Higher Mediterranean Diet scores are not cross-sectionally associated with better cognitive scores in 20- to 70-year-old Dutch adults: The NQplus study

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Abbreviation list

AD; Alzheimer’s Disease

AQuAA; Activity Questionnaire for Adults and Adolescents

BMI; Body Mass Index

CES-D; Center for Epidemiologic Studies Depression Scale

FFQ; Food Frequency Questionnaire

LFT; Letter Fluency Test

MCI; Mild Cognitive Impairment

MedDiet; Mediterranean Diet

METC-WU; Medical Ethical Committee of Wageningen University

MMSE; Mini-Mental State Examination

MUFA:SFA ratio; ratio of Monounsaturated Fatty Acids to Saturated Fatty Acids

NQplus; Nutrition Questionnaires plus

PUFA; polyunsaturated fatty acids

RBMT; Rivermead Behavioural Memory Tests

SDMT; Symbol Digit Modalities Test

SQUASH; Short Questionnaire to Assess Health enhancing physical activity

SRT; Story Recall Test

ABSTRACT

Adherence to the Mediterranean Diet (MedDiet) has been suggested to reduce the risk of age-related cognitive decline. Therefore, we hypothesized that adults consuming a more Mediterranean-like diet were more likely to have better cognitive scores. We investigated cross-sectional associations between MedDiet adherence and cognitive performance using data of 1,607 Dutch men and women aged 20-70 years. Dietary intake was assessed using a 183-item Food Frequency Questionnaire. MedDiet adherence was defined by a 0-9 point scale; which was based on intakes of vegetables, legumes, fruits/nuts, cereals, fish/seafood, meat/poultry, dairy, ethanol and the MUFA:SFA ratio. Cognitive function was assessed with a neuropsychological test battery. Linear regression analyses adjusted for relevant covariates showed a significant inverse association between MedDiet adherence and everyday memory: specifically β=-0.107±0.046 points (*p*=0.02) for the total population and β=-0.139±0.055 points (*p*=0.01) for those aged ≥50 years. Further exploration of the individual MedDiet food groups suggested that the association between MedDiet and every day memory was predominantly driven by the MUFA:SFA ratio. Moreover, associations were observed between higher ethanol intake with better semantic memory and language production (β=0.016±0.008 *p*=0.05), higher vegetable intake with better processing speed (β=0.005±0.002, *p*=0.02), and higher legumes intake with poorer processing speed (β=-0.014±0.006, *p*=0.03). Thus, in this Dutch cohort, higher MedDiet adherence was associated with poorer everyday memory.

Keywords: Mediterranean diet; cognitive performance; middle-age; observational; cross-sectional

1. Introduction

An increasing number of older adults is affected by cognitive decline and dementia [1]. As there is no treatment for dementia yet, a preventive approach is of major importance [2]. Diet has been suggested to play an important role in the development of dementia and cognitive decline [3]. Therefore, diet quality scores, especially the Mediterranean Diet (MedDiet) [4], have received increased attention during the past years. MedDiet is characterized by a high consumption of plant-based foods including fruits, vegetables, legumes, whole grain cereals, nuts and seeds; moderate consumption of fish and wine; and a low consumption of dairy products and meat, especially red meat, and high consumption of olive oil instead of butter. As a result, MedDiet is a diet high in polyunsaturated fatty acids (PUFA), dietary fibers and antioxidants, and has a high Monounsaturated Fatty Acids to Saturated Fatty Acids (MUFA:SFA) ratio.

Adherence to MedDiet-like dietary patterns has been associated with a decreased risk of coronary heart diseases, diabetes mellitus and hypertension as well as a lower risk of depression, Mild Cognitive Impairment (MCI), and Alzheimer's Disease (AD) [5]. Many of these neuropathological states are characterized by a strong inflammatory component [6], high oxidative stress [7], vascular impairment [8], and compromised glucose metabolism [9]. Various food groups of the MedDiet pattern have been associated with a better regulation of these biological systems [10, 11] and may slow-down cognitive decline through these mechanisms [12-14].

However, studies examining associations between MedDiet pattern and cognitive status or cognitive decline are still inconclusive [15-17]. In earlier cross-sectional studies, Ye et al. showed a beneficial association between MedDiet and cognitive performance [18], whereas Samieri et al. showed no association [19] and Katsiardanis et al. showed a positive association in men, but a negative association in women [20]. Also longitudinal studies showed mixed findings; the majority of these studies observed an association between higher MedDiet adherence with less cognitive decline [21-28], while no associations were observed in other studies [29-32]. A first randomized controlled trial, the PREDIMED study, showed a protective effect of MedDiet on cognitive decline [33].

As cognitive decline may already be evident in mid-life, preventive measures during this life-stage may be of importance [34]. However, to the best of our knowledge, only two studies examined the association between MedDiet adherence and cognitive performance in participants with a mean age of respectively 57 and 59 years [18, 19]. It was hypothesized that individuals consuming a more Mediterranean-like diet would have better cognitive scores and that these associations would be stronger in those aged 50 years and over. Therefore, our objective was to investigate the association between MedDiet adherence and cognitive performance in a cohort of 1,607 Dutch men and women aged 20-70 years and in a subsample of participants aged 50 years and over.

2. Methods and materials

2.1 Study population

This study was conducted using cross-sectional data of the Nutrition Questionnaires plus (NQplus) study; a large prospective cohort study among 2,048 Dutch men and women aged 20-70 years living in the central part of the Netherlands [35, 36]. Participants were recruited from 2011 until 2013 via random sampling from the municipality registries of Ede, Wageningen, Renkum, and Arnhem by sending (electronic) invitations, and 2) sending invitation letters to all households of Veenendaal. Of the total study population (*n*=2,048), *n*=422 were excluded due to missing or unreliable dietary information (cut-offs for total energy <800 or >4,000 kcal/d for men and <500 or >3,500 kcal/d for women, based on [37]) and *n*=19 did not (reliably) complete any of the three cognitive tests. Thus, the final sample for the current analyses included 1,607 individuals. The study was approved by the Medical Ethical Committee of Wageningen University (METC-WU) on July 7th 2011 (protocol number 10/32) and was conducted according to the declaration of Helsinki. All participants provided written informed consent.

2.2 MedDiet Score

All participants completed a 183-item semi-quantitative general Food Frequency Questionnaire (FFQ) to assess habitual dietary intake during the past four weeks, validated for energy intake, macronutrients, dietary fiber, and selected vitamins [38-40]. Nutrient and food intakes were adjusted for energy by means of the residual method [41]. A more detailed description of the FFQ can be found elsewhere [35]. Subsequently, a MedDiet Score indicating the degree of adherence to the traditional

MedDiet was calculated. The MedDiet Score was first constructed by Trichopoulou et al. [42] and revised to include fish intake in 2002 [43]. For food groups that were expected to be beneficial (vegetables, legumes, fruits and nuts, cereals, fish and seafood and MUFA:SFA ratio), a value of 0 was assigned to persons whose energy-adjusted consumption was below the median and a value of 1 to persons whose consumption was at or above the median. In contrast, for food groups presumed to be unhealthy (meat and poultry and dairy products), an opposite score was assigned. Finally, for ethanol intake, a value of 1 was assigned to men and women with moderate intakes (respectively between 10 and 50 g per day and between 5 and 25 g per day) and a value of 0 to people with intakes that were not within the sex-specific range. Thus, the total MedDiet Score ranged from 0 (minimal adherence) to 9 (maximal adherence) and was categorized into three categories of increasing adherence to the MedDiet: 0-3 (low adherence), 4-5 (intermediate adherence), and 6-9 (high adherence).

2.3 Cognitive performance

Cognitive performance was assessed using three standardized neuropsychological tests. The Letter Fluency Test (LFT) [44] was used to evaluate semantic memory and language production. During the LFT participants received 60 seconds per trial to generate as many words as possible using the letters D, A, and T. The Symbol Digit Modalities Test (SDMT) [45, 46] was used to measure information processing speed were individuals had to pair nine abstract symbols to the numbers 1 through 9 in a written examination. The participant was limited to 60 seconds for completing this test of which scores could range from 0 to 110. The Story Recall Test (SRT) is a subtest of the Rivermead Behavioural Memory Tests (RBMT) and was used to assess everyday memory [47]. For the SRT, participants were asked to listen to a story and to recall the story immediately. For scoring, the story was split in 21 elements with 1 point given for each correctly recalled element or synonym and 0.5 point for each partially correctly recalled element or synonym. All cognitive tests were performed and scored according to a standardized protocol by trained research assistants.

2.4 Other measures and covariates

Anthropometric measurements were performed by trained research assistants according to a standardized protocol. Height was measured without shoes with a stadiometer (SECA, Germany) to the nearest 0.1 cm. Weight was measured using a digital scale (SECA, Germany) to the nearest 0.1 kg after participants were asked to take off their shoes, sweaters and to empty their pockets. Body Mass Index (BMI) was calculated as weight (kg)/height (m)^2. Information on demographics and lifestyle was obtained through online self-administered questionnaires. The general questionnaire included questions about age, sex, education (low: no education or primary or lower vocational education as highest completed education; intermediate: completed lower secondary or intermediate vocational education; high: completed higher secondary education, higher vocational education or university), history and prevalence's of diseases including diabetes mellitus and cardiovascular health, social activities, and smoking (never/former/current). Physical activity was assessed using a combination of questions from the Short Questionnaire to Assess Health enhancing physical activity (SQUASH) [48] and the Activity Questionnaire for Adults and Adolescents (AQuAA) [49]. Since baseline data for physical activity were not available for all participants, missing data were imputed using data obtained at 1-year of follow-up. The Center for Epidemiologic Studies Depression Scale was used to assess depressive symptoms [50]. Information on medication and nutritional supplement use was registered during the physical examination. Fasting blood samples were collected by venipuncture. Total cholesterol and HDL-cholesterol was determined with enzymatic methods [51]. LDL-cholesterol was calculated with the Friedewald equation [52].

2.5 Statistical analyses

Statistical analyses were performed using the software IBM SPSS statistic version 23.0 (IBM Statistics, IBM Corporation, New York, NY, USA). Participants' characteristics were presented as percentages for categorical variables, mean (SD) for normally distributed continuous variables and median (interquartile range) for non-normally distributed continuous variables. To compare baseline characteristics between MedDiet Score categories, the chi-square test was used for categorical variables, one-way ANOVA for normally distributed continuous variables and Kruskal-Wallis for non-normally distributed variables. Multivariate linear regression analyses were used to assess associations between MedDiet Scores and cognitive performance as a continuous outcome measure, shown as β (SE). The analyses were performed for all participants and for three subgroups including people older than 40, 45, and 50 years of age. To estimate the probability of poor cognitive performance, Cox proportional hazard analysis with robust error variance were conducted. MedDiet was included continuously and a participant belonging to the worst 10% of cognitive performers was defined as a poor performer. Hazard ratios with corresponding 95% confidence intervals (95%CI) were calculated. By assigning a constant risk period to all participants in the study, the obtained hazard ratio can be interpreted as a prevalence ratio (PR). This PR corresponds to the probability of being defined as a poor cognitive performer with every MedDiet point increase. Model 1 was adjusted for age, sex, and level of education (low, intermediate, high). Model 2 was further adjusted for BMI (kg/m^2), total energy intake (kcal), moderate physical activity (min/week), smoking status (never/former/current), social activities (number of social clubs attended), and number of dietary supplements used. Covariate selection was primarily based on current literature. More specifically, literature suggesting an association between the MedDiet and the specific covariate combined with literature pointing towards an association between the specific covariate and cognition. Multivariate regression analyses were also conducted for each of the individual MedDiet food groups as the primary predictor. In these MedDiet food group analyses, model 1 and model 2 were similar to the analyses for the MedDiet score and model 3 was additionally adjusted for the other food groups comprising the MedDiet score. A two-sided p-value < 0.05 was considered significant.

3. Results

3.1 Population characteristics

The 1,607 participants were on average 52.9 years old and 52% were men. Median BMI was 25.9 kg/m^2, 62% of the participants had a high education level, and 9% were current smokers. Individual median (25-75th percentile) food group intakes were 128 (80-177) g/day for vegetables, 25 (15-40) g/day for legumes, 212 (97-256) g/day for fruits and nuts, 191 (153-232) g/day for cereals, 17 (11-25) g/day for fish, 66 (41-89) g/day for meat, 314 (206-437) g/day for dairy, and 7 (2-15) g/day for ethanol. The mean MedDiet Score was 4.5±1.7 where 29% of the participants had a "low adherence" (0-3 points), 43% a "medium adherence" (4-5 points) and 28% a "high adherence" (6-9 points). Participants with a higher MedDiet adherence were significantly older, higher educated, had a lower BMI, and higher HDL-cholesterol levels, than those with a low MedDiet adherence (Table 1). Additionally, participants with a higher MedDiet adherence were less often smokers, had a higher ethanol intake, and were more likely to be supplement users. Furthermore, participants with a high MedDiet adherence had lower intakes of proteins, total fat and saturated fat, and higher intakes of PUFA, vitamin C, D, E, B6, retinol activity and folic acid equivalents than participants with a low MedDiet adherence (data not shown). With respect to the cognitive scores, semantic memory and language production and processing speed scores, evaluated with LFT and SDMT, did not significantly differ between MedDiet adherence categories. In contrast, everyday memory performance, assessed with SRT, was significantly lower among participants with a higher MedDiet adherence.

3.2 MedDiet and cognitive performance

Table 2 shows the results of the linear regression analyses that were performed for all participants (n=1,604) and for a subgroup including participants aged 50 years and over (n=1,063). Unadjusted models showed an association between a higher MedDiet adherence and higher LFT scores. This association was significant for the total population (β=0.110±0.049, p=0.03), but not for the older subgroup (β=0.054±0.060, p=0.37). However, after adjustment for covariates this association attenuated and became non-significant. Significant unfavorable associations were observed for MedDiet adherence and every day memory. In model 2, each additional MedDiet point was associated with a -0.107 decrease in SRT points in the total population (β=-0.107±0.046, p=0.02) and with a -0.139 decrease in SRT points in the subgroup including participants older than 50 years (β-0.139± 0.055, p=0.01). This roughly suggests that in order to recall 1 story item less, the MedDiet score has to increase with 10 points. No associations were observed between MedDiet adherence and processing speed as assessed with the SDMT.

3.3 MedDiet food groups and cognitive performance

Linear regression analyses with individual MedDiet food groups showed a positive association between ethanol consumption and semantic memory and language, assessed with the LFT, in all models (β for model 3=0.016±0.008 per g/day, p=0.05; Table 3)). Additionally, for each unit increase in fish and seafood consumption (g/day), the LFT score increased with 0.012 points (p=0.02) in model 1. This association attenuated after adjustment for demographic, lifestyle, and nutritional factors. Regarding information processing speed, significant associations were observed for vegetables (β=0.005±0.002, p=0.02) and legumes (β=-0.014±0.006, p=0.03) (model 3). Moreover, a higher MUFA:SFA ratio was inversely associated with lower SRT scores in model 2 (β=-0.733±0.325, *p*=0.02), which attenuated after further adjustment for other MedDiet food groups (β=-0.552±0.353, *p*=0.12) (model 3).

4. Discussion

Our analyses in a Dutch population of generally healthy adults showed an inverse association between higher MedDiet adherence and everyday memory. This association was largely driven by the MedDiet food group representing the MUFA:SFA ratio. Analyses on individual MedDiet food groups also showed positive associations of ethanol consumption with semantic memory and language production, and vegetable intake with information processing speed. The intake of legumes was inversely associated with information processing speed.

Our findings are consistent with other cross-sectional studies such as the Nurses' Health Study (*n*=10,670 women aged 45-70 years) [19] and Greek Velestino Study (*n*=237 men aged >65 years) [20], which also showed no associations between MedDiet adherence and cognitive performance [19]. However, our results are in contrast with a cross-sectional study performed in 1,269 Puerto Rican adults aged 45 to 75 years living in the Boston area, showing better cognitive function with higher adherence to the MedDiet [18]. Four longitudinal studies are also consistent with our findings and did not show an association between MedDiet adherence and cognitive decline; i.e. the French SU.VI.MAX study with a follow-up of 13 years performed in 3,083 participants with a mean age of 65 years [29], the American Women's Health Study with analyses on 4-year cognitive change in 6,174 women aged >65 years [30], a Greek cohort of 732 men and women >60 years of age with Mini-Mental State Examination (MMSE) scores determined 6-13 years after dietary evaluations [31], and the Women's Antioxidant Cardiovascular Study performed in 2,504 US female health professionals [32]. Conversely, our results are in contrast with multiple other longitudinal studies, which observed that higher adherence to MedDiet was associated with less cognitive decline [21-28].

The discrepancies between studies may be related to various methodologic differences. First, the MedDiet score in most studies was based on population-specific medians. If a study was conducted in a non-Mediterranean population, it is very likely that these population-specific medians differ from population-specific medians that would be obtained from a Mediterranean population. To illustrate, compared to the dietary intakes in our population, the traditional Mediterranean diet comprises higher mean intakes of fruit (410 g/d vs. 199 g/d) and vegetables (169 vs. 138 g/d), and lower intakes of dairy (219 vs. 332 g/d) and meat/poultry (44 vs. 67 g/d). Intakes of fish (16 vs. 21 g/d) and legumes (26 vs. 32 g/d) are rather comparable [53]. As such, the attempt to define MedDiet adherence with a population-based MedDiet Score could constrain the complexity of local diets and hide potential healthy features of modern dietary patterns. For that reason, the ability to represent the traditional dietary pattern of the Mediterranean area has been criticized [54]. An alternative approach to population-based medians is to use predefined absolute levels of intake of foods and food categories. This approach has so far been used in only a few of the studies on dietary patters in relation to cognitive decline [25, 26, 28, 55-57] and incident Alzheimer's Disease [58]. As also discussed by Morris in 2016, several advantages of the use of absolute food intake levels are increased ability to compare findings among studies, optimum levels of brain benefit for individual dietary components become clear, and the findings are more easily translated into a dietary advice in servings per day for the general public [59]. Second, the dietary assessment methods differ between the studies. The French study by Kesse-Guyot et al. used six 24-h recalls [29] and the remaining observational studies all used FFQs. The applied FFQs may greatly vary, for instance depending on the number of food items queried. As such, different FFQs may provide dietary intake estimates that are not equally precise and accurate. Third, also the cognitive tests used differ between studies, which may have affected the sensitivity to detect potential associations as well. For instance, many of the studies discussed above only used the MMSE or an adapted version of this test [20, 21, 23, 27, 28, 31] or they only showed an association with the MMSE and not with the domain-specific neuropsychological tests if these were performed as well [18, 22]. It should be noted here that the MMSE is designed as a cognitive screening instrument and considered global and non-sensitive to assess cognitive functioning [60], whereas the domain-specific neuropsychological tests are considered to be more sensitive to detect cognitive deficits. Fourth, there were large differences in sample size between studies and prospective studies had varying follow-up times. Fifth, also the age range of the population under study may have been an important factor contributing to the detection of potential associations. Contrasting with most prior studies, the current cohort included participants with a relatively large age range (20-70 years) and a relatively young mean age (53 years). However, we also conducted sensitivity analyses using data of participants aged >50 years only, which did not result in different findings compared to the findings of the total population. Finally, MedDiet is an *a priori* defined dietary pattern taking into account possible synergistic and antagonistic interactions between food groups of a complex diet. The individual MedDiet food groups received equal weights, i.e. contribute equally to the MedDiet score. It is very likely though that not all food groups have the same impact on health outcomes and thus also not on cognitive performance [61]. However, Trichopoulou et al observed lower mortality rates with increasing MedDiet scores, where such association was much less evident when studying the individual components, suggesting that the sum score is the important exposure [43]. Furthermore, certain food groups of the MedDiet Score are correlated (e.g. fruits, vegetables, and dietary fiber [62]) and consequently indirectly weigh more heavily with the score than others. All in all, aforementioned aspects may partly explain the different findings across studies.

When looking at the individual food groups, we observed a positive association of ethanol consumption with semantic memory and language production, but a marginally inverse association with everyday memory. As reported by a recent review [63], the impact of alcohol consumption on cognitive performance is still not clear. Previous studies suggest associations of light-to-moderate alcohol consumption with a reduced risk of dementia and AD, but associations with vascular dementia, cognitive decline and pre-dementia are less clear. The positive association as observed in our study may be due to the antioxidant properties of phenols and polyphenols in wine, which is the typical MedDiet beverage [64, 65] and was also the most preferred alcoholic beverage in the current study population [36]. We also showed a positive association of vegetable intake with information processing speed. Vegetable intake has also been beneficially linked with cognition in previous studies studying the MedDiet [24, 28] and also in other cohorts focusing on vegetable intake in relation to cognitive decline [66-69]. Our observation that higher intake of legumes was associated with lower processing speed is in contrast with the finding of Chen et al [69], while Nooyens et al observed no association with legumes [68]. Mechanistically, legumes have been suggested to lower LDL cholesterol [70, 71] and reduce blood pressure [72]. Thus, data on the role of legumes in relation to cognition are mixed and warrant further study. Moreover, we observed that a higher

MUFA:SFA ratio was associated with a lower performance on the domain-specific test that was used to assess everyday memory. This result is in contrast with evidence supporting that MedDiet and high MUFA:SFA ratio is associated with both lower incidence of vascular comorbidity and better cognitive performance. Samieri et al. observed a strong association of the MUFA:SFA ratio with global cognition and verbal memory in the Nurse's Health Study, which was subsequently postulated to be due to a reduction of blood pressure and improvements in blood lipid profile, insulin sensitivity, and glycemic control by replacing dietary SFA with MUFA [24]. These results were further confirmed by the PREDIMED intervention study in which improved cognitive function was shown for the MedDiet intervention group supplemented with extra virgin olive oil in comparison to the control diet group [33].

Finally, there are several strengths and limitations of the present study that need to be discussed. First, we used a FFQ that was validated for energy intake, macronutrients, dietary fiber, and selected vitamins [38-40]. Second, we used multiple sensitive cognitive tests with proven validity [73-75]. Third, MedDiet adherence was assessed using the score developed by Trichopoulou [42], which is currently the most commonly used score in this research field. One of the limitations of our study is the cross-sectional design, which makes it impossible to draw conclusions about causality. Furthermore, although we carefully controlled for many of the major possible confounders, our study lacks information about the presence of a potential effect modifier, i.e. the APOE ε4 allele, which has been associated with a strong predisposition to neurodegenerative disorders [76]. At last, it should be noted that we studied multiple associations, which were not adjusted for multiple testing. Thus, some findings could be due to chance.

In conclusion, our study did not support the hypothesis that higher adherence to MedDiet is cross-sectionally associated with better cognitive function in adults aged 20-70 years, but did show an inverse association between MedDiet adherence and everyday memory.

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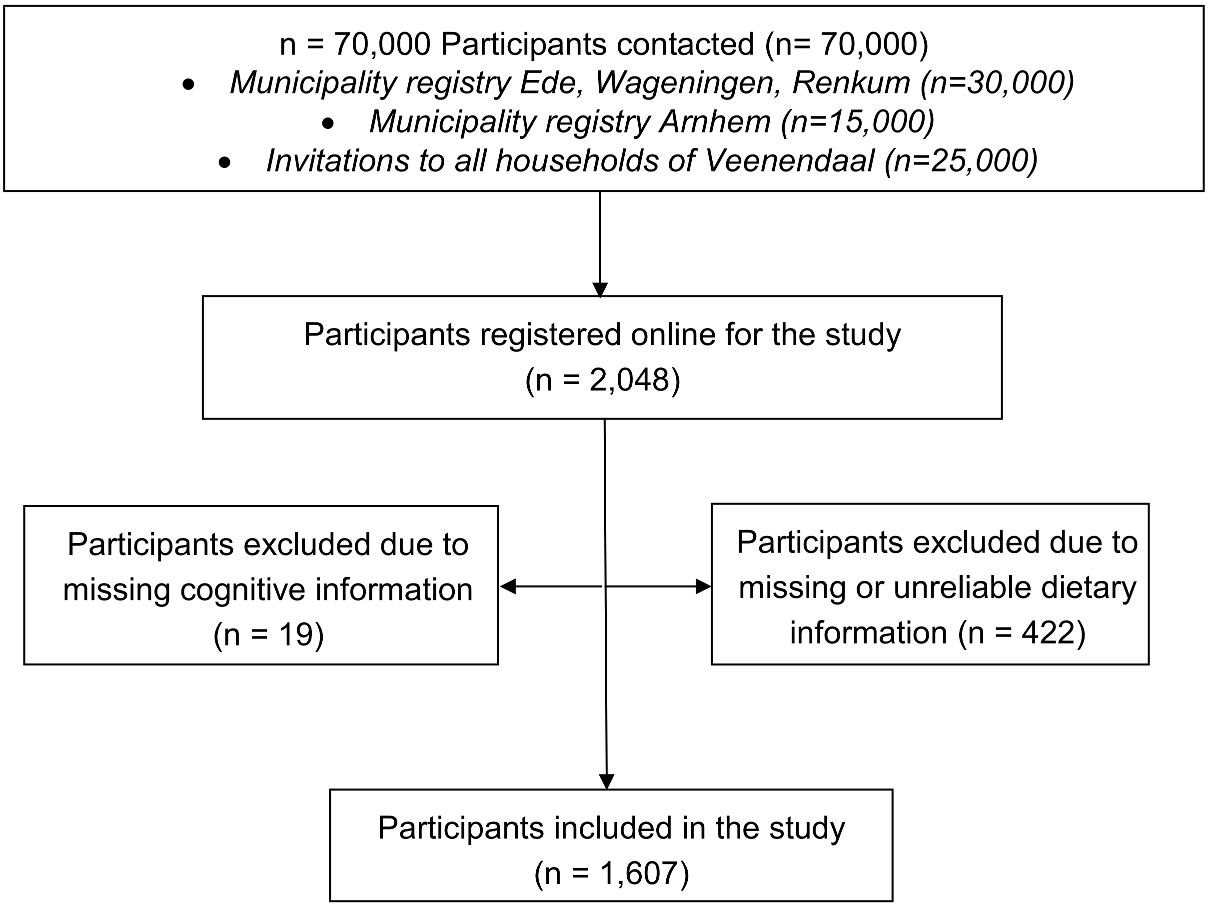

Figure 1. Study flow of the NQplus study.

Table 1 - Demographic, clinical and dietary characteristics by MedDiet Score category of Dutch participants of the NQplus study

Characteristic	***n***	**Mediterranean Diet Score**			***p*-value** [b]
		Low (0-3)	**Medium (4-5)**	**High (6-9)**	
n (%)	1,607	465 (29)	694 (43)	448 (28)	
Sex, *n* (%) males		229 (49)	384 (55)	224 (50)	0.07
Age (y)	1,607	51±12	53±12	54±11	**<0.0001**
Educational level, *n* (%)	1,600				**0.02**
Low		45 (10)	43 (6)	27 (6)	
Intermediate		156 (33)	205 (30)	125 (28)	
High		263 (57)	443 (64)	293 (66)	
BMI (kg/m^2)	1,606	26.5±4.3	25.8±4.0	25.5±4.0	**0.001**
Total energy intake (kcal/day)	1,607	2028 ± 540	2052 ± 568	2024 ± 571	0.66
Ethanol intake (g/day)[a]	1,607	4.1 (11.4)	8.3 (14.9)	9.2 (14.3)	**<0.0001**
Smoking status, *n* (%)	1,370				**0.002**
Never		215 (55)	296 (50)	187 (48)	
Former		130 (33)	244 (42)	180 (46)	
Current		45 (12)	49 (8)	24 (6)	
Moderate physical activity (min/wk)[a]	1,472	2160 (1500)	2120 (1685)	2285 (1781)	0.29
Hypertension, *n* (%)	1,607	113 (25)	176 (26)	100 (22)	0.50
Stroke, *n* (%)	1,607	3 (1)	6 (1)	5 (1)	0.75
Plasma total cholesterol (mmol/l)	1,552	5.38 ± 1.06	5.38 ±1.04	5.40 ± 1.04	0.93
Plasma LDL-cholesterol (mmol/l)	1,549	3.28 ± 0.94	3.26 ± 0.91	3.24 ± 0.93	0.76
Plasma HDL-cholesterol (mmol/l)	1,551	1.52 ± 0.43	1.57 ± 0.48	1.64 ± 0.44	**0.001**
Diabetes, *n* (%)	1,607	21 (5)	24 (4)	10 (2)	0.17
Depression, *n* (%)	1,607	45 (10)	51 (7)	36 (8)	0.36
Social clubs attended (*n*)[a]	1,361	1 (1)	1 (1)	1 (1)	0.72
>1 Supplement use, *n* (%)	1,607	169 (36)	297 (43)	198 (44)	**0.03**
Cognitive tests[c]					
Mean LFT (semantic memory and language production)	1,604	12.9 ± 3.3	13.0 ± 3.3	13.2 ± 3.6	0.38
SDMT (processing speed)	1,604	36.1 ± 6.8	35.9 ± 7.1	35.9 ± 7.3	0.87
Mean SRT (everyday memory)	1,582	8.2 ± 3.0	7.8 ± 2.8	7.7 ± 3.0	**0.009**

Values of continuous normally distributed variables are reported as mean ± SD.
[a] Values of continuous not normally distributed variables are reported as median (IQR).
[b] Significance (p<0.05) was tested with analysis of variance (ANOVA) or Kruskal-Wallis test for continuous variables or χ^2 analysis for categorical variables. Statistically significant *p*-values are reported in **bold**.
Low education level: no education or primary or lower vocational education as highest completed education; intermediate education level: completed lower secondary or intermediate vocational education; high education level: completed higher secondary education, higher vocational education or university.
[c] Higher score is better.
BMI: Body Mass Index. LFT: Letter Fluency Test; SDMT: Symbol Digit Modalities Test; SRT: Story Recall; SD: Standard Deviation; IQR: Interquartile Range.

Table 2 - Associations of MedDiet Score on cognitive performance among all Dutch participants of the NQplus study and among participants aged more than 50 years old

Cognitive performance	All participants					> 50 years old participants		
	n	**β (SE)**	***p*-value**¶	**PR**	**95%CI**	***n***	**β (SE)**	***p*-value**[a]
Semantic memory and language production (LFT)								
Unadjusted	1,604	0.110 (0.049)	**0.03**	0.98	0.90-1.06	1,063	0.054 (0.060)	0.37
Model 1	1,597	0.056 (0.047)	0.24	1.02	0.94-1.10	1,058	-0.039 (0.057)	0.50
Model 2	1,270	0.022 (0.053)	0.68	1.06	0.97-1.16	871	-0.074 (0.063)	0.24
Processing speed (SDMT)								
Unadjusted	1,604	-0.044 (0.102)	0.66	0.99	0.92-1.07	1,063	0.101 (0.114)	0.38
Model 1	1,597	0.021 (0.087)	0.81	1.00	0.93-1.07	1,058	-0.031 (0.107)	0.78
Model 2	1,270	0.003 (0.097)	0.98	0.99	0.91-1.07	871	-0.059 (0.117)	0.61
Everyday memory (SRT)								
Unadjusted	1,582	-0.101 (0.042)	**0.02**	1.03	0.94-1.12	1,046	-0.060 (0.050)	0.24
Model 1	1,575	-0.101 (0.040)	**0.01**	1.04	0.95-1.13	1,041	-0.114 (0.049)	**0.02**
Model 2	1,253	-0.107 (0.046)	**0.02**	1.03	0.93-1.14	858	-0.139 (0.055)	**0.01**

[a] Significance ($p<0.05$) was tested with linear regression analysis. Values are reported as β coefficients (SE) with statistically significant *p*-values in **bold.**
Model 1. Adjusted for age (years), sex, educational level (low/intermediate/high).
Model 2. Further adjusted for: BMI (kg/m^2), energy intake (kcal), moderate physical activity (min/week), smoking status (never/former/current), social activities (number of social clubs attended) and number of supplements used.

Abbreviations: SE, Standard Error; BMI, Body Mass Index

Table 3 - Associations of each MedDiet Score component on cognitive performance at baseline among all Dutch participants of the NQplus study

Cognitive performance	**Unadjusted model**		**Model 1**		**Model 2**		**Model 3**	
	β (SE)	***p*** [a]	**β (SE)**	***p*** [a]	**β (SE)**	***p*** [a]	**β (SE)**	***p*** [a]
Semantic memory and language production (LFT)								
Vegetables (g/day)	0.003 (0.001)	**0.002**	0.002 (0.001)	0.09	0.001 (0.001)	0.45	0.000 (0.001)	0.71
Legumes (g/day)	0.005 (0.003)	0.13	0.005 (0.003)	0.10	0.004 (0.003)	0.22	0.004 (0.003)	0.25
Fruits and nuts (g/day)	0.001 (0.001)	0.39	0.000 (0.001)	0.93	0.000 (0.001)	0.61	-0.001 (0.001)	0.51
Cereals (g/day)	0.000 (0.001)	0.94	-0.001 (0.001)	0.35	-0.001 (0.001)	0.57	0.000 (0.001)	0.88
Fish and seafood (g/day)	0.017 (0.005)	**0.001**	0.012 (0.005)	**0.02**	0.010 (0.006)	0.08	0.008 (0.006)	0.16
MUFA:SFA ratio	0.418 (0.357)	0.241	0.426 (0.340)	0.21	0.470 (0.374)	0.21	0.312 (0.405)	0.44
Meat (g/day)	-0.006 (0.002)	**0.007**	-0.003 (0.002)	0.24	0.001 (0.002)	0.75	0.001 (0.003)	0.62
Dairy products (g/day)	0.000 (0.000)	0.74	0.000 (0.000)	0.39	0.000 (0.001)	0.54	0.000 (0.001)	0.97
Ethanol (g/day)	0.014 (0.007)	**0.04**	0.017 (0.007)	**0.02**	0.018 (0.008)	**0.02**	0.016 (0.008)	**0.05**
Processing speed (SDMT)								
Vegetables (g/day)	0.006 (0.002)	**0.01**	0.002 (0.002)	0.21	0.003 (0.002)	0.22	0.005 (0.002)	**0.02**
Legumes (g/day)	-0.012 (0.006)	**0.07**	-0.006 (0.005)	0.25	-0.010 (0.006)	0.09	-0.014 (0.006)	**0.03**
Fruits and nuts (g/day)	-0.004 (0.001)	**0.005**	-0.002 (0.001)	0.10	-0.002 (0.001)	0.24	-0.002 (0.001)	0.22
Cereals (g/day)	0.009 (0.003)	**0.001**	0.000 (0.002)	0.99	0.000 (0.002)	0.89	0.001 (0.003)	0.79
Fish and seafood (g/day)	-0.018 (0.011)	0.10	-0.001 (0.009)	0.89	-0.008 (0.011)	0.47	-0.010 (0.011)	0.35
MUFA:SFA ratio	1.415 (0.741)	0.056	0.201 (0.627)	0.75	0.401 (0.687)	0.56	0.967 (0.745)	0.20
Meat (g/day)	-0.011 (0.005)	**0.02**	-0.003 (0.004)	0.47	-0.002 (0.005)	0.64	-0.003 (0.005)	0.45
Dairy products (g/day)	-0.001 (0.001)	0.50	0.001 (0.001)	0.42	0.001 (0.001)	0.44	0.001 (0.001)	0.40
Ethanol (g/day)	-0.055 (0.014)	**<0.0001**	0.017 (0.013)	0.19	0.020 (0.015)	0.17	0.024 (0.016)	0.13
Everyday memory (SRT)								
Vegetables (g/day)	-0.001 (0.001)	0.25	-0.002 (0.001)	0.09	-0.001 (0.001)	0.29	-0.001 (0.001)	0.47
Legumes (g/day)	-0.001 (0.003)	0.77	0.000 (0.003)	0.87	-0.001 (0.003)	0.73	0.000 (0.003)	0.97
Fruits and nuts (g/day)	-0.001 (0.001)	0.06	0.000 (0.001)	0.40	-0.001 (0.001)	0.27	-0.001 (0.001)	0.28
Cereals (g/day)	0.002 (0.001)	0.06	0.000 (0.001)	0.72	0.001 (0.001)	0.63	0.000 (0.001)	0.98
Fish and seafood (g/day)	-0.007 (0.005)	0.13	-0.004 (0.004)	0.40	-0.007 (0.005)	0.16	-0.005 (0.005)	0.37
MUFA:SFA ratio	-0.042 (0.311)	0.89	-0.377 (0.295)	0.20	-0.733 (0.325)	**0.02**	-0.552 (0.353)	0.12

Meat (g/day)	-0.003 (0.002)	0.14	-0.002 (0.002)	0.35	-0.002 (0.002)	0.34	-0.002 (0.002)	0.30
Dairy products (g/day)	0.000 (0.000)	0.75	0.001 (0.000)	0.15	0.001 (0.000)	0.11	0.001 (0.000)	0.24
Ethanol (g/day)	-0.021 (0.006)	**0.001**	-0.009 (0.006)	0.14	-0.013 (0.007)	0.06	-0.011 (0.007)	0.12

[a] Significance (p<0.05) was tested with linear regression analysis performed using each MedDiet component as primary predictor. Values are reported as β coefficients (SE) with statistically significant p-values in **bold**.
Model 1. Adjusted for age (years), sex, educational level (low/intermediate/high).
Model 2. Further adjusted for: BMI (kg/m^2), energy intake (kcal), moderate physical activity (min/week), smoking status (never/former/current), social activities (number of social clubs attended) and number of supplements used.
Model 3. Further adjusted for other MedDiet food groups
Abbreviations: SE, Standard Error; MUFA:SFA ratio, Monounsaturated Fatty Acids: Saturated Fatty Acids ratio; BMI, Body Mass Index

Supplemental Table 1 - Associations between MedDiet Score and cognitive performance among Dutch participants of the NQplus study aged 40+, 45+ and 50+ years of age

Cognitive performance	40+ years			45+ years			50+ years		
	n	**β (SE)**	***p*-value¶**	***n***	**β (SE)**	***p*-value¶**	***n***	**β (SE)**	***p*-value¶**
Semantic memory and language production (LFT)									
Unadjusted	1,363	0.074 (0.054)	0.17	1,239	0.068 (0.056)	0.23	1,063	0.054 (0.060)	0.37
Model 1	1,358	0.007 (0.051)	0.89	1,234	-0.004 (0.053)	0.94	1,058	-0.039 (0.057)	0.50
Model 2	1,103	-0.035 (0.057)	0.54	1,015	-0.036 (0.058)	0.54	871	-0.074 (0.063)	0.24
Processing speed (SDMT)									
Unadjusted	1,363	-0.009 (0.107)	0.93	1,239	0.020 (0.109)	0.86	1,063	0.101 (0.114)	0.38
Model 1	1,358	-0.036 (0.094)	0.70	1,234	-0.026 (0.098)	0.79	1,058	-0.031 (0.107)	0.78
Model 2	1,103	-0.068 (0.104)	0.51	1,015	-0.073 (0.107)	0.49	871	-0.059 (0.117)	0.61
Everyday memory (SRT)									
Unadjusted	1,344	-0.077 (0.046)	0.09	1,221	-0.064 (0.047)	0.18	1,046	-0.060 (0.050)	0.24
Model 1	1,339	-0.097 (0.044)	**0.03**	1,216	-0.091 (0.045)	**0.05**	1,041	-0.114 (0.049)	**0.02**
Model 2	1,089	-0.100 (0.049)	**0.04**	1,001	-0.101 (0.051)	**0.05**	858	-0.139 (0.055)	**0.01**

¶ Significance ($p<0.05$) was tested with linear regression analysis. Values are reported as β coefficients (SE) with statistically significant *p*-values in **bold.**
Model 1. Adjusted for age (years), sex, educational level (low/intermediate/high).
Model 2. Further adjusted for: BMI (kg/m^2), energy intake (kcal), moderate physical activity (min/week), smoking status (never/former/current), social activities (number of social clubs attended) and number of supplements used.

Abbreviations: SE, Standard Error; BMI, Body Mass Index