Mediterranean Diet and Age-Related Cognitive Decline.

Olga Goda
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Abstract

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Methods: An exhaustive search of online medical literature was performed using MEDLINE-PubMed, Web of Science, and CINAHL-EBSCO. Keywords used included: Mediterranean Diet, cognition, cognitive function decline, and older adult population. Articles that assessed cognitive function through RCTs in an aging population on the Mediterranean diet were selected. The quality of relevant articles was evaluated using the GRADE guidelines.

Results: Nine articles were reviewed for relevancy and 3 studies that were RCTs and met eligibility criteria were chosen for analysis. The first study was done on a group of an older Mediterranean population with cardiovascular (CV) risk factors. It was not originally designed to do a cognitive function assessment, which was done at the end using two screening tests. The second study was a post hoc analysis of the first study and used a comprehensive battery of neurophysiological tests to analyze cognitive function. Both of the above studies found that a long-term adherence to the Mediterranean diet was associated with an improved cognitive function. The third study was done on a healthy Australian population staying on the MedDiet for a short period of time. No significant statistical differences in cognitive functioning were detected in healthy older adults. The overall quality of the studies is low to moderate based on Grade guidelines.

Conclusion: Studies investigating the MedDiet as a prevention of cognitive decline due to aging fail to provide strong evidence of its beneficial effect. Further research with larger study samples and longer periods of time is necessary to produce a better quality of evidence regarding a benefit of MedDiet in an aging population.

Keywords: Mediterranean diet, cognition, cognitive function decline, older adult population.

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Mediterranean Diet and Age-Related Cognitive Decline

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Biography

Olga Goda was born and raised in Ukraine where she studied biology and medical science. While living in Japan, she was involved in a biomedical research project with a focus on a neuro-stem cells application as a therapeutic modality for neurodegenerative disorders. Her experience working in a field of alternative medicine sparked her interest in using nutrition as a complimentary approach in prevention of age-related changes of cognitive function.
Abstract

Background: Some published studies reported beneficial effects of the Mediterranean Diet (MedDiet) on cognitive function in an aging population. But evidence from a limited number of randomized controlled trials (RCTs) is scarce and inconsistent. It is not clear whether a MedDiet offers benefits in maintaining cognitive function or in preventing cognitive decline in the older adult.

Methods: An exhaustive search of online medical literature was performed using MEDLINE-PubMed, Web of Science, and CINAHL-EBSCO. Keywords used included: Mediterranean Diet, cognition, cognitive function decline, and older adult population. Articles that assessed cognitive function through RCTs in an aging population on the Mediterranean diet were selected. The quality of relevant articles was evaluated using the GRADE guidelines.

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Conclusion: Studies investigating the MedDiet as a prevention of cognitive decline due to aging fail to provide strong evidence of its beneficial effect. Further research with larger study samples and longer periods of time is necessary to produce a better quality of evidence regarding a benefit of MedDiet in an aging population.

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List of Abbreviations

ANOVA Analysis of Variance
ANCOVA Analysis of Covariance
AD Alzheimer Disease
BVRT Benton Visual Retention Test
CDT Clock Drawing Test
CI Confidence Interval
CVRFs Cardio-Vascular Risk Factors
CVDs Cardio-Vascular Diseases
DSF Digit Span Forward
ELF Excluded Letter Fluency
EVOO Extra-Virgin Olive Oil
GRADE Grading of Recommendations, Assessment, Development, and Evaluation
HabDiet Habitual diet
ILF Initial Letter Fluency
LNS Letter-Number Sequencing
MedDiet Mediterranean Diet
MCI Mild Cognitive Impairment
MMSE Mini-Mental State Examination
MUFA Monounsaturated Fats
RAVLT Rey Auditory Verbal Learning Test
RCT Randomized Controlled Trial
SD Standard Deviation
TOL Tower of London
WAIS-IV Wechsler Adult Intelligence Scale
WHO World Health Organization
Mediterranean Diet and Age-Related Cognitive Decline

BACKGROUND

According to the World Health Organization (WHO), at present, there are about 47 million people worldwide living with dementia, with 9.9 million new cases developing annually.¹ Dementia is a gradual, progressive disease that predominantly develops in older populations, although, it is not a part of a normal aging process.² It affects many aspects of an individual’s life including memory and thinking, judgment and behavior, the ability to learn, the use of language, and independent executive functioning. Initially, dementia is exhibited as forgetfulness and mild cognitive impairment (MCI), but eventually it leads to severe debilitation requiring continuous, around-the-clock assistance. Individuals afflicted by dementia become disoriented in time and place, not able to recognize their family members or carry on with daily activities. Dementia is a leading cause of disability among aging populations and it takes heavy physical, emotional, and financial tolls on individuals, their families, and a society.¹

Currently, there is no known effective treatment of dementia, and it is important to identify effective measures that can prevent cognitive decline or delay a progression of pathological processes leading to dementia. Numerous epidemiologic studies²⁻⁴ presented evidence that modifiable factors such as an active life style, weight reduction, smoking cessation, better education, and a healthy diet may play a role in delaying dementia by reducing vascular pathology and neurodegeneration. There is a considerable amount of evidence⁴⁻⁷ supporting a notion that dietary habits, particularly a Mediterranean Diet (MedDiet), can slow down age-related cognitive decline and possibly delay onset of dementia. In addition, numerous publications⁵,⁸⁻¹¹ present data that a MedDiet is associated with overall decrease in mortality, incidence of cardiovascular diseases (CVDs), neoplastic processes, diabetes, and obesity.
Health benefits of the Mediterranean Diet can probably be contributed to its components with high content of antioxidants and anti-inflammatory substances such as flavonoids, carotenoids, omega-3 and -6 polyunsaturated fatty acids, vitamins E and B.\textsuperscript{12,15} Specifically, extra virgin olive oil (EVOO) and mixed nuts are rich in phenolic compounds, monounsaturated fats (MUFA), and alpha-linolenic acid, all of which can counteract oxidative stress leading to neurodegeneration in the brain.\textsuperscript{15-18} Consumption of the MedDiet is associated with a beneficial effect to Alzheimer and Parkinson’s diseases.\textsuperscript{13,19} Reduced deposition of amyloid and Tau proteins was detected in the brains of patients after 9 years on a MedDiet.\textsuperscript{3} Also, according to Pelletier et al\textsuperscript{19} who conducted magnetic resonance imaging study on older individual, a MedDiet may preserve white matter microstructure and benefit brain connectivity. Another proposed mechanism of a beneficial effect of a MedDiet is a reduction of vascular pathology that is common in older age. Normal decline of cognitive function due to aging can be accelerated by a presence of cardiovascular risk factors (CVDFs), which are linked to an early onset of MCI and dementia.\textsuperscript{20,21}

Although, many epidemiologic population studies\textsuperscript{7,13} point to beneficial effects of the MedDiet on cognitive function, their results are inconsistent and heterogeneous in quality. As previously mentioned, some studies\textsuperscript{9,10,18,19} found a positive association between the MedDiet and cognitive function, yet others failed to demonstrate its beneficial effect.\textsuperscript{22,23} Specifically, neither the French Study\textsuperscript{22} on middle-age adults nor the Women’s Health study\textsuperscript{23} on healthy female professionals found association between a MedDiet and cognitive performance.

The goal of this systemic review is to clarify whether a Mediterranean diet has a beneficial effect on cognitive function based on data analysis of three randomized controlled trials (RCTs)\textsuperscript{15,25,26} available at this time.
METHODS

An exhaustive online search of medical literature was performed in May 2017 using MEDLINE-PubMed, Web of Science, and CINAHL-EBSCO databases. The keywords used during this search were Mediterranean Diet, cognition, cognitive function decline, and older adult population. The search criteria were narrowed to randomized control trials, articles published within past 5 years, studies on human subjects, and English language publications.

The articles that assessed cognitive functions in a group of older aging populations on the MedDiet were included. References of the included studies and other relevant articles were examined for further sources. Applicable articles were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) working group guidelines.24

RESULTS

The initial search of the medical literature using above-named keywords yielded 54 articles. After screening abstracts and titles for eligibility, a total of 3 articles that met inclusion criteria were chosen for a review.15,25,26 One of the included articles15 was located by using the name of the trial and the first author’s name that were obtained from the published protocol, which was present in the initial search result.27 The quality of evidence presented in the articles was evaluated using GRADE guidelines (see Table I), and a summary of the 3 studies and their difference can be seen in Table II.

All of the included articles were randomized control trials. Two of the 3 chosen studies25,26 examined an effect of the MedDiet supplemented with either olive oil or nuts in a group of Mediterranean aging population with increased risk of CV disease. The Valls-Pedret et al study26 was a post hoc study of the Martinez-Lapiscina et al study,25 which didn't have a
baseline measurement of cognitive function. The Valls-Pedret et al study\textsuperscript{26} performed cognitive functions measurements in a greater extent at the beginning and the end of the trial. Both of these long-term studies\textsuperscript{25,26} found a statistically significant difference in various aspects of cognitive function (see Table III and IV). The third study\textsuperscript{15} was done on an Australian aging population, which were physically and cognitively healthy. This study used an extensive battery of the neurophysiological tests for a cognitive functions assessment and found no evidence of cognition improvement in elderly healthy adults after 6 months of being on a MedDiet (See Table V).

**The PREDIMED-NAVARRA, Martínez-Lapiscina et al (2013)**

The PREDIMED parallel-group randomized controlled trial\textsuperscript{28} was originally designed to investigate the effects of a MedDiet on the prevention of cardiovascular disease (CVD) in comparison with a low-fat diet among an older Mediterranean population. The PREDIMED-NAVARRA study\textsuperscript{25} used a subsample from the PREDIMED trial\textsuperscript{28} to assess the effect of the MedDiet on cognitive functions after a mean 6.5 years of follow up. The primary outcome of this study was cognitive performance scores on two global screening tests for dementia, the Mini Mental State Examination (MMSE) and a Spanish version of the Clock Drawing Test (CDT).\textsuperscript{25}

All participants were screened and recruited by blinded general practitioners in the primary care practice setting. Study participants of a mean age of 74.6 ± 5.7 years were a community dwelling population at a high CV risk. High CV risk was due to the presence of type-2 diabetes or at least 3 of the following: smoking, hypertension, dyslipidemia, being overweight or obese, or a family history of an early onset of CVD. Patients were excluded if they had a prior history of illiteracy, severe chronic illness, CVD, or other conditions specified in a study protocol.\textsuperscript{28}
Study randomization was a computerized process that was performed after initial screening for eligibility. Computer-generated random-number sequence was used to assigned study participants, who where well balanced in their baseline characteristics, to one of the 3 groups. This study was single-blinded due to a nature of intervention; generally, it is not feasible to blind study participants to their assigned diet. All investigators, including medical personal and researchers were blinded to a group assignment.25

Study participants in 2 experimental groups, either Mediterranean Diet supplemented with Extra Virgin Olive Oil (MedDiet+EVOO) or Mediterranean Diet supplemented with Nuts (MedDiet+Nuts), received either 1 liter/week of EVOO or 30 g/day of mixed nuts (walnuts, almonds, hazelnuts). The control group was on a fat-reduced diet without energy restrictions or increased physical activity and received non-food gifts as compliance incentive. Participants were extensively educated regarding the diet during quarterly follow-up sessions and adherence to the diet was validated by annual questionnaires administered by a trained dietitian. A diet adherence was the lowest in the controlled group assigned to a low-fat diet.25

Initially, 1055 participants were recruited for the study, 86 of them died (8.2%) during the mean 6.5 years of follow up. Out of 969 participants who were alive, 522 (53%) participants agreed and underwent neurophysiological testing over a period of 8 months at the primary care centers. A total number of analyzed participants was 224 in the MedDiet+EVOO group, 166 in the MedDiet+Nuts group, and 132 in the low-fat diet control group. A number of participants required for each of 3 groups was determine to be 132, which allows to detect 1 Unit mean difference in MMSE between experimental groups and control with 90% power. Dropout rates for 3 groups were 46%, which include 36% in the MedDiet+EVOO group, 52.8%, in the
MedDiet+Nuts group and 62.5% in the Control Group on a low-fat diet. High dropout rates in this trial indicate a high risk of an attrition bias.

Statistical analyses were performed on an intention-to-treat principle and general linear models were used to make an adjustment for possible confounding factors including sex, age, education, dyslipidemia, diabetes, and body mass index, and physical activity among others. Quantitative data for experimental groups were reported as multivariable-adjusted mean scores of cognitive function and compared with control at the 95% confidence interval (CI) and the p-value of <0.05.

After 6.5 years of follow up the unadjusted mean MMSE and CDT scores were significantly higher for participants in the MedDiet+ EVOO group, but was not significantly different in the MedDiet+Nuts group in comparison with the low-fat control group. In multivariate regression analysis, the adjusted mean global cognitive functions scores on MMSE and CDT tests were significantly higher in the MedDiet+ EVOO group and higher in the MedDiet+Nuts group in comparison to the control group. See Table III for a summary of the results for this study. Results of the evaluation are presented in Table II.

**Valls-Pedret et al (2015)**

This was a post hoc single-blinded randomized controlled trial of the Martinez-Lapiscina et al study with participation of the same 6 researchers. This parallel-group study was done for a period of median 4.1 years on the PREDIMED trial subsample of cognitively healthy older Mediterranean population at high CV risk. The primary study outcome was rates of cognitive changes, which were tested twice by the extensive neurophysiological battery at the beginning and the end of the trial. The MMSE, Rey Auditory Verbal Learning Test (RAVLT), Animal Semantic Fluency, Digit Span subtest from the Wechsler Memory Scale, and the Color
Trail Tests were used to assess cognition in 3 composites that included memory, frontal, and
global functions.26

The study candidates were recruited at the PREDIMED center. The PERIMED study
protocol 28 was followed and same eligibility criteria were applied in electing of the study
participants. The exclusion criteria specific for this trial were Spanish language difficulties, mild
cognitive impairment, and depression. A total of 447 eligible candidates were randomly assigned
to either a Mediterranean diet supplemented with olive oil (MedDiet+EVOO diet), a
Mediterranean diet supplemented with mixed nuts (MedDiet+Nuts), or a low-fat control diet
groups. The randomization was done through computer-generated random-number sequence in
blocks of 50.26

The mean age of study participants was 66.8 years and majority of their characteristics
were well balanced, except that the participants in the MedDiet+EVOO group were older (a
mean of 2 years). Experimental groups received a diet advice on the intervention diet and food
supplements during quarterly education sessions. Good adherence to an interventional diet was
confirmed by a validated 14-item questionnaire and a measurement of changes in biomarkers
specific to each intervention, urinary hydroxityrosil for MedDiet+EVOO and alpha-linolenic
acid for MedDiet +Nuts. The low-fat diet control group participants had annual visits for
duration of initial 3 years, followed by a protocol amendment requiring an adjustment of
educational sessions to the same frequency as the experimental groups. Participants in this
group received non-food gifts.26

Neurophysiological testing was performed at a baseline and towards the end of the trial
after the median follow up of 4.1 years. The MMSE was used in the assessment of the global
function of participants, and the RAVLT and the Wechsler Memory Scale were used in
assessment of the immediate and episodic memory. The animal fluency test, the Digit Span subset of the Wechsler Adult intelligence Scale (WAIS), and the Color Trail Test were added during the trial later on to assess changes in language and frontal function. These tests were done in a smaller number of participants (total n=96: 41, 25, and 30, respectively). The adjusted cognitive composites were calculated for each individual from the aforementioned tests and presented as mean standardized scores (mean z scores with 95% CI). The t test, analysis of variance (ANOVA) or x² tests, and analysis of covariance (ANCOVA) were used to make adjustments for imbalances and variables. Significant differences were determined at the p < 0.05.²⁶

From the total of 447 participants, 360 underwent cognitive testing at the end of the trial. Follow up losses were sufficiently addressed and due to withdrawals, refusal to undergo retesting, illness, or death. Further, a total of 6 participants were excluded from the analysis due to depression. The final analysis included 334 participants in 3 groups, 122 in the MedDiet+EVOO group, 112 in the MedDiet+Nuts group, and 95 in the control group. A total dropout rate from the trial was 25.3%, including 18.1 %, in the MedDiet+EVOO group, 28.8% in the MedDiet+Nuts group, and 34.5% in the control group. More losses among the control possibly introduced bias towards a benefit in this group.²⁶

According to multivariate analyses, at the end of the trial there was an improvement in the 2 RAVLTs scores that measure episodic declarative memory in all 3 groups, with significant differences for participants in the MedDiet+EVOO group. No significant improvements in any other cognitive tests were detected between the groups. On the composite scores, significant improvement in the frontal and global cognition was reported for the MedDiet+EVOO group and significant improvement in memory was reported for the MedDiet+Nuts group in comparison to
the control. It was observed that Color Trail Test 2 score deteriorated at the end of the trial in all participants, but to a significantly lesser degree in the MedDiet+EVOO group. Results of the tests are presented in Table II and IV.

It is important to note that at the end of the trial higher incidence of mild cognitive impairment was detected in the MedDiet+EVOO group (13.4%), in comparison to the MedDiet+Nuts group (7.1%) and the control group (12.6%).

The MedLey study, Knight et al (2016)

This study was a first parallel group randomized controlled trial to investigate association between a MedDiet and cognitive function in Non-Mediterranean healthy older adults without increased CV risk or other pathology. The primary outcome of this trial was age-related cognitive function in 2 cohorts of healthy older adults (over 65 years old) that were randomly assigned to either a MedDiet or a Habitual Diet (HabDiet). During 6 months of this trial, cognitive function was assessed repeatedly at the baseline and then at 3 and 6 months. Comprehensive neurophysiological battery composed of 11 cognitive tests was used to assess non-pathological age-related changes in fluid cognition. Five primary composites of cognitive function assessment were: executive function, memory, speed processing, visual-special memory, and total age-related cognitive function. All composites were calculated as the mean of summed Z score of the following tests: Dodrill’s version of the Stroop Test, Initial Letter Fluency (ILF), Excluded Letter Fluency (ELF), and D-KEFS version of the Tower of London (TOL) for executive function; Rey and Schmidt’s, Rey Auditory Verbal Learning Test (RAVLT), Digit Span Forward (DSF), Digit Span Backward (DSB), and Letter-Number Sequencing (LNS) for memory; Symbol Search and Coding from Wechsler Adult Intelligence
Scale (WAIS-IV) for speed of processing; and The Benton Visual Retention Test (BVRT) for visual-special memory. Results of all 11 tests were combined to determine a score for total cognitive function.15

Participants were recruited on a voluntarily basis at the Samson Institute for Health Research, South Australia. They were elderly Australian adults over 65 years old, proficient in English, and with normal cognitive function. Individuals with MCI, dementia, previous brain injury, stroke, CVD, malignancy, or any other diseases of major organs were excluded from the trial. Candidates who were trying to loose weight, taking appetite suppressants, or smoking, were also excluded.3 After initial screening eligible participants were randomly assigned to either an experimental group on the Cretan Mediterranean diet or to a control group on a Habitual diet.6,12 Minimized randomization, which lessens potential of selection bias, was used for allocation. Researchers who were in charge of randomization, administration, and assessment of cognitive tests scores were blinded to the group assignments.15

Study sample size was determined from the previous research27 together with power calculations and estimated to require 128 participants for 2 groups, with 64 in each. This sample size would have 80% power to detect significant changes at \( p<0.05 \). Out of initially recruited 166 participants, 137 completed the trial and were analyzed, 70 participants in the experimental group and 67 participants in the control group. Participants in both groups were well balanced in their baseline characteristics. Cofounding factors (BMI, family history of chronic conditions, stress, and depressive symptoms) were recorded and appropriate adjustments were made in computing of study outcome. Study dropout rates were 17.6% for the MedDiet group and 17.3% for the HabDiet group and all well accounted for.15
The interventional Mediterranean Diet used in the MedLey trial was based on the Cretan Mediterranean Diet\textsuperscript{6} and MedDiet food pyramids\textsuperscript{12} and included EVOO, legumes, yogurt, fish, and mixed nuts among other ingredients. It is important to note that a MedDiet used in this trial wasn't supplemented with additional quantities of olive oil and nuts unlike the PREDIMED-NAVARRA and MedLey studies.\textsuperscript{25,26} Throughout duration of the trial an experimental group received MedDiet food supplies and a control group received monetary gift vouchers. All study participants had ongoing visits with a qualified dietitian to reassure adherence to the diet. Study compliance was high at 92\% and monitored by measuring specific serum biomarkers, urinary metabolites, and by food records and questionnaires. Descriptive statistics were done to record changes in food consumption and significant increase in intake of EVOO, legumes, nuts, and fish was noted in the MedDiet group.\textsuperscript{15}

Assessment of the effect of a Mediterranean Diet in comparison to a habitual control diet was performed on an intention to treat principle using Mixed Factorial Repeated Measures ANCOVA with simple main effects contrasts. Multivariable adjusted mean scores of cognitive function between intervention and control were reported with adjusted differences at the 95\% CI and p-value of <0.05. Cognitive function measurements included total age related cognitive performance, executive functioning, speed of processing, memory, and visual special ability. In summary, the study did not find significant difference in cognitive function among healthy aging population on a MedDiet in comparison to the HabDiet after 6 months of the RCT.\textsuperscript{15} Results of multivariable adjusted mean differences between 2 groups are presented in Table V.

**DISCUSSION**

Dementia is a worldwide problem that is common in well-developed and low-income countries with increasing aging populations. It is one of the major causes of disability and
dependency for older adults and leads to a significant personal and financial burden on the patients, their families, and a society as a whole.\textsuperscript{1} Growing evidence from literature and numerous epidemiologic studies found association between a Mediterranean diet and cognitive function improvement.\textsuperscript{9,10,18,19,30} Use of a MedDiet has been proposed as a preventive measure, which delay cognitive decline due to vascular or neurodegenerative pathologies.\textsuperscript{3,13,15-18}

This systematic review covers 3 available RCTs\textsuperscript{5,25,26} that investigated effects of a Mediterranean diet on cognitive function in older adult populations. Two of these studies\textsuperscript{25,26} found significant differences in some aspects of cognitive performance in a sample of elderly adults with increased risk of CVD. Results of these studies suggest that a long-term use of a MedDiet is associated with improved cognitive function in older population. On contrary, the third, short-term study\textsuperscript{15} that investigated a MedDiet effect among healthy older adults reported null findings. The reviewed studies have certain limitations and provided inconsistent and contradictory results. Quality of the evidence from the reviewed studies was evaluated and considered to be low and moderate based on the GRADE guidelines.\textsuperscript{24} Grade evidence profile can be seen in Table I.

The major common limitations of the above studies\textsuperscript{15,25,26} include one-way blinding, possible recruitment bias, a small sample size, and high attrition bias (see Table II for comparison). All three studies were single-blinded due to a nature of the intervention. In general, it is not feasible to conduct double-blinding in this type of trial when food is used as an experimental intervention. Study participants were well aware of their diet, received extensive nutritional counseling, and had to fill out dietary questionnaires to assure adherence. Data collectors, researchers, and medical personal involved in these RCTs were blinded.\textsuperscript{15,25,26}
It is highly probable that recruitment bias was present in all reviewed studies, since study participants who showed interest in MedDiet were more likely to signed up for a trial. In addition, the Martinez-Lapiscina et al\textsuperscript{25} and Valls-Pedret et al studies\textsuperscript{26} were confined to the Mediterranean region and were done in a group of aging adults with high risk of CVD, while recruitment for the MedLey study\textsuperscript{15} was done at one center in Australia and included very healthy, well-educated elder adults who were eager to make valuable social contribution. Lack of diversity in population samples make it difficult to arrive to a conclusion regarding applicability of these studies to general elderly population. Some reports\textsuperscript{22,29} indicate that an effect of a MedDiet on a rate of cognitive decline and dementia might be determined by cultural or racial differences.

All of the reviewed studies\textsuperscript{15,25,26} had a relatively small sample size and high drop out rates in all groups. Attrition bias was especially high in the PREDIMED-NAVARRA study\textsuperscript{26} (average: 46\%) and much less in the MedLey study\textsuperscript{15} (average: 17\%). Lower drop out rate in the MedLey study\textsuperscript{15} was most likely due to a short duration of the trial (6 months) with frequent follow-ups to assure high adherence (92\%). Also, the PREDIMED-NAVARRA and Valls-Pedret et al studies had much higher drop out rates in the control group with possible bias towards benefit.\textsuperscript{25,26}

Each of the reviewed studies had additional unique limitations.\textsuperscript{15,25,26} The PREDIMED-NAVARRA longitudinal study\textsuperscript{25} was not originally intended to investigate effects of the MedDiet on cognition and didn't include a baseline cognitive functions assessment. Also, it was assumed that study participants were similar in regards to their cognition due to their similar basic characteristics, proper trial randomization, and proper adjustments of cofounders.\textsuperscript{25} Two tests, used in this study, MMSE and CDT, are designed as dementia screening tools, offer a
limited measure of general cognitive function and are insufficient for a comprehensive assessment. The Valls-Pedret et al study\textsuperscript{26} was a post hoc analysis, which was done on a subset of participants from the PREDIMED-NAVARRA trial.\textsuperscript{25} Although, it offered extensive assessment of cognitive functions through comprehensive neurophysiological battery, it had very wide CIs, inconsistency in testing, participation of the same 6 researchers from the Martinez-Lapiscina et al study,\textsuperscript{26} and a conflict of interest due to partial funding by the nut companies. The MedLey study\textsuperscript{15} with null findings was a very short in duration, which might be not enough to observe a full effect of the MedDiet on cognitive functions. This study has been extended to 18 months and its results are still unpublished.

It is difficult to combine and compare data of these studies due to a use of different experimental and control groups from different regions, use of different variations of MedDiet and a control diet, and use of different neurophysiological tests for a cognitive functions assessment.

Both, Martinez-Lapiscina et al\textsuperscript{25} and Valls-Pedret et al\textsuperscript{26} longitudinal studies found significant difference in cognitive performance in a group of elderly adults with increased risk of CVDs from the Mediterranean region while the Knight et al study\textsuperscript{15} produced null results in a group of very healthy, physically and mentally fit individuals from Australia. It is possible that a beneficial effect of MedDiet is specific to Mediterranean population and it may delay cognitive decline due to vascular pathology, but not due to normal aging.\textsuperscript{11,13,15,25} Based on results of these studies it is difficult to conclude whether a MedDiet is beneficial in maintaining cognitive function, in preventing cognitive decline due to aging, or in slowing down pathological processes. Null finding in the Knight et al study\textsuperscript{15} may indicate that benefits contributed to a MedDiet may be due to a synergetic effect of more active, healthy life style.\textsuperscript{13,30}
In regards to a cognitive function assessment, results of the reviewed studies are inconsistent. While Martinez-Lapiscina et al\textsuperscript{25} found significant difference in cognitive performance on the MMSE, Valls-Pedret et al\textsuperscript{26} reported negative findings on the same test. Valls-Pedret et al\textsuperscript{26} reported different results of a cognitive assessment in two experimental groups. In multivariate analyses significant improvement in episodic declarative memory was detected in the MedDiet+EVOO group and on the composite scores significant improvements were detected in the frontal and global cognition for the MedDiet+EVOO group, and in memory for the MedDiet+Nuts group. Different results of cognitive performance in two experimental groups might indicate that individual components of the MedDiet (EVOO or Nuts) affect various aspects of global cognition. This view is supported by other publications suggesting that a beneficial effect of a MedDiet might be due to its individual components.\textsuperscript{5,6,13} The null finding in cognitive function improvement among healthy older adults reported by Knight et al may be due to a short duration of the trial on a small sample of healthy individuals with initially high level of cognitive function.\textsuperscript{15}

Martinez-Lapiscina et al\textsuperscript{25} and Valls-Pedret et al\textsuperscript{26} studies had two experimental groups in which a MedDiet was supplemented with either EVOO or mixed nuts, and used a low-fat diet as control; while Knight et al\textsuperscript{15} used Cretan version of a MedDiet, which contained EVOO and mixed nut, but not in excessive amount, a control group in is this study was on a habitual Western diet. The first studies reported The Knight et al\textsuperscript{15} proposed that improvements of cognitive function reported by Martinez-Lapiscina et al\textsuperscript{25} and Valls-Pedret et al\textsuperscript{26} might be due to amplified levels of EVOO and mixed nuts, that are rich in MUFA and polyphenolic compounds from oil an alpha-linolenic acid from nuts.
It will be necessary to conduct future longitudinal RCTs that are based on a standard definition of MedDiet,\textsuperscript{13,14} use a representative sample of aging population allowing generalization, reports a diet adherence based on nutrients and not food components,\textsuperscript{13} and employs a comprehensive neurophysiological battery offering an extensive assessment of cognitive function. In addition, future RCTs need to clarify which of individual components of MedDiet work and whether the MedDiet is beneficial in maintaining cognitive function, preventing cognitive decline due to aging, or in slowing down pathological processes. All the above questions must be addressed before making medical recommendations and changing practice guidelines in regards to benefits of Mediterranean diet on cognition.

**CONCLUSION**

The effect of the Mediterranean diet on cognitive function of the general aging population remains unclear from the 3 RCTs presented in this systematic review. Although, results of 2 reviewed studies indicate that the Mediterranean diet supplemented with olive oil or nuts might be beneficial for cognitive function in Mediterranean older adults with increased risk of CVDs, several limitations and inconsistent evidence preclude generalization of these results to average aging adults. The current evidence obtained from the only one available RCT that investigated an effect of a MedDiet in the healthy aging population, did not demonstrate a statistically significant difference in cognitive function of this group in comparison to a habitual diet control. To further clarify results of these findings, future RCT performed on a larger, more representative population samples for a longer trial duration, using a consistent choice of MedDiet nutrients and comprehensive neurophysiological battery are necessary. Further more, it is important to clarify whether a MedDiet is effective in prevention of cognitive decline due to normal aging or dementia development due vascular and neurodegenerative pathologies.
References


## Tables

### Table I: GRADE Evidence Profile of Reviewed Articles

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Publication Bias</th>
<th>Upgrade Criteria</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martinez-Lapiscina et al&lt;sup&gt;25&lt;/sup&gt;</td>
<td>RCT</td>
<td>Not Serious</td>
<td>Serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Not Serious</td>
<td>Serious&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Unlikely</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Valls-Pedres et al&lt;sup&gt;26&lt;/sup&gt;</td>
<td>RCT</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Serious&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Likely&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>MedLey Study by Knight et al&lt;sup&gt;15,27&lt;/sup&gt;</td>
<td>RCT</td>
<td>Serious&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Unlikely</td>
<td></td>
<td>Moderate</td>
</tr>
</tbody>
</table>

<sup>a</sup> The Martinez-Lapiscina et al study didn't have a baseline cognitive functions measurements (CF wasn't planned to be a primary outcome) and cognitive functions were assessed by 2 tests vs. comprehensive battery

<sup>b</sup> High attrition rates

<sup>c</sup> The Valls-Pedres et al study was partially funded by the Nuts Commission. Six authors of this study were also involved in the Martinez-Lapiscina et al study

<sup>d</sup> The MedLey Study by Knight et al had a short duration (6 month) and investigated a different group of population making comparison difficult
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Mean Age (years)</th>
<th>Intervention Groups</th>
<th>Control Group</th>
<th>Duration (Years)</th>
<th>Number of participants</th>
<th>CF Assessment</th>
<th>Attrition Rate (%)</th>
<th>Study Outcome (statistically significant difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martinez-Lapiscina et al</td>
<td>Mediterraean Older Adults with CV risk</td>
<td>74.6 ± 5.7</td>
<td>2 groups: MedDiet + EVOO</td>
<td>Low-fat diet</td>
<td>6.5</td>
<td>Total: 522, Each Group: 224, 166, 132</td>
<td>MMSE, CDT at the end of the trial</td>
<td>Total: Gr.1: 36%, Gr.2: 52.8%, Control: 62.5%</td>
<td>Cognitive performance scores on global screening tests for dementia, were significantly higher than in a control group</td>
</tr>
<tr>
<td>Valls-Pedres et al</td>
<td>Mediterraean Cognitively Healthy Older Adults with CV risk</td>
<td>66.9</td>
<td>2 groups: MedDiet + EVOO</td>
<td>Low-fat diet</td>
<td>4.1</td>
<td>447 (130,112,95)</td>
<td>Baseline and at termination CF in 3 composites: memory, frontal, global Tests: MMSE, RAVLT, Wechsler memory scale, Color Trail Test</td>
<td>Total: 25.3% Gr.1: 18.1% Gr.2: 28.8% Control: 34.5%</td>
<td>MedDiet + EVOO: significant improvement on the RAVLT (measures episodic declarative memory). Composite scores: MedDiet + EVOO: Significant improvement in the frontal and global cognition MedDiet +Nuts group: significant improvement on memory composite score</td>
</tr>
<tr>
<td>MedLey Study by Knight et al</td>
<td>Australian Healthy Older Adults</td>
<td>72.0 ± 4.94</td>
<td>1 group: MedDiet Recorded nutrient intake High adherence rate at 90%</td>
<td>Habitual Western diet</td>
<td>0.5</td>
<td>137 (70, 63)</td>
<td>Comprehensive neurophysiological test battery in 5 composites variables: speed of processing, memory, executive function, visual and special abilities, age-related CF at 0, 3, 6 months</td>
<td>Gr.1: 17.6% Control: 17.3%</td>
<td>No evidence of improvement of cognitive function among healthy older adults on a MedDiet</td>
</tr>
</tbody>
</table>

Abbreviations: CDT = Clock Drawing Test, EVOO = extra virgin olive oil, MedDiet = Mediterranean diet, MMSE = Mini-Mental State Examination.
<table>
<thead>
<tr>
<th></th>
<th>MedDiet + EVOO Mean (95% CI)</th>
<th>MedDiet + Nuts Mean (95% CI)</th>
<th>Control (low fat diet) Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>n=224</td>
<td>n=166</td>
<td>n=132</td>
</tr>
<tr>
<td>MMSE</td>
<td>27.73 (27.27 - 28.19)</td>
<td>27.68 (27.20 - 28.16)</td>
<td>27.11 (26.61 – 27.61)</td>
</tr>
<tr>
<td>Adjusted difference vs. control (95% CI)</td>
<td>+0.62 (+0.18 to +1.05)</td>
<td>+0.57 (+0.11 to +1.03)</td>
<td>0 (reference)</td>
</tr>
<tr>
<td>p Value (vs Control)</td>
<td>0.005</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>CDT</td>
<td>5.31 (4.98 - 5.64)</td>
<td>5.13 (4.78 - 5.47)</td>
<td>5.31 (4.98 to 5.64)</td>
</tr>
<tr>
<td>Adjusted difference vs. control (95% CI)</td>
<td>+0.51 (+0.20 to +0.82)</td>
<td>+0.33 (+0.003 to +0.67)</td>
<td>0 (reference)</td>
</tr>
<tr>
<td>p Value (vs Control)</td>
<td>0.001</td>
<td>0.048</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CDT= Clock Drawing Test, CI = confidence interval, EVOO = extra virgin olive oil, MedDiet = Mediterranean diet, MMSE = Mini-Mental State Examination.
## Table IV. Summary of Important Findings in Valls-Pedres et al Study
### (Baseline Cognitive Test Scores and Changes)

<table>
<thead>
<tr>
<th>Variable</th>
<th>MedDiet + EVOO Mean (95% CI)</th>
<th>MedDiet + Nuts Mean (95% CI)</th>
<th>Control (low fat diet) Mean (95% CI)</th>
<th>P-Value across groups (covariance adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>n=127</td>
<td>n=112</td>
<td>n=95</td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>28.01 (27.79 to 28.24)</td>
<td>28.11 (27.87 - 28.35)</td>
<td>28.38 (28.12 to 28.65)</td>
<td>.10</td>
</tr>
<tr>
<td>Change</td>
<td>0.16 (-0.12 to 0.44)</td>
<td>-0.07 (-0.36 to 0.23)</td>
<td>-0.26 (-0.57 to 0.06)</td>
<td>.15</td>
</tr>
<tr>
<td>RAVLT, Total learning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>39.31 (37.92 to 40.70)</td>
<td>39.46 (37.98 to 40.94)</td>
<td>39.46 (37.98 to 40.94)</td>
<td>.98</td>
</tr>
<tr>
<td>Change</td>
<td>4.50 (3.24 to 5.77)</td>
<td>4.26 (2.91 to 5.60)</td>
<td>2.10 (0.64 to 3.57)</td>
<td>.04</td>
</tr>
<tr>
<td>Color Trail Test, part 1b,c</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>62.60 (56.29 to 68.91)</td>
<td>61.15 (53.56 to 68.74)</td>
<td>57.00 (49.61 to 64.38)</td>
<td>.53</td>
</tr>
<tr>
<td>Change</td>
<td>-5.77 (-11.25 to -0.28)</td>
<td>-2.44 (-5.29 to 10.26)</td>
<td>4.53 (-2.11 to 11.17)</td>
<td>.045</td>
</tr>
<tr>
<td>Color Trail Test, part 2b,c</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>136.55 (123.19 - 149.90)</td>
<td>131.59 (115.13 - 148.05)</td>
<td>129.99 (114.39 to 145.60)</td>
<td>.81</td>
</tr>
<tr>
<td>Change</td>
<td>5.66 (-10.23 to 21.55)</td>
<td>24.23 (1.36 to 47.10)</td>
<td>37.56 (18.14 to 56.97)</td>
<td>.045</td>
</tr>
</tbody>
</table>

### Summary of Significant Findings for Baseline Cognitive Function* (Fully Covariance Adjusted Models)
#### Comparisons across groups

<table>
<thead>
<tr>
<th>Memory</th>
<th>Baseline</th>
<th>Change</th>
<th></th>
<th></th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.02 (-0.11 to 0.15)</td>
<td>0.04 (-0.09 to 0.18)</td>
<td>0.06 (-0.25 to 0.13)</td>
<td></td>
<td>.82</td>
</tr>
<tr>
<td></td>
<td>0.013 (-0.13 to 0.16)</td>
<td>0.09 (-0.05 to 0.23)</td>
<td>0.04 (-0.02 to 0.27)</td>
<td></td>
<td>.04</td>
</tr>
<tr>
<td>Frontal</td>
<td>0.04 (-0.11 to -0.34)</td>
<td>0.12 (-0.11 to -0.34)</td>
<td>0.04 (-0.02 to 0.27)</td>
<td></td>
<td>.50</td>
</tr>
</tbody>
</table>
### Table V. Summary of Primary Outcome Findings in MedLey Study

Multivariable-Adjusted Mean Differences in MedDiet in comparison to Control (Habitual Western Diet)

<table>
<thead>
<tr>
<th>Cognitive Function composite</th>
<th>Adjusted Difference vs Control</th>
<th>95% CI</th>
<th>P-Value vs. Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total age related cognitive function</td>
<td>+8.00</td>
<td>(-4.00-19.9)</td>
<td>0.19</td>
</tr>
<tr>
<td>Executive function</td>
<td>+2.53</td>
<td>(-2.58-7.65)</td>
<td>0.33</td>
</tr>
<tr>
<td>Memory</td>
<td>+2.00</td>
<td>(-3.88-7.88)</td>
<td>0.50</td>
</tr>
<tr>
<td>Speed of Processing</td>
<td>+3.24</td>
<td>(-1.21-7.70)</td>
<td>0.15</td>
</tr>
<tr>
<td>Visual-special</td>
<td>+0.21</td>
<td>(-0.38-0.81)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval, MedDiet = Mediterranean diet