WF, Cunnane SC, Galli C, et al. Evidence for the unique function of docosahexaenoic acid (DHA) during the evolution of the modern hominid brain. Lipids. 1999;34(3):39–47.

[10] Féart C. Adherence to a Mediterranean diet, cognitive decline, and risk of dementia. JAMA. 2009;302(6):638–648.

[11] Samieri C, Okereke OI, E. Devore E, Grodstein F. Longterm adherence to the Mediterranean diet is associated with overall cognitive status, but not cognitive decline, in women. J Nutr. 2013;143(4):493–499.

[12] Anastasiou CA, Yannakoulia M, Kosmidis MH, Dardiotis E, Hadjigeorgiou GM, Sakka P, et al. Mediterranean diet and cognitive health: initial results from the Hellenic longitudinal investigation of ageing and diet. Plos One. 2017;12(8):e0182048.

[13] Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. BMJ. 2008;337:1344–1344.

[14] Martinez-Lapiscina EH, Clavero P, Toledo E, Estruch R, Salas-Salvadó J, San Julián B, et al. Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial. Journal of Neurology. Neurosurg Psychiatry. 2013;84(12):1318–1325.

[15] Valls-Pedret C, Sala-Vila A, Serra-Mir M, Corella D, de la Torre R, Martínez-González MÁ, et al. Mediterranean diet and Age-related cognitive decline: a randomized clinical trial. JAMA. 2015;175(7):1094–103.

[16] Samieri C, Grodstein F, Rosner BA, Kang JH, Cook NR, Manson JE, et al. Mediterranean diet and cognitive function in older age: results from the women's health study. Epidemiology. 2013;24(4):490–499.

[17] Scarmeas N, et al. Mediterranean diet and mild cognitive impairment. Arch Neurol Psychiatry. 2009;66(2):216-225.

[18] Scarmeas N, Stern Y, Tang M-X, Mayeux R, Luchsinger JA. Mediterranean diet and risk for Alzheimer's disease. Ann Neurol. 2011;59(6):912–921.

[19] Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. The New England J Med. 2003;348(26):2599–2608.

[20] Sofi F, Macchi C, Abbate R, Gensini GF, Casini A. Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score. Public Health Nutr. 2014;17(12):2769–2782.

[21] Zaninotto P, Batty GD, Allerhand M, Deary IJ. Cognitive function trajectories and their determinants in older people: 8 years of follow-up in the English longitudinal study of ageing. J Epidemiol Community Health. 2018;72(8):685–694.

[22] Feart C, Samieri C, Barberger-Gateau P. Mediterranean diet and cognitive function in older adults. Curr Opin Clin Nutr Metab Care. 2010;13(1):14–8.

[23] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dementia. 2011;7(3):263–9.

[24] World Health Organization. The ICD 10 classification of mental and behavioral disorders: clinical descriptions and diagnostic guidelines. Geneva: World Health Organization; 1992.

[25] Elias MF, Robbins MA, Budge MM, Elias PK, Brennan SL, Johnston C, et al. Homocysteine, folate, and vitamins B6 and B12 blood levels in relation to cognitive performance: the Maine-Syracuse study. Psychosomatic Med. 2006;68(4):547–54.

[26] Crichton GE, Bryan J, Murphy KJ, Buckley J. Review of dairy consumption and cognitive performance in adults: findings and methodological issues. Dementia Geriatric Cognitive Disorders. 2010;30:352–361.

[27] Crichton GE, Elias MF, Alkerwi A. Chocolate intake is associated with better cognitive function: the Maine-Syracuse longitudinal study. Appetite. 2016;100:126–132.

[28] Dearborn PJ, Elias MF, Sullivan KJ, Sullivan CE, Robbins MA. Poorer visual acuity is associated with declines in cognitive performance across multiple cognitive domains: the Maine-Syracuse longitudinal study. J Int Neuropsychological Soc. 2018;24(07):746–754.

[29] Hand DJ, Taylor CC. Multivariate analysis of variance and repeated measures: a practical approach for behavioural scientists. London: Chapman and Hall; 1987.

[30] Dumas JA, Bunn JY, Nickerson J, Crain KI, Ebenstein DB, Tarleton EK, et al. Dietary saturated fat and monounsaturated fat have reversible effects on brain function and the secretion of pro-inflammatory cytokines in young women. Metabolism. 2016;65(10):1582–8.

[31] Munoz-Garcia MI, Martínez-González MA, Martín-Moreno JM, Razquin C, Cervantes S, Guillén-Grima F, Toledo E. Sugar-sweetened and artificially-sweetened beverages and changes in cognitive function in the SUN project. Nutr Neurosci. 2019: 1–9. doi:10.1080/1028415X.2019.1580919

[32] McEvoy CT, Guyer H, Langa KM, Yaffe K. Neuroprotective diets are associated with better cognitive function: the health and retirement study. J Am Geriatrics Soc. 2017;65(8):1857–1862.

[33] Pelletier A, Barul C, Féart C, Helmer C, Bernard C, Periot O, et al. Mediterranean diet and preserved brain structural connectivity in older subjects. Alzheimer's Dementia. 2015;11(9):1023–1031.

[34] Martínez-González MA, Salas-Salvadó J, Estruch R, Corella D, Fitó M, Ros E. Benefits of the Mediterranean diet: insights from the PREDIMED study. Prog Cardiovasc Diseases. 2015;58(1):50–60.

[35] Davis CR, et al. A Mediterranean diet lowers blood pressure and improves endothelial function: results from the MedLey randomized intervention trial. Am J Clin Nutr. 2017;105(6):1305–1313.

[36] Knight A, Bryan J, Murphy K. Is the Mediterranean diet a feasible approach to preserving cognitive function and reducing risk of dementia for older adults in Western countries? New insights and future directions. Ageing Res Rev. 2016;25:85–101.

[37] Dyall SC. Long-chain omega-3 fatty acids and the brain: a review of the independent and shared effects of EPA, DPA and DHA. Front Aging Neurosci. 2015;7:52.

[38] Piefke M, Onur ÖA, Fink GR. Aging-related changes of neural mechanisms underlying visual-spatial working memory. Neurobiol Aging. 2012;33(7):1284–1297.

[39] Salthouse TA. When does age-related cognitive decline begin? Neurobiol Aging. 2009;30(4):507–514.

[40] Salthouse TA.What cognitive abilities are involved in trailmaking performance? Intelligence. 2011;39(4):222–232.

[41] Miller LJ, Myers A, Prinzi L, Mittenberg W. Changes in intellectual functioning associated with normal aging. Arch Clin Neuropsychol. 2009;24(7):681–8.

[42] Valls-Pedret C, Lamuela-Raventós RM, Medina-Remón A, Quintana M, Corella D, Pintó X, et al. Polyphenolrich foods in the Mediterranean diet are associated with better cognitive function in elderly subjects at high cardiovascular risk. J Alzheimer's Dis. 2012;29:773–782.

[43] Trichopoulou A, Kyrozis A, Rossi M, Katsoulis M, Trichopoulos D, La Vecchia C, Lagiou P. Mediterranean diet and cognitive decline over time in an elderly Mediterranean population. Eur JNutr. 2015;54(8):1311–21.

[44] Koyama A, Houston DK, Simonsick EM, Lee JS, Ayonayon HN, Shahar DR, et al. Association between the Mediterranean diet and cognitive decline in a Biracial population. J Gerontology Ser A Biol Sci Med Sci. 2015;70(3):354–359.