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1 **Higher Mediterranean diet scores are not cross-sectionally associated with**
2 **better cognitive scores in 20-70 year old Dutch adults: the NQplus study**

3

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17

18 **Abbreviation list**

19 AD; Alzheimer's Disease

20 AQuAA; Activity Questionnaire for Adults and Adolescents

21 BMI; Body Mass Index

22 CES-D; Center for Epidemiologic Studies Depression Scale

23 FFQ; Food Frequency Questionnaire

24 LFT; Letter Fluency Test

25 MCI; Mild Cognitive Impairment

26 MedDiet; Mediterranean Diet

27 METC-WU; Medical Ethical Committee of Wageningen University

28 MMSE; Mini-Mental State Examination

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

30 NQplus; Nutrition Questionnaires plus

31 PUFA; polyunsaturated fatty acids

32 RBMT; Rivermead Behavioural Memory Tests

33 SDMT; Symbol Digit Modalities Test

34 SQUASH; Short Questionnaire to Assess Health enhancing physical activity

35 SRT; Story Recall Test

36 **ABSTRACT**

37 Adherence to the Mediterranean Diet (MedDiet) has been suggested to reduce the
38 risk of age-related cognitive decline. Therefore, we hypothesized that adults
39 consuming a more Mediterranean-like diet were more likely to have better cognitive
40 scores. We investigated cross-sectional associations between MedDiet adherence
41 and cognitive performance using data of 1,607 Dutch men and women aged 20-70
42 years. Dietary intake was assessed using a 183-item Food Frequency Questionnaire.
43 MedDiet adherence was defined by a 0-9 point scale; which was based on intakes of
44 vegetables, legumes, fruits/nuts, cereals, fish/seafood, meat/poultry, dairy, ethanol
45 and the MUFA:SFA ratio. Cognitive function was assessed with a neuropsychological
46 test battery. Linear regression analyses adjusted for relevant covariates showed a
47 significant inverse association between MedDiet adherence and everyday memory:
48 specifically $\beta=-0.107\pm0.046$ points ($p=0.02$) for the total population and $\beta=-$
49 0.139 ± 0.055 points ($p=0.01$) for those aged ≥ 50 years. Further exploration of the
50 individual MedDiet food groups suggested that the association between MedDiet and
51 every day memory was predominantly driven by the MUFA:SFA ratio. Moreover,
52 associations were observed between higher ethanol intake with better semantic
53 memory and language production ($\beta=0.016\pm0.008$ $p=0.05$), higher vegetable intake
54 with better processing speed ($\beta=0.005\pm0.002$, $p=0.02$), and higher legumes intake
55 with poorer processing speed ($\beta=-0.014\pm0.006$, $p=0.03$). Thus, in this Dutch cohort,
56 higher MedDiet adherence was associated with poorer everyday memory.

57

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

60 **1. Introduction**

61

62 An increasing number of older adults is affected by cognitive decline and dementia
63 [1]. As there is no treatment for dementia yet, a preventive approach is of major
64 importance [2]. Diet has been suggested to play an important role in the development
65 of dementia and cognitive decline [3]. Therefore, diet quality scores, especially the
66 Mediterranean Diet (MedDiet) [4], have received increased attention during the past
67 years. MedDiet is characterized by a high consumption of plant-based foods
68 including fruits, vegetables, legumes, whole grain cereals, nuts and seeds; moderate
69 consumption of fish and wine; and a low consumption of dairy products and meat,
70 especially red meat, and high consumption of olive oil instead of butter. As a result,
71 MedDiet is a diet high in polyunsaturated fatty acids (PUFA), dietary fibers and
72 antioxidants, and has a high Monounsaturated Fatty Acids to Saturated Fatty Acids
73 (MUFA:SFA) ratio.

74 Adherence to MedDiet-like dietary patterns has been associated with a
75 decreased risk of coronary heart diseases, diabetes mellitus and hypertension as
76 well as a lower risk of depression, Mild Cognitive Impairment (MCI), and Alzheimer's
77 Disease (AD) [5]. Many of these neuropathological states are characterized by a
78 strong inflammatory component [6], high oxidative stress [7], vascular impairment [8],
79 and compromised glucose metabolism [9]. Various food groups of the MedDiet
80 pattern have been associated with a better regulation of these biological systems [10,
81 11] and may slow-down cognitive decline through these mechanisms [12-14].

82 However, studies examining associations between MedDiet pattern and cognitive
83 status or cognitive decline are still inconclusive [15-17]. In earlier cross-sectional
84 studies, Ye et al. showed a beneficial association between MedDiet and cognitive

85 performance [18], whereas Samieri et al. showed no association [19] and
86 Katsiardanis et al. showed a positive association in men, but a negative association
87 in women [20]. Also longitudinal studies showed mixed findings; the majority of these
88 studies observed an association between higher MedDiet adherence with less
89 cognitive decline [21-28], while no associations were observed in other studies [29-
90 32]. A first randomized controlled trial, the PREDIMED study, showed a protective
91 effect of MedDiet on cognitive decline [33].

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

102

103 **2. Methods and materials**

104

105 *2.1 Study population*

106 This study was conducted using cross-sectional data of the Nutrition Questionnaires
107 plus (NQplus) study; a large prospective cohort study among 2,048 Dutch men and
108 women aged 20-70 years living in the central part of the Netherlands [35, 36].

109 Participants were recruited from 2011 until 2013 via random sampling from the
110 municipality registries of Ede, Wageningen, Renkum, and Arnhem by sending
111 (electronic) invitations, and 2) sending invitation letters to all households of
112 Veenendaal. Of the total study population ($n=2,048$), $n=422$ were excluded due to
113 missing or unreliable dietary information (cut-offs for total energy <800 or $>4,000$
114 kcal/d for men and <500 or $>3,500$ kcal/d for women, based on [37]) and $n=19$ did
115 not (reliably) complete any of the three cognitive tests. Thus, the final sample for the
116 current analyses included 1,607 individuals. The study was approved by the Medical
117 Ethical Committee of Wageningen University (METC-WU) on July 7th 2011 (protocol
118 number 10/32) and was conducted according to the declaration of Helsinki. All
119 participants provided written informed consent.

120

121 *2.2 MedDiet Score*

122 All participants completed a 183-item semi-quantitative general Food Frequency
123 Questionnaire (FFQ) to assess habitual dietary intake during the past four weeks,
124 validated for energy intake, macronutrients, dietary fiber, and selected vitamins [38-
125 40]. Nutrient and food intakes were adjusted for energy by means of the residual
126 method [41]. A more detailed description of the FFQ can be found elsewhere [35].
127 Subsequently, a MedDiet Score indicating the degree of adherence to the traditional

128 MedDiet was calculated. The MedDiet Score was first constructed by Trichopoulou et
129 al. [42] and revised to include fish intake in 2002 [43]. For food groups that were
130 expected to be beneficial (vegetables, legumes, fruits and nuts, cereals, fish and
131 seafood and MUFA:SFA ratio), a value of 0 was assigned to persons whose energy-
132 adjusted consumption was below the median and a value of 1 to persons whose
133 consumption was at or above the median. In contrast, for food groups presumed to
134 be unhealthy (meat and poultry and dairy products), an opposite score was assigned.
135 Finally, for ethanol intake, a value of 1 was assigned to men and women with
136 moderate intakes (respectively between 10 and 50 g per day and between 5 and 25
137 g per day) and a value of 0 to people with intakes that were not within the sex-
138 specific range. Thus, the total MedDiet Score ranged from 0 (minimal adherence) to 9
139 (maximal adherence) and was categorized into three categories of increasing
140 adherence to the MedDiet: 0-3 (low adherence), 4-5 (intermediate adherence), and 6-
141 9 (high adherence).

142

143 *2.3 Cognitive performance*

144 Cognitive performance was assessed using three standardized neuropsychological
145 tests. The Letter Fluency Test (LFT) [44] was used to evaluate semantic memory and
146 language production. During the LFT participants received 60 seconds per trial to
147 generate as many words as possible using the letters D, A, and T. The Symbol Digit
148 Modalities Test (SDMT) [45, 46] was used to measure information processing speed
149 where individuals had to pair nine abstract symbols to the numbers 1 through 9 in a
150 written examination. The participant was limited to 60 seconds for completing this test
151 of which scores could range from 0 to 110. The Story Recall Test (SRT) is a subtest
152 of the Rivermead Behavioural Memory Tests (RBMT) and was used to assess

153 everyday memory [47]. For the SRT, participants were asked to listen to a story and
154 to recall the story immediately. For scoring, the story was split in 21 elements with 1
155 point given for each correctly recalled element or synonym and 0.5 point for each
156 partially correctly recalled element or synonym. All cognitive tests were performed
157 and scored according to a standardized protocol by trained research assistants.

158

159 *2.4 Other measures and covariates*

160 Anthropometric measurements were performed by trained research assistants
161 according to a standardized protocol. Height was measured without shoes with a
162 stadiometer (SECA, Germany) to the nearest 0.1 cm. Weight was measured using a
163 digital scale (SECA, Germany) to the nearest 0.1 kg after participants were asked to
164 take off their shoes, sweaters and to empty their pockets. Body Mass Index (BMI)
165 was calculated as weight (kg)/height (m)². Information on demographics and lifestyle
166 was obtained through online self-administered questionnaires. The general
167 questionnaire included questions about age, sex, education (low: no education or
168 primary or lower vocational education as highest completed education; intermediate:
169 completed lower secondary or intermediate vocational education; high: completed
170 higher secondary education, higher vocational education or university), history and
171 prevalence's of diseases including diabetes mellitus and cardiovascular health, social
172 activities, and smoking (never/former/current). Physical activity was assessed using a
173 combination of questions from the Short Questionnaire to Assess Health enhancing
174 physical activity (SQUASH) [48] and the Activity Questionnaire for Adults and
175 Adolescents (AQuAA) [49]. Since baseline data for physical activity were not
176 available for all participants, missing data were imputed using data obtained at 1-year
177 of follow-up. The Center for Epidemiologic Studies Depression Scale was used to

178 assess depressive symptoms [50]. Information on medication and nutritional
179 supplement use was registered during the physical examination. Fasting blood
180 samples were collected by venipuncture. Total cholesterol and HDL-cholesterol was
181 determined with enzymatic methods [51]. LDL-cholesterol was calculated with the
182 Friedewald equation [52].

183

184 *2.5 Statistical analyses*

185 Statistical analyses were performed using the software IBM SPSS statistic version
186 23.0 (IBM Statistics, IBM Corporation, New York, NY, USA). Participants'
187 characteristics were presented as percentages for categorical variables, mean (SD)
188 for normally distributed continuous variables and median (interquartile range) for non-
189 normally distributed continuous variables. To compare baseline characteristics
190 between MedDiet Score categories, the chi-square test was used for categorical
191 variables, one-way ANOVA for normally distributed continuous variables and Kruskal-
192 Wallis for non-normally distributed variables. Multivariate linear regression analyses
193 were used to assess associations between MedDiet Scores and cognitive
194 performance as a continuous outcome measure, shown as β (SE). The analyses
195 were performed for all participants and for three subgroups including people older
196 than 40, 45, and 50 years of age. To estimate the probability of poor cognitive
197 performance, Cox proportional hazard analysis with robust error variance were
198 conducted. MedDiet was included continuously and a participant belonging to the
199 worst 10% of cognitive performers was defined as a poor performer. Hazard ratios
200 with corresponding 95% confidence intervals (95%CI) were calculated. By assigning
201 a constant risk period to all participants in the study, the obtained hazard ratio can be
202 interpreted as a prevalence ratio (PR). This PR corresponds to the probability of

203 being defined as a poor cognitive performer with every MedDiet point increase.

204 Model 1 was adjusted for age, sex, and level of education (low, intermediate, high).

205 Model 2 was further adjusted for BMI (kg/m²), total energy intake (kcal), moderate
206 physical activity (min/week), smoking status (never/former/current), social activities
207 (number of social clubs attended), and number of dietary supplements used.

208 Covariate selection was primarily based on current literature. More specifically,
209 literature suggesting an association between the MedDiet and the specific covariate
210 combined with literature pointing towards an association between the specific
211 covariate and cognition. Multivariate regression analyses were also conducted for
212 each of the individual MedDiet food groups as the primary predictor. In these
213 MedDiet food group analyses, model 1 and model 2 were similar to the analyses for
214 the MedDiet score and model 3 was additionally adjusted for the other food groups
215 comprising the MedDiet score. A two-sided *p*-value < 0.05 was considered
216 significant.

217

218 **3. Results**

219

220 *3.1 Population characteristics*

221 The 1,607 participants were on average 52.9 years old and 52% were men. Median
222 BMI was 25.9 kg/m², 62% of the participants had a high education level, and 9%
223 were current smokers. Individual median (25-75th percentile) food group intakes were
224 128 (80-177) g/day for vegetables, 25 (15-40) g/day for legumes, 212 (97-256) g/day
225 for fruits and nuts, 191 (153-232) g/day for cereals, 17 (11-25) g/day for fish, 66 (41-
226 89) g/day for meat, 314 (206-437) g/day for dairy, and 7 (2-15) g/day for ethanol. The
227 mean MedDiet Score was 4.5±1.7 where 29% of the participants had a “low
228 adherence” (0-3 points), 43% a “medium adherence” (4-5 points) and 28% a “high
229 adherence” (6-9 points). Participants with a higher MedDiet adherence were
230 significantly older, higher educated, had a lower BMI, and higher HDL-cholesterol
231 levels, than those with a low MedDiet adherence (Table 1). Additionally, participants
232 with a higher MedDiet adherence were less often smokers, had a higher ethanol
233 intake, and were more likely to be supplement users. Furthermore, participants with a
234 high MedDiet adherence had lower intakes of proteins, total fat and saturated fat, and
235 higher intakes of PUFA, vitamin C, D, E, B6, retinol activity and folic acid equivalents
236 than participants with a low MedDiet adherence (data not shown). With respect to the
237 cognitive scores, semantic memory and language production and processing speed
238 scores, evaluated with LFT and SDMT, did not significantly differ between MedDiet
239 adherence categories. In contrast, everyday memory performance, assessed with
240 SRT, was significantly lower among participants with a higher MedDiet adherence.

241

242 *3.2 MedDiet and cognitive performance*

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

257

258 *3.3 MedDiet food groups and cognitive performance*

259 Linear regression analyses with individual MedDiet food groups showed a
260 positive association between ethanol consumption and semantic memory and
261 language, assessed with the LFT, in all models (β for model 3= 0.016 ± 0.008 per
262 g/day, $p=0.05$; Table 3)). Additionally, for each unit increase in fish and seafood
263 consumption (g/day), the LFT score increased with 0.012 points ($p=0.02$) in
264 model 1. This association attenuated after adjustment for demographic, lifestyle,
265 and nutritional factors. Regarding information processing speed, significant
266 associations were observed for vegetables ($\beta=0.005\pm 0.002$, $p=0.02$) and
267 legumes ($\beta=-0.014\pm 0.006$, $p=0.03$) (model 3). Moreover, a higher MUFA:SFA

268 ratio was inversely associated with lower SRT scores in model 2 ($\beta=-$
269 0.733 ± 0.325 , $p=0.02$), which attenuated after further adjustment for other
270 MedDiet food groups ($\beta=-0.552\pm 0.353$, $p=0.12$) (model 3).

271

272 **4. Discussion**

273

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

281 Our findings are consistent with other cross-sectional studies such as the Nurses'
282 Health Study ($n=10,670$ women aged 45-70 years) [19] and Greek Velestino Study
283 ($n=237$ men aged >65 years) [20], which also showed no associations between
284 MedDiet adherence and cognitive performance [19]. However, our results are in
285 contrast with a cross-sectional study performed in 1,269 Puerto Rican adults aged 45
286 to 75 years living in the Boston area, showing better cognitive function with higher
287 adherence to the MedDiet [18]. Four longitudinal studies are also consistent with our
288 findings and did not show an association between MedDiet adherence and cognitive
289 decline; i.e. the French SU.VI.MAX study with a follow-up of 13 years performed in
290 3,083 participants with a mean age of 65 years [29], the American Women's Health
291 Study with analyses on 4-year cognitive change in 6,174 women aged >65 years
292 [30], a Greek cohort of 732 men and women >60 years of age with Mini-Mental State
293 Examination (MMSE) scores determined 6-13 years after dietary evaluations [31],
294 and the Women's Antioxidant Cardiovascular Study performed in 2,504 US female
295 health professionals [32]. Conversely, our results are in contrast with multiple other

296 longitudinal studies, which observed that higher adherence to MedDiet was
297 associated with less cognitive decline [21-28].

298 The discrepancies between studies may be related to various methodologic
299 differences. First, the MedDiet score in most studies was based on population-
300 specific medians. If a study was conducted in a non-Mediterranean population, it is
301 very likely that these population-specific medians differ from population-specific
302 medians that would be obtained from a Mediterranean population. To illustrate,
303 compared to the dietary intakes in our population, the traditional Mediterranean diet
304 comprises higher mean intakes of fruit (410 g/d vs. 199 g/d) and vegetables (169 vs.
305 138 g/d), and lower intakes of dairy (219 vs. 332 g/d) and meat/poultry (44 vs. 67
306 g/d). Intakes of fish (16 vs. 21 g/d) and legumes (26 vs. 32 g/d) are rather
307 comparable [53]. As such, the attempt to define MedDiet adherence with a
308 population-based MedDiet Score could constrain the complexity of local diets and
309 hide potential healthy features of modern dietary patterns. For that reason, the ability
310 to represent the traditional dietary pattern of the Mediterranean area has been
311 criticized [54]. An alternative approach to population-based medians is to use
312 predefined absolute levels of intake of foods and food categories. This approach has
313 so far been used in only a few of the studies on dietary patterns in relation to cognitive
314 decline [25, 26, 28, 55-57] and incident Alzheimer's Disease [58]. As also discussed
315 by Morris in 2016, several advantages of the use of absolute food intake levels are
316 increased ability to compare findings among studies, optimum levels of brain benefit
317 for individual dietary components become clear, and the findings are more easily
318 translated into a dietary advice in servings per day for the general public [59].
319 Second, the dietary assessment methods differ between the studies. The French
320 study by Kesse-Guyot et al. used six 24-h recalls [29] and the remaining

321 observational studies all used FFQs. The applied FFQs may greatly vary, for instance
322 depending on the number of food items queried. As such, different FFQs may provide
323 dietary intake estimates that are not equally precise and accurate. Third, also the
324 cognitive tests used differ between studies, which may have affected the sensitivity to
325 detect potential associations as well. For instance, many of the studies discussed
326 above only used the MMSE or an adapted version of this test [20, 21, 23, 27, 28, 31]
327 or they only showed an association with the MMSE and not with the domain-specific
328 neuropsychological tests if these were performed as well [18, 22]. It should be noted
329 here that the MMSE is designed as a cognitive screening instrument and considered
330 global and non-sensitive to assess cognitive functioning [60], whereas the domain-
331 specific neuropsychological tests are considered to be more sensitive to detect
332 cognitive deficits. Fourth, there were large differences in sample size between
333 studies and prospective studies had varying follow-up times. Fifth, also the age range
334 of the population under study may have been an important factor contributing to the
335 detection of potential associations. Contrasting with most prior studies, the current
336 cohort included participants with a relatively large age range (20-70 years) and a
337 relatively young mean age (53 years). However, we also conducted sensitivity
338 analyses using data of participants aged >50 years only, which did not result in
339 different findings compared to the findings of the total population. Finally, MedDiet is
340 an *a priori* defined dietary pattern taking into account possible synergistic and
341 antagonistic interactions between food groups of a complex diet. The individual
342 MedDiet food groups received equal weights, i.e. contribute equally to the MedDiet
343 score. It is very likely though that not all food groups have the same impact on health
344 outcomes and thus also not on cognitive performance [61]. However, Trichopoulou et
345 al observed lower mortality rates with increasing MedDiet scores, where such

346 association was much less evident when studying the individual components,
347 suggesting that the sum score is the important exposure [43]. Furthermore, certain
348 food groups of the MedDiet Score are correlated (e.g. fruits, vegetables, and dietary
349 fiber [62]) and consequently indirectly weigh more heavily with the score than others.
350 All in all, aforementioned aspects may partly explain the different findings across
351 studies.

352 When looking at the individual food groups, we observed a positive association of
353 ethanol consumption with semantic memory and language production, but a
354 marginally inverse association with everyday memory. As reported by a recent review
355 [63], the impact of alcohol consumption on cognitive performance is still not clear.
356 Previous studies suggest associations of light-to-moderate alcohol consumption with
357 a reduced risk of dementia and AD, but associations with vascular dementia,
358 cognitive decline and pre-dementia are less clear. The positive association as
359 observed in our study may be due to the antioxidant properties of phenols and
360 polyphenols in wine, which is the typical MedDiet beverage [64, 65] and was also the
361 most preferred alcoholic beverage in the current study population [36]. We also
362 showed a positive association of vegetable intake with information processing speed.
363 Vegetable intake has also been beneficially linked with cognition in previous studies
364 studying the MedDiet [24, 28] and also in other cohorts focusing on vegetable intake
365 in relation to cognitive decline [66-69]. Our observation that higher intake of legumes
366 was associated with lower processing speed is in contrast with the finding of Chen et
367 al [69], while Nooyens et al observed no association with legumes [68].
368 Mechanistically, legumes have been suggested to lower LDL cholesterol [70, 71] and
369 reduce blood pressure [72]. Thus, data on the role of legumes in relation to cognition
370 are mixed and warrant further study. Moreover, we observed that a higher

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

382 Finally, there are several strengths and limitations of the present study that need
383 to be discussed. First, we used a FFQ that was validated for energy intake,
384 macronutrients, dietary fiber, and selected vitamins [38-40]. Second, we used
385 multiple sensitive cognitive tests with proven validity [73-75]. Third, MedDiet
386 adherence was assessed using the score developed by Trichopoulou [42], which is
387 currently the most commonly used score in this research field. One of the limitations
388 of our study is the cross-sectional design, which makes it impossible to draw
389 conclusions about causality. Furthermore, although we carefully controlled for many
390 of the major possible confounders, our study lacks information about the presence of
391 a potential effect modifier, i.e. the APOE ϵ 4 allele, which has been associated with a
392 strong predisposition to neurodegenerative disorders [76]. At last, it should be noted
393 that we studied multiple associations, which were not adjusted for multiple testing.
394 Thus, some findings could be due to chance.

395 In conclusion, our study did not support the hypothesis that higher adherence to
396 MedDiet is cross-sectionally associated with better cognitive function in adults aged
397 20-70 years, but did show an inverse association between MedDiet adherence and
398 everyday memory.

399

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416 **Author Contributions:** E.J.M.F. and J.H.M.d.V. designed the NQplus study;
417 A.v.d.W. and L.v.L. collected the data; A.B. and E.M.B-B. analysed the data; A.B.
418 drafted the manuscript; E.M.B-B. and O.v.d.R. finalized the manuscript. All authors
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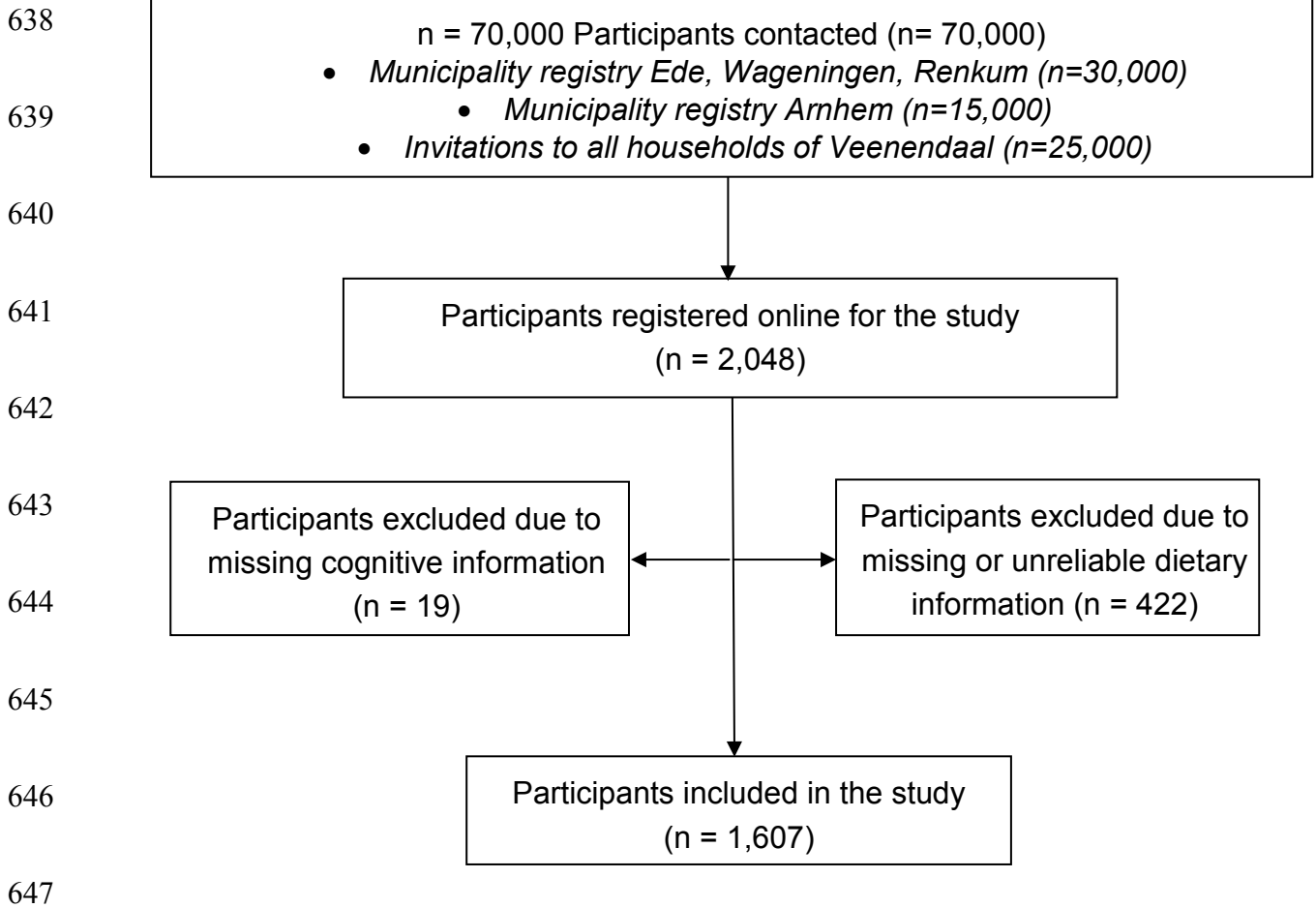
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637



648 **Figure 1. Study flow of the NQplus study.**

649

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
<i>Cognitive tests^c</i>					
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 \pm 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		
	<i>n</i>	β (SE)	<i>p</i> -value [†]	PR	95%CI	<i>n</i>	β (SE)	<i>p</i> -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/m²), 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		
	<i>n</i>	β (SE)	<i>p</i> -value [¶]	<i>n</i>	β (SE)	<i>p</i> -value [¶]	<i>n</i>	β (SE)	<i>p</i> -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/m²), 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