

Effect of an internet-based, personalized nutrition randomized trial on dietary changes associated with the Mediterranean diet: the Food4Me Study

Article

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Title

Effect of an internet-based personalized nutrition randomized trial on dietary changes associated with the Mediterranean diet: the Food4Me study^{1,2}

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1 **Abstract (words count=286)**

2 **Background**

3 Little is known about the efficacy of personalized nutrition (PN) interventions for improving
4 consumption of a Mediterranean diet (MD).

5 **Objective**

6 The objective was to evaluate the effect of a PN intervention on dietary changes associated
7 with the MD.

8 **Design**

9 Participants (n=1607) were recruited into a 6-month, internet-based, PN randomized
10 controlled trial (Food4Me) designed to evaluate the effect of PN on dietary change.
11 Participants were randomized to receive conventional dietary advice (Control; L0) or PN
12 advice based on current diet (L1), diet and phenotype (L2) or diet, phenotype and genotype
13 (L3). Dietary intakes from food frequency questionnaires at baseline and 6 months were
14 converted to a MD score. Linear regression compared participant characteristics between
15 high (>5) and low (\leq 5) MD scores. Differences in MD scores between treatment arms at
16 month 6 were evaluated using contrast analyses.

17 **Results**

18 At baseline, high MD scorers had 0.5 kg/m² lower BMI ($P=0.007$) and 0.03 higher PAL
19 ($P=0.003$) than low scorers. MD scores at month 6 were greater in individuals randomized to
20 PN (L1, L2 and L3) compared with Control (PN: 5.20 ± 0.05 vs. Control: 5.48 ± 0.07
21 respectively; $P=0.002$). There was no significant difference in MD scores at month 6

22 between PN advice based on L1 vs. L2 and L3. However, differences in MD scores at month
23 6 were greater in L3 vs. L2 (L3: 5.63 ± 0.10 vs. L2: 5.38 ± 0.10 respectively; $P=0.029$).

24 **Conclusions**

25 Higher MD scores at baseline were associated with healthier lifestyles and lower adiposity.
26 Following the intervention, MD scores were greater in individuals randomized to PN
27 compared with the Control, with the addition of DNA-based dietary advice resulting in the
28 largest differences in MD scores. Although differences were significant, their clinical
29 relevance is modest.

30 INTRODUCTION

31 The burden of non-communicable diseases and obesity has grown rapidly in the past 30
32 years (1), with poor lifestyle choices, including unhealthy dietary patterns and increased
33 sedentary behaviors, as the primary causes (2). Diets with high intakes of energy-dense and
34 high-refined carbohydrate foods, are associated with obesity and type II diabetes (3, 4). In
35 contrast, the Mediterranean diet (MD), characterized by low intakes of sugary snacks and
36 beverages, and high intakes of fruit and vegetables has been consistently associated with a
37 beneficial effect on health (5), including non-communicable diseases (6, 7) and obesity (8-
38 10). In addition, randomized controlled trials (RCTs) show that MD-based interventions
39 reduce risk of cardiovascular disease in both primary and secondary prevention studies (11,
40 12).

41 Several approaches for scoring the MD have been developed (13, 14), including the
42 PREDIMED 14-point score (15, 16). The latter identified 14 dietary components that best
43 characterized the MD and demonstrated that higher MD scores were associated with up to
44 30% lower incidence of cardiovascular events (15, 17). Based on such evidence, there is
45 strong reason to believe that changing dietary intakes so that they align better with the MD
46 would produce substantial public health benefit (18). However, achieving such changes may
47 be challenging with current intervention strategies using “one size fits all” approaches,
48 which have shown limited effect on population-level disease and obesity prevalence (1).
49 Alternative strategies for facilitating improvements in diet and lifestyle include personalized
50 nutrition (PN) approaches (19, 20). PN interventions are tailored to key characteristics of the
51 individual participants, including current diet, phenotype and genotype. Although genetic-
52 based personalized interventions designed to change risk behaviors (e.g. smoking and diet)

53 have shown mixed results (21), recent genetic-based PN interventions have demonstrated
54 encouraging changes in dietary behaviors (20, 22). Furthermore, internet-based dietary
55 interventions offer the advantage of being scalable and more cost-effective than face-to-
56 face interventions (23). The Food4Me proof-of-principle (PoP) study was the first internet-
57 based study to demonstrate that PN advice was more effective in improving dietary intakes,
58 including lowering intakes of red meat and improving diet quality when compared with
59 conventional “one size fits all” population-based advice (24). Given that the MD is widely
60 recognized as a healthy eating pattern, in this analysis we used the MD score an external
61 (objective) reference to investigate whether internet-based PN advice improved the
62 "healthfulness" of participants' diets.

63 The Food4Me PoP study was a 6-month, internet-based, PN intervention across 7 European
64 countries designed to improve dietary intakes. The present paper aimed to evaluate the
65 effect of this PN intervention by comparing differences in MD score at month 6 between
66 treatment groups.

67

68 **METHODS**

69 **Study design**

70 The Food4Me PoP study (25) was a 6-month, 4-arm, internet-based, randomized controlled
71 trial (RCT) conducted across 7 European countries, designed to compare the effects of
72 personalized dietary and physical activity advice with generalized advice in changing dietary
73 and lifestyle behaviors (26). The intervention was intended to emulate a “real-life” internet-
74 based PN service, where all advice was delivered via the internet. Participants were recruited

75 to the intervention study via the Food4Me website (25) and were asked via email to complete
76 online questionnaires and provide biological samples at 3 fixed time-points i.e. after baseline
77 and 3 and 6 months. Online information about the study was available to participants
78 including e.g. video clips describing how to make anthropometric measurements and to
79 collect biological samples. This design was complimented by an online interface through
80 which participants could interact via email with the dietitians, nutritionists and researchers at
81 each center during the 6 months intervention. The primary aims of the Food4Me study were
82 to i) determine whether personalization of dietary advice assisted and/or motivated
83 participants to choose a healthier diet in comparison with non-personalized, conventional
84 healthy eating guidelines and ii) whether personalization based on individualized phenotypic
85 or phenotypic and genotypic information was more effective in assisting and/or motivating
86 study participants to make, and to sustain, appropriate healthy changes, than personalization
87 based on diet alone. To address these aims, participants were randomized to one of four
88 intervention arms using an urn randomization scheme (27) and received either non-
89 personalized, generalized dietary advice (Control; Level 0), or one of three levels of PN. To
90 encourage dietary and lifestyle change, behavioral change techniques derived from work by
91 Michie et al. on smoking cessation and dietary behavior change were used (28, 29).
92 Participants were asked to complete online an food frequency questionnaire (FFQ), Baecke
93 Physical Activity Questionnaire, wear accelerometers and provide self-measured
94 anthropometric information, buccal swabs and dry blood spot cards (further details are
95 provided below).

96

97 **Ethical approval and participant consent**

98 1607 participants were randomized into the study and were recruited between August 2012
99 and August 2013 from the following centers: University College Dublin (Ireland), Maastricht
100 University (The Netherlands), University of Navarra (Spain), Harokopio University (Greece),
101 University of Reading (United Kingdom, UK), National Food and Nutrition Institute (Poland)
102 and Technical University of Munich (Germany). The Research Ethics Committees at each
103 University or Research Centre delivering the intervention granted ethical approval for the
104 study. The Food4Me trial was registered as a RCT (NCT01530139) at Clinicaltrials.gov. All
105 participants expressing an interest in the study were asked to sign online consent forms at
106 two stages in the screening process. These consent forms were automatically directed to the
107 local study investigators to be counter-signed and archived (26).

108

109 **Eligibility criteria**

110 Based on sample size calculations we aimed to recruit a total of 1,540 study participants. As
111 per the eligibility criteria, participants aged ≥ 18 years of age were included in the study. The
112 following sets of exclusion criteria were applied: (i) pregnant or lactating; (ii) no or limited
113 access to the Internet; (iii) following a prescribed diet for any reason, including weight loss,
114 in the last 3 months; (iv) diabetes, coeliac disease, Crohn's disease, or any metabolic disease
115 or condition altering nutritional requirements such as thyroid disorders, allergies or food
116 intolerances.

117

118 **Intervention arms**

119 Individuals were allocated to each treatment using an urn randomization scheme. Those
120 randomized to Level 1 (L1) received personalized dietary advice based on current diet and

121 physical activity (PA) alone, Level 2 (L2) received personalized dietary advice based on
122 dietary, PA and phenotypic data and Level 3 (L3) received personalized dietary advice based
123 on dietary, PA, phenotypic and genotypic data. Personalized dietary feedback was based on
124 how intakes of specific nutrients compared with recommended intakes, which was then
125 translated into advice on changing intakes of food groups (fruits and vegetables, whole grain
126 products, fish, dairy products and meat). Personalized phenotypic feedback utilized
127 anthropometric measurements and nutrient- and metabolic-related biomarkers to derive
128 personalized feedback and specific variants in five nutrient-responsive genes were used to
129 provide personalized genotypic feedback. Personalized advice on PA was based on
130 responses to the Baecke Questionnaire and accelerometer data.

131 Participants randomized to the control group (L0) received dietary advice based on
132 population-level healthy eating guidelines. This non-personalized dietary advice was derived
133 from national dietary recommendations in each of the seven European countries and
134 included generalized advice on the food groups listed above. In addition, these
135 recommendations included a generic PA recommendation. Further details of the Food4Me
136 PoP study are provided elsewhere (26).

137

138 **Personalized feedback report**

139 Participants randomized to L1, L2 and L3 received personalized feedback reports via email at
140 baseline, month 3 and month 6 of the intervention. For those randomized to PN, algorithms
141 were used to provide participants with 3 specific dietary goals according to the individual's
142 intakes of nutrients. For participants randomized to L2 and L3, the dietary advice was also
143 based on phenotypic data (L2) and phenotypic plus genotypic data (L3). Reported intakes

144 were compared with recommended intakes and determined to be adequate, high or low. If
145 intakes were too high or too low, contributing foods were identified and specific messages
146 developed to advise change in intake of those foods. Estimations of healthy behaviors were
147 explained using a three-color sliding scale: green representing “Good, no change
148 recommended,” amber representing “Improvement recommended” and red representing
149 “Improvement strongly recommended”. For the genotype-based information, risk was
150 indicated using “Yes” or “No” according to whether the participant did, or did not, carry the
151 higher risk variant for each of the 5 nutrient-related genes included in the study.
152 Additionally, each report contained a personalized message from the dietitian/ nutritionist
153 to the participant. Further details of the protocol are provided elsewhere (26).

154

155 **Participant characteristics and dietary intakes**

156 Following randomization, participants completed online questionnaires on socio-
157 demographic, health and anthropometric characteristics at baseline. Participants also
158 completed an online FFQ to estimate usual dietary intake at baseline and at months 3 and 6
159 of the intervention. This FFQ, which was developed and validated for the Food4Me Study
160 (30, 31), included 157 food items consumed frequently in each of the 7 recruitment
161 countries. Intakes of foods and nutrients were computed in real time using a food
162 composition database based on McCance & Widdowson’s “The composition of foods” (32).
163 Intakes were assessed using a standardized set of recommendations (26) for foods and food
164 groups that were integrated and harmonized across 8 European countries (UK, Ireland,
165 Germany, The Netherlands, Spain, Greece, Poland and Norway) (33-36). Further details are
166 provided elsewhere (30).

167 Adherence to the MD was estimated based on the PREDIMED 14-point criteria (11, 16)
168 **(Supplemental Table 1)**. FFQs at baseline and month 6 were used to derive each of the
169 following criteria: higher intake of olive oil than other culinary fat, higher intake of white
170 meat than red meat, high intake of fruit (including natural fruit juice), vegetables, olive oil,
171 legumes, nuts, fish, wine and tomato-based sauces and a limited intake of red and
172 processed meats, fats and spreads, soft drinks and commercial bakery goods, sweets and
173 pastries (11). Participants scored 1 point for each of the 14 criterion they met and 0 for each
174 they did not meet; points were summed to create an overall MD score, ranging from 0-14
175 (16). A dichotomous variable for MD score was created: “Low” (operationalized as a score
176 ≤ 5) and “High” (score >5) based on a median MD score of 5 at baseline.

177

178 **Anthropometric, socio-demographic and physical activity measures**

179 Body weight (kg), height (m) and waist circumference (WC; cm) were self-measured and
180 self-reported. Participants were provided with information sheets and online video
181 instructions in their own language on how to complete the measurements. Body mass index
182 (BMI; kg/m^2) was estimated from body weight and height. Self-reported measurements
183 were validated in a sub-sample of the participants ($n=140$) and showed a high degree of
184 reliability (37). Physical activity level (PAL, ratio between total energy expenditure and basal
185 metabolic rate (BMR)), moderate and vigorous PA (MVPA), the percentage of individuals
186 meeting PA recommendations (>150 min moderate PA or >75 min vigorous PA or an
187 equivalent combination of moderate and vigorous PA per week (38)) and time spent in
188 sedentary behaviors (SB) were estimated from triaxial accelerometers (TracmorD, Philips
189 Consumer Lifestyle, The Netherlands).

190 Participants self-reported smoking habits and occupations. Occupations were grouped
191 according to the European classifications of occupations and the respective salaries of these
192 occupations. If the standard deviation of the salary for each occupation was >0.5 away from
193 the mean European salary they were placed in Group 1, between 0.5 to -0.5 were placed
194 into Group 2 and <-0.5 were placed into Group 3. The following groups and group names
195 were generated: Group 1: “Professional and managerial”; Group 2: “Intermediate”; Group 3:
196 “Routine and manual” (39, 40). Categories for “Students” and “Retired and unemployed”
197 were added.

198

199 **Statistical analyses**

200 Data were analyzed using Stata (version 13; StataCorp, College Station, TX, USA) based on
201 intention-to-treat (ITT) analysis of all individuals randomized into the intervention with
202 baseline data ($n=1480$). Logistic and multiple linear regression were used to test for
203 significant differences between groups at baseline for categorical and continuous variables
204 respectively. Comparisons between low and high MD scores at baseline were adjusted for
205 baseline age, sex and country. Physical activity outcomes were further adjusted for baseline
206 wear time and season. To answer our primary research question (“What effect does a PN
207 intervention have on dietary changes associated with the MD?”) we used a linear mixed
208 model (LMM) with fixed effects for participants with time-point (baseline and follow-up),
209 baseline age, sex and country as covariates. To remove treatment differences at baseline
210 the parameter estimates (treatment arms) were specified at month 6 only. Contrast
211 analyses to compare between treatment arms. The principal assessment of differences in
212 MD scores used Contrast 1 comparing L0 (Control) with the mean of L1-L3 (mean of all three

213 personalized nutrition arms). Contrast 2, comparison of L1 with L2-L3, tested whether
214 personalization based on phenotypic or phenotypic plus genotypic information differed
215 from that based on dietary assessment only. Contrast 3, comparison of L2 with L3, tested
216 whether the addition of genotypic information promoted changes which differed from
217 those using phenotypic and dietary information only. Based on recommendations by White
218 *et al.* (41) for the robust analysis of RCTs with missing outcome data, sensitivity analyses
219 investigated the impact of running an ITT analysis based on the last observation carried
220 forward (LOCF) method (n=1480) and a complete case (CC) analysis (n=1270). Additional
221 sensitivity analyses adjusted for over- and under-reporters of total energy intake: under-
222 reporting was operationalized as energy intake less than $BMR \times 1.1$ (42), where BMR was
223 calculated according to the Oxford equation (43) and over-reporting as more than 4500
224 kcal/day (44). Furthermore, analyses in individuals who were randomized to L3 were
225 stratified by carriage of the risk genotype for *MTHFR*, *FTO*, *TCF7L2*, *APOE(e4)* and *FADS1* to
226 identify genes that may be driving any added benefit of providing genetic information.
227 Participants were coded "0" for no copies of the risk allele, "1" if they had one copy of the
228 risk allele and "2" if they had two copies of the risk allele for each gene. A second variable
229 was generated to indicate if an individual had no copies ("0"), one copy ("1") or two copies
230 ("2") of the risk genotype for any of these genes. Results were deemed significant at $P < 0.05$.

231

232 RESULTS

233 A total of 1607 participants were randomized into the intervention. Following dropouts
234 immediately after randomization (n=127), 1480 participants provided dietary data at
235 baseline and after 6 months intervention, outcome dietary data were available for 1270

236 participants (**Figure 1**). Information on how included participants compared with those who
237 dropped out are summarized in **Supplemental Table 2**.

238

239 **Socio-demographic, anthropometric and health-related characteristics by MD score**

240 The average age of participants was 39.9 (13.0) years, 59% were female and 97% were
241 Caucasian (**Table 1**). Participants with a high MD score at baseline were on average 1.5 years
242 older than those with a low score ($P=0.005$). There were no differences in sex or ethnicity
243 between high and low scorers. 39% of participants were in professional and managerial
244 occupations, whereas 26 and 10% of participants were in intermediate and routine and
245 manual occupations, respectively. No significant differences in occupations were observed
246 between high and low MD scorers (Table 1).

247 High MD scorers weighed 2.3 kg less ($P=0.003$), had 0.5 kg/m² lower BMI ($P=0.007$) and 1.9
248 cm lower WC ($P<0.001$) than low scorers (Table 1). High MD scorers spent less time in
249 sedentary behaviors ($P=0.005$), had higher PAL ($P=0.003$) and MVPA ($P<0.001$) and met
250 more PA recommendations ($P=0.022$) than low scorers (Table 1). More low MD scorers
251 wanted to lose weight than high scorers (49 vs. 45%; $P=0.041$; Table 1), whereas more high
252 scorers reported being on a restricted diet (9 vs. 6%; $P=0.014$; Table 1).

253 On average, 6% fewer high MD scorers were on prescribed medication ($P=0.004$) than low
254 scorers. No significant differences in total blood cholesterol or percentage of smokers were
255 identified between MD scorers (Table 1).

256

257 **Dietary intakes by MD score**

258 Although energy intakes did not differ, EI: BMR ratio was higher in high MD scorers than low
259 MD scorers (1.72 ± 0.70 vs. 1.62 ± 0.63); $P=0.012$; **Table 2**). As expected, high MD scorers
260 had lower percentage energy intakes from total fat ($P<0.001$) and SFA ($P<0.001$) and higher
261 percentage energy intakes from MUFA ($P=0.009$) and PUFA ($P<0.001$) than low scorers
262 (Table 2). Percentage energy intakes from protein and sugars were 1.2 and 1.7% higher in
263 high MD scorers than low scorers ($P<0.001$), whereas percentage energy intakes from
264 carbohydrates were 0.8% lower ($P=0.042$). Salt intake did not differ significantly between
265 high and low MD scorers (Table 2).

266 More high MD scorers met the recommendations for oily fish (36% more; $P<0.001$), red
267 meat (7%; $P=0.006$) and fruit and vegetables (41%; $P<0.001$) than low scorers (Table 2). No
268 significant differences in wholegrains or low-fat dairy products were observed between MD
269 scorers (Table 2).

270

271 **Differences in MD scores following intervention**

272 After 6 months intervention, improvements in MD scores were greater in individuals
273 randomized to PN (mean L1, L2 and L3) compared with Control (L0) (PN: 5.20 ± 0.05 vs.
274 Control: 5.48 ± 0.07 , respectively, $P=0.002$; **Table 3**). MD scores at month 6 in participants
275 receiving PN advice based on current diet alone (L1) were not significantly different from
276 those randomized to L2 and L3 (who received advice based on current diet + phenotype (L2)
277 and diet + phenotype + genotype (L3); Table 3). However, MD scores at month 6 for
278 participants receiving PN advice in L3 (diet + phenotype + genotype) were greater than in
279 participants in L2 at month 6 (L3: 5.63 ± 0.10 vs. L2: 5.38 ± 0.10 , respectively, $P=0.029$; Table

280 3). MD scores at month 3 between interventions arms were lower in those randomized to
281 L2 compared with L3 ($P=0.010$; **Supplemental Table 3**).

282 MD scores at month 6 when stratified by country were not significantly different for Control
283 vs. PN (mean L1, L2 and L3). For the Netherlands only, MD scores was higher for L3
284 participants than for L2 participants ($P=0.013$; **Supplemental Table 4**). When Mediterranean
285 (Greece and Spain) and non-Mediterranean countries (the UK, Ireland, the Netherlands,
286 Germany and Poland) were grouped, the effect of PN (mean L1, L2 and L3) vs. Control on
287 MD scores at month 6 was significant in non-Mediterranean countries only (PN: 5.31 ± 0.09
288 vs. Control: 5.02 ± 0.06 ; $P=0.007$; data not shown).

289

290 **Sensitivity analyses**

291 To determine whether our findings were robust to alternative analysis strategies, an ITT
292 analysis based on LOCF and a CC analysis were also undertaken. Results showed that the
293 pattern of significant findings were consistent across LMM, LOCF and CC analysis and that
294 use of LMM produced the most conservative estimate of MD score at month 6
295 (**Supplemental Table 5**).

296 To understand the influence of genetic risk on MD score at month 6, analyses were stratified
297 by non-risk and risk carriers for each of the 5 genes. For *FTO* and *MTHFR* genes, MD score at
298 month 6 was higher in individuals randomized to PN compared with the Control in risk-
299 carriers only. The effect of PN on MD score at month 6 was similar for risk and non-risk
300 carriers for *APOE* and *TCF7L2* but was only significant for non-risk carriers of *FADS1*
301 (**Supplemental Table 6**). As summarized in **Supplemental Table 7**, disclosure of genetic

302 information made little difference to MD score at month 6 for individuals randomized to PN
303 compared with the Control, although differences were apparent between L2 and L3.
304 Adjustment for under- and over-reporters did not change the pattern of results (data not
305 shown). Stratifying analyses by carriage of a risk allele for any one of the 5 genes studied
306 showed that in participants with two copies of a risk allele of any of the 5 genes, MD scores
307 at month 6 were greater between participants randomized to PN (mean L1, L2 and L3) than
308 those randomized to Control (5.69 ± 0.11 vs. 5.14 ± 0.08 ; $P < 0.001$; data not shown).
309 However, no significant differences in MD between PN and Control were observed in
310 individuals carrying one or no copies of the risk alleles for any of the 5 genes and no
311 significant differences between levels of PN were observed (data not shown).

312

313 **DISCUSSION**

314 **Main findings**

315 The main findings from our secondary analysis in the Food4Me PoP study show that PN
316 advice aiming to improve dietary intakes brought about changes in dietary behaviors that
317 were in line with the MD. We observed that PN was more effective than generalized dietary
318 advice (Control) in improving MD scores. Furthermore, the addition of genotypic
319 information to PN advice improved MD scores compared with PN advice based on diet and
320 phenotype alone.

321

322 **Comparison with other studies**

323 The aim of the Food4Me PoP study was to improve dietary intakes of food groups and
324 nutrient (26) and findings from this intervention demonstrated that PN (mean L1, L2 and L3)

325 was more effective than “one size fits all” generalized dietary advice for lowering red meat
326 (8.5%; $P=0.046$), salt intake (6.3%; $P=0.008$) and improving HEI (2.6%; $P=0.010$) (24). The
327 present findings confirm that changes in dietary intakes associated with PN advice also
328 result in significant improvements in dietary patterns, as estimated from the 14-point
329 PREDIMED MD score. In contrast to the main analysis of the PN intervention, our secondary
330 analysis of difference in MD scores between treatment arms suggest that the provision of
331 genotype-based advice offers added benefit compared to PN advice based on diet and
332 phenotype only. Although previous findings relating to whether the provision of genetic
333 information improves dietary behaviors are encouraging (20, 22), further research is needed
334 to determine if the apparent benefit is generalizable (e.g. applies to multiple types of
335 genetic information and in different population groups) and results in sustained
336 improvements in both diet and health outcomes. Moreover, the Food4Me PoP study was
337 designed to improve overall diet, and not MD in particular, and thus the present findings
338 should not be considered in isolation.

339 Previous studies have evaluated the associations between adherence to the MD and health
340 outcomes, including obesity, metabolic syndrome and type II diabetes. We confirmed
341 findings from the PREDIMED study, showing that individuals with low MD adherence were
342 more likely to be current smokers, have higher BMI and WC and lower PA (10, 18). The
343 PREDIMED study found that low-economic status was associated with low-MD adherence
344 and, although not statistically significant in the Food4Me study, we observed higher
345 percentages of individuals in routine and manual occupations in the low MD score group
346 compared with the high score group. As reported by Hu *et al.* (18), we also observed that
347 older individuals were slightly more likely to have higher PREDIMED scores.

348 Our findings support the beneficial effect a MD on dietary quality, as evidenced by lower
349 intakes of SFA and higher intakes of MUFA and PUFA and more individuals meeting food-
350 based dietary recommendations. In Food4Me, higher MD score was associated with higher
351 intakes of sugar, although this may be due to higher fruit juice intake.

352 To our knowledge, no previous studies have evaluated the effect of different levels of PN on
353 difference in MD score. In the PREDIMED Study, 1,551 individuals were randomized to
354 receive either leaflets providing generalized dietary advice based on American Heart
355 Association guidelines (control) or personalized advice in one of two Mediterranean diet
356 groups (45). Participants randomized to personalized advice received motivational
357 interviews every three months to negotiate nutritional goals, as well as group educational
358 sessions on a quarterly basis. Participants exposed to the MD-based intervention increased
359 consumption of olive oil, nuts, vegetables, legumes and fruit and reduced consumption of
360 meat and pastries, cakes and sweets, thus improving overall dietary patterns and supporting
361 the use of PN in facilitating change towards a Mediterranean-style diet. Previous PN
362 interventions have achieved improvements in sodium intake in individuals at higher
363 genotypic-based risk (20), however, the Food4Me PoP study was the first to examine the
364 effect of including genotype-based PN on overall patterns of healthy eating. Our study
365 facilitated the comparison of PN intervention across 7 European countries, which showed
366 that differences in MD scores between treatment arms were only evident in non-
367 Mediterranean countries. Baseline MD scores were low in Greece compared with Spain and
368 changes following intervention were smaller compared with all other countries, which
369 warrants further investigation.

370

371 **Strengths and limitations**

372 The present study had a number of strengths. Our participants were drawn from 7 European
373 countries, facilitating the comparison of MD between Mediterranean and non-
374 Mediterranean countries. Our estimation of MD was based on the PREDIMED 14-point
375 score, which is a validated and widely-used MD score. We estimated changes in MD score in
376 the largest study of PN in European adults to date. Furthermore, we confirmed the
377 robustness of our findings by showing the same pattern of results when using three
378 recommended analytical approaches for RCTs with missing outcome data (LMM, LOCR and
379 CC analyses).

380 A limitation of our study is that data were self-measured and self-reported via the internet,
381 which may have introduced measurement error. Nonetheless, the accuracy of internet-
382 based, self-reported anthropometric have been confirmed in our study (37). Dietary intakes
383 were estimated by a FFQ which is subject to misreporting error (46) but this was minimized
384 by prior validation against a 4-day weighed food record (31). Small sample size limited our
385 power to investigate the effect of individual genes in the present study. Additionally, 97% of
386 our study participants were Caucasians and thus research in wider ethnicity groups is
387 required to generalize our findings to other populations. Our sample is a self-selected group
388 of individuals, who may be more health-conscious than the general population. However,
389 characterization of the profile of our participants suggests that they would benefit from
390 improved diet and PA (47). Furthermore, the Food4Me PoP study did not aim to change MD
391 scores specifically, rather overall diet, which may indirectly have improved MD scores.

392

393 **Implications of findings**

394 PN is a more effective approach for improving MD score than generalized dietary advice. A
395 systematic review and meta-analysis of observational by Sofi *et al.* (2010) found that a 2-
396 point increase (10 point scale) in adherence to the MD was associated with a significant
397 reduction of overall mortality [relative risk (RR) = 0.92; 95% CI: 0.90, 0.94], cardiovascular
398 incidence or mortality (RR = 0.90; 95% CI: 0.87, 0.93) and cancer incidence or mortality (RR =
399 0.94; 95% CI: 0.92, 0.96) (5). There is also accumulating evidence from intervention studies
400 that randomization to the MD reduced CVD risk in both primary and secondary prevention
401 studies (9, 12). The 0.5 unit advantage in PREDIMED score (14 point scale) for PN in the
402 present study indicates that the potential health benefit may be relatively modest. The
403 challenge for those developing future dietary interventions is to produce bigger, and
404 sustained, dietary changes. This study suggests that providing individuals with more
405 detailed, tailored recommendations based on a combination of their diet, phenotype, and
406 genotype is advantageous. In addition, internet-based approaches offer significant
407 opportunities for scaling up PN interventions in a cost effective manner.

408

409 **Conclusions**

410 Following a 6-month RCT, MD score were greater in individuals who received PN advice,
411 compared with those who received non-personalized advice. Furthermore, improvements in
412 MD score were greater in individuals who received PN based on diet, phenotype and
413 genotype compared with advice based on diet and phenotype alone.

414

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417 JCM contributed to the research design. JCM was the Food4Me Proof of Principle study
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420 study. CCM, SNC, RSC, CW, CBO, HF, CFMM, AM, RF, SK, LT, CPL, MG, AS, MCW and JCM
421 conducted the intervention. CCM, CFMM and WHS contributed to physical activity
422 measurements. KML and CCM wrote the paper and performed the statistical analysis and
423 are joint first authors. All authors contributed to a critical review of the manuscript during
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Table 1 Socio-demographic characteristics of participants according to Mediterranean diet (MD) score at baseline¹

	All	Low MD score ³	High MD score ⁴	P ⁵
n	1480	880	600	
MD score	5.12 ± 1.68	3.99 ± 1.02	6.77 ± 0.92	<0.001
Age, years	39.9 ± 13.0	39.3 ± 12.9	40.8 ± 13.1	0.005
Female, %	58.5	57.2	60.3	0.21
Ethnicity, %				
Caucasian	96.8	97.3	96.0	0.42
Occupation, %				
Professional and managerial	39.2	38.1	40.9	0.39
Intermediate occupations	26.1	26.3	25.7	0.39
Routine and manual	9.7	11.2	7.7	0.09
Student	15.0	15.0	14.9	0.24
Retired or Unemployed	10.0	9.4	10.9	0.70
Anthropometrics				
Body weight, kg	74.8 ± 15.9	75.7 ± 15.8	73.4 ± 15.9	0.003
BMI, kg/m ²	25.5 ± 4.87	25.7 ± 4.79	25.2 ± 4.97	0.007
Waist circumference, cm	85.7 ± 13.8	86.5 ± 13.8	84.6 ± 13.8	<0.001
Overweight or obese, %	46.2	48.6	42.5	0.001
Physical activity ²				
PAL	1.73 ± 0.18	1.72 ± 0.17	1.75 ± 0.19	0.003
MVPA, min/d	57.0 ± 45.0	54.0 ± 42.9	61.5 ± 47.7	<0.001
Meet PA recommendations, %	77.3	75.7	79.6	0.022
Sedentary behavior, min/d	746 ± 75.5	748 ± 75.3	742 ± 75.8	0.005
Dietary conditions, %				
Want to lose weight	47.4	49.0	45.0	0.041
Restricted diet	7.0	5.7	8.8	0.014
Health and disease history				
Total blood cholesterol, mmol/L	4.56 ± 0.95	4.59 ± 0.97	4.52 ± 0.93	0.09
Medication use, %	29.7	32.2	26.2	0.004
Current smoker, %	11.8	11.8	11.7	0.56

1, Values represent means and SD or percentages. MD, Mediterranean diet; BMI, body mass index; MVPA, Moderate and vigorous physical activity; PAL, physical activity level

2, PA measures were available in 1285 participants only.

3, Low Mediterranean diet (MD) score: ≤5

4, High Mediterranean diet (MD) score: >5

5, Multiple linear regression and logistic regression were used to test for significant differences between groups in continuous and categorical variables, respectively. Analyses were adjusted for age, sex and country.

Table 2 Dietary intakes of participants according to Mediterranean diet (MD) score at baseline¹

	All	Low MD score ²	High MD score ³	P ⁴
n	1480	880	600	
MD score	5.12 ± 1.68	3.99 ± 1.02	6.77 ± 0.92	<0.001
Nutrient intake				
Total energy, kcal/d	2558 ± 1085	2519 ± 1073	2614 ± 1101	0.14
EI:BMR ratio	1.66 ± 0.66	1.62 ± 0.63	1.72 ± 0.70	0.012
Total fat, % energy	35.9 ± 5.91	36.4 ± 5.71	35.2 ± 6.12	<0.001
SFA, % energy	14.1 ± 3.14	14.9 ± 3.16	13.0 ± 2.73	<0.001
MUFA, % energy	13.7 ± 3.12	13.6 ± 2.85	13.9 ± 3.48	0.009
PUFA, % energy	5.7 ± 1.44	5.6 ± 1.38	5.9 ± 1.52	<0.001
Protein, % energy	17.1 ± 3.71	16.6 ± 3.49	17.8 ± 3.91	<0.001
Carbohydrate, % energy	46.0 ± 7.60	46.3 ± 7.28	45.5 ± 8.03	0.042
Sugars, % energy	21.1 ± 5.97	20.4 ± 5.70	22.1 ± 6.21	<0.001
Dietary fiber, g/d	29.8 ± 14.6	26.8 ± 12.4	34.4 ± 16.4	<0.001
Salt, g/d	7.37 ± 3.72	7.43 ± 3.84	7.28 ± 3.54	0.18
Meeting dietary recommendations, %				
Oily fish	32.1	17.6	53.3	<0.001
Wholegrains	74.2	73.9	74.7	0.37
Red meat	50.5	47.8	54.5	0.006
Fruit and vegetables	52.0	35.3	76.3	<0.001
Low fat dairy	6.9	5.5	9.0	0.06

1, Values represent means ± SD or percentages; MD, Mediterranean diet; EI, energy intake; BMI, body mass index; SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids

2, Low Mediterranean diet score: ≤5

3, High Mediterranean diet score: >5

4, Multiple linear regression were used to test for significant differences between groups and were adjusted for age, sex and country.

Table 3 Effect of personalized nutrition intervention on Mediterranean diet (MD) score components at baseline and month 6¹

	Control Mean (L0)	Personalized nutrition Mean (L1, L2, L3)	Personalized nutrition			P L0 vs (L1+L2+L3)	P L1 vs (L2+L3)	P L2 vs L3
			L1	L2	L3			
n at baseline	360	1120	373	376	371			
MD score at baseline	5.17 ± 0.09	5.10 ± 0.05	5.16 ± 0.09	5.05 ± 0.09	5.09 ± 0.09	0.49	0.36	0.75
MD score at month 6	5.20 ± 0.05	5.48 ± 0.07	5.43 ± 0.10	5.38 ± 0.10	5.63 ± 0.10	0.002	0.46	0.029
Component scores at month 6								
Olive oil ratio	0.55 ± 0.02	0.60 ± 0.02	0.56 ± 0.03	0.61 ± 0.03	0.62 ± 0.03	0.08	0.022	0.73
Olive oil intake	0.012 ± 0.003	0.002 ± 0.004	0.002 ± 0.005	0.005 ± 0.005	0.001 ± 0.005	0.039	0.99	0.31
Vegetables	0.60 ± 0.02	0.62 ± 0.02	0.61 ± 0.03	0.63 ± 0.03	0.63 ± 0.03	0.47	0.41	0.91
Fruit	0.58 ± 0.01	0.67 ± 0.02	0.67 ± 0.03	0.66 ± 0.02	0.69 ± 0.03	0.001	0.99	0.33
Processed meat	0.90 ± 0.01	0.92 ± 0.01	0.92 ± 0.02	0.92 ± 0.02	0.93 ± 0.02	0.07	0.54	0.43
Fat spreads	0.40 ± 0.02	0.45 ± 0.02	0.46 ± 0.03	0.43 ± 0.03	0.45 ± 0.03	0.09	0.54	0.52
Fizzy drinks	0.98 ± 0.01	0.97 ± 0.01	0.98 ± 0.01	0.98 ± 0.01	0.97 ± 0.01	0.67	0.92	0.51
Wine	0.07 ± 0.01	0.07 ± 0.01	0.06 ± 0.01	0.06 ± 0.01	0.07 ± 0.01	0.94	0.81	0.53
Fish	0.33 ± 0.01	0.36 ± 0.02	0.34 ± 0.03	0.33 ± 0.03	0.35 ± 0.03	0.79	0.97	0.52
Legumes	0.15 ± 0.01	0.13 ± 0.02	0.11 ± 0.02	0.12 ± 0.02	0.15 ± 0.02	0.28	0.40	0.13
Nuts	0.14 ± 0.01	0.16 ± 0.02	0.17 ± 0.02	0.13 ± 0.02	0.18 ± 0.02	0.39	0.53	0.07
Sweets and pastries	0.19 ± 0.01	0.23 ± 0.02	0.24 ± 0.03	0.21 ± 0.03	0.21 ± 0.03	0.17	0.56	0.51
White meat	0.29 ± 0.01	0.30 ± 0.02	0.31 ± 0.03	0.28 ± 0.03	0.30 ± 0.03	0.70	0.42	0.52
Tomato sauce	0.011 ± 0.003	0.020 ± 0.005	0.017 ± 0.007	0.014 ± 0.007	0.030 ± 0.007	0.15	0.51	0.040

1, Values represent adjusted means ± SE; contrast analyses were used to test for significant differences between groups; linear mixed models were adjusted for baseline age, sex and country. L0, Level 0 - Control, generalized advice; L1, Level 1 – personalized advice based on diet alone; L2, Level 2 – personalized advice based on diet and phenotype; L3, Level 3 – personalized advice based on diet, phenotype and genotype.

FIGURE LEGENDS

Figure 1 Consort diagram of participants randomized into the Food4Me Proof of Principle Study * Total number of participants reporting one or more exclusion criteria

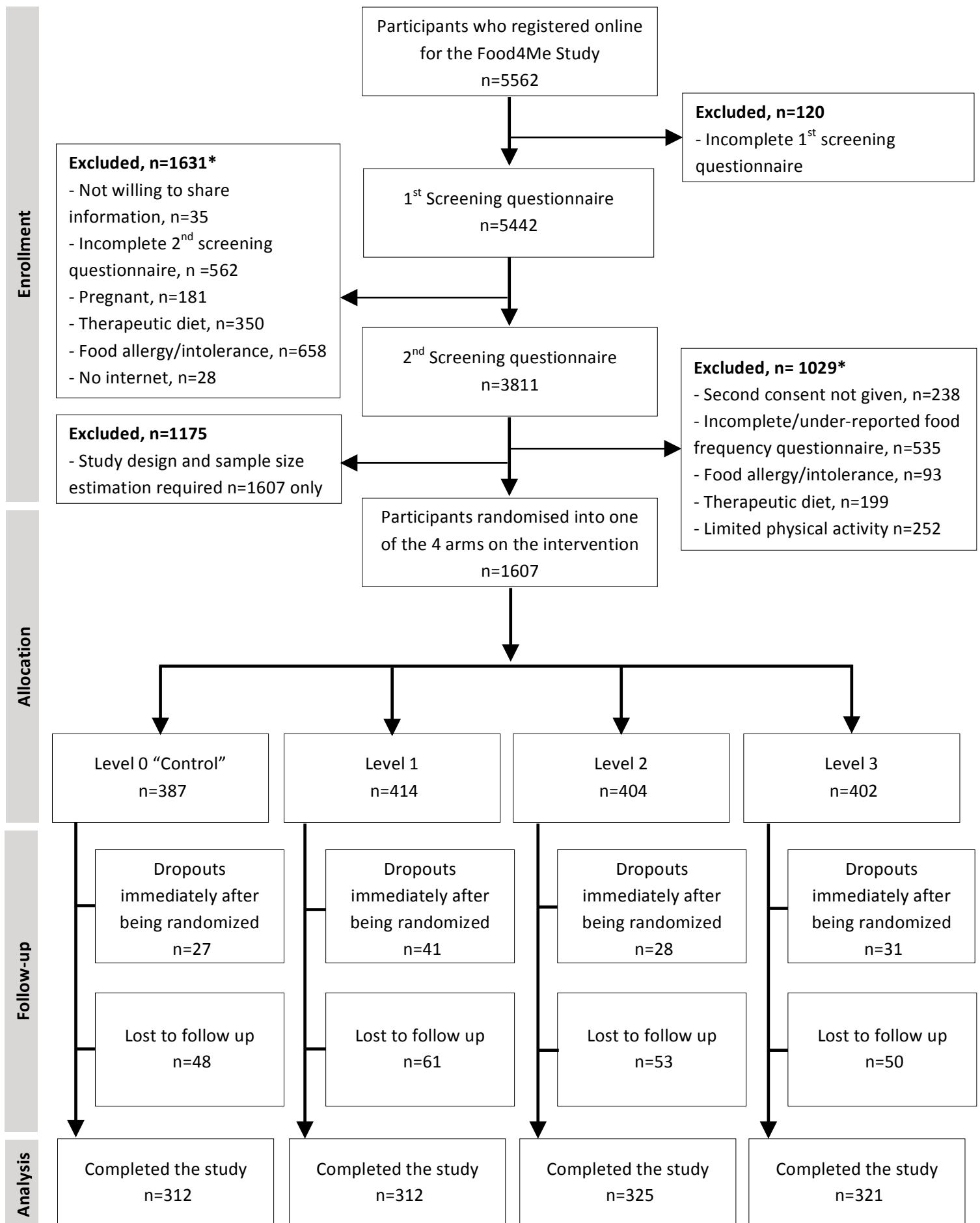


Figure 1

Online Supplemental Material

Title

Effect of an internet-based personalized nutrition intervention on dietary changes associated with the Mediterranean diet: the Food4Me study

Online Supplemental Material

Supplemental Table 1 Scoring system for the PREDIMED-based Mediterranean diet (MD) score

Point	PREDIMED scoring system	Serving size	Food4Me MD scoring system
1	Olive oil more than other culinary fat	-	More olive oil than other culinary fat (butter and other vegetable oils): operationalized as a ratio of olive oil to other culinary fat and a score of >0g
2	Olive oil (≥4 tbsp/d)	11g	Olive oil (≥44g)
3	Vegetables (≥2 servings/d)	80g	Vegetables (≥160g/d)
4	Fresh fruits (including natural fruit juice; ≥3 servings/d)	80g for fresh or 150ml for juice	Fresh fruit and juice (≥240g/d); fruit juice was capped at 150g/d
5	Red and processed meats (<1 serving/d)	150g	Red and processed meat
6	Spread fats (butter, margarine, cream; <1 serving/d)	12g	Fats and spreads
7	Soda drinks (<1 drink/d)	250ml	Fizzy Soft Drinks E.g. Coca Cola / Lemonade
8	Wine with meals (only for habitual drinkers; ≥7 glasses/wk)	175ml	Wine (≥175ml/d)
9	Legumes (≥3 servings/wk)	150g	Legume (≥64.29g/d)
10	Fish (especially fatty fish), seafood (≥3 servings/wk)	150g	Fish and seafood (≥64.29g/d)
11	Commercial bakery goods, sweets, and pastries§ (<3 servings/wk)	60g	Sweets and snacks (all except crisps; <25.7g/d)
12	Tree nuts and peanuts†(≥3 servings/wk)	30g	Nuts And Seeds (≥12.86g/d)
13	White meat Instead of red meat	-	More chicken (processed chicken, grilled chicken) than red meat (Beef, Pork, Burgers, Sausages): operationalized as a ratio of chicken to red meat and a score of >0g
14	Sofrito (sauce made with tomato and onion, leek, or garlic, simmered with olive oil; ≥2 servings/wk)	-	Tomato sauces (≥90g)

Supplemental Table 2 Baseline characteristics of participants who completed the intervention and those who dropped out by month 6¹

	Completers (n=1270)		Dropouts (n=337)		p ²
	Mean	SD	Mean	SD	
Age, years	40.8	13.0	34.8	12.3	<0.001
Female, %	57.4		66.8		0.017
Ethnicity					
Caucasian, %	96.9		96.1		0.83
Occupation, %					
Professional and managerial	40.0		34.6		0.53
Intermediate occupations	26.1		25.5		0.98
Routine and manual	9.5		11.1		0.42
Student	14.0		21.2		0.13
Retired	3.0		2.4		0.39
Unemployed	7.4		5.3		0.88
Anthropometrics					
Body weight, kg	74.6	15.7	75.4	17.0	<0.001
BMI, kg/m ²	25.4	4.8	25.9	5.5	<0.001
Waist circumference, cm	85.9	13.7	84.6	14.7	0.015
Height, m	1.7	0.1	1.7	0.1	0.89
Physical activity					
PAL	1.7	0.2	1.7	0.2	0.86
Sedentary behaviour, min/d	747	75.2	732	77.1	0.31
Medication use, %					
Prescribed medication	30.5		27.6		0.67
Non-prescribed medication	10.3		7.7		0.32
Health and disease					
Total cholesterol, mmol/L	4.6	1.0	4.3	0.9	0.06
Current smoker, %	11.7		13.7		0.66
Cancer, %	1.6		0.3		0.21
High blood pressure, %	7.9		6.8		0.21
Heart disease, %	1.4		1.2		0.61
Diabetes, %	0.6		0.6		0.61
Blood disorders, %	1.1		0.6		0.29

1, Values represent means, SD or percentages; BMI, body mass index; PAL, Physical activity level

2, Multiple linear regression and logistic regression were used to test for significant differences between groups in continuous and categorical variables, respectively. Analyses were adjusted for age, sex and country.

Supplemental Table 3 Effect of personalized nutrition intervention on Mediterranean diet (MD) score components at baseline and month 3¹

	Control Mean (L0)	Personalized nutrition Mean (L1, L2, L3)	Personalized nutrition			P L0 vs (L1+L2+L3)	P L1 vs (L2+L3)	P L2 vs L3
			L1	L2	L3			
n at baseline	360	1120	373	376	371			
MD score at baseline	5.17 ± 0.09	5.10 ± 0.05	5.16 ± 0.09	5.05 ± 0.09	5.09 ± 0.09	0.49	0.36	0.75
MD score at month 3	5.26 ± 0.05	5.41 ± 0.07	5.42 ± 0.09	5.27 ± 0.09	5.54 ± 0.09	0.08	0.89	0.010
Component scores at month 3								
Olive oil ratio	0.55 ± 0.02	0.62 ± 0.01	0.63 ± 0.02	0.58 ± 0.02	0.65 ± 0.02	0.008	0.66	0.035
Olive oil intake	0.012 ± 0.003	0.006 ± 0.004	0.005 ± 0.006	0.002 ± 0.006	0.011 ± 0.006	0.29	0.77	0.20
Vegetables	0.63 ± 0.02	0.60 ± 0.02	0.55 ± 0.03	0.60 ± 0.03	0.64 ± 0.03	0.18	0.02	0.24
Fruit	0.60 ± 0.02	0.65 ± 0.02	0.65 ± 0.03	0.63 ± 0.03	0.66 ± 0.03	0.08	0.94	0.39
Processed meat	0.90 ± 0.01	0.92 ± 0.01	0.91 ± 0.02	0.91 ± 0.02	0.93 ± 0.02	0.28	0.51	0.57
Fat spreads	0.41 ± 0.02	0.44 ± 0.02	0.44 ± 0.03	0.44 ± 0.03	0.44 ± 0.03	0.20	0.95	0.98
Fizzy drinks	0.98 ± 0.01	0.98 ± 0.01	0.98 ± 0.01	0.98 ± 0.01	0.97 ± 0.01	0.72	0.58	0.13
Wine	0.07 ± 0.01	0.07 ± 0.01	0.07 ± 0.01	0.07 ± 0.01	0.07 ± 0.01	0.86	0.60	0.85
Fish	0.33 ± 0.01	0.33 ± 0.02	0.32 ± 0.03	0.32 ± 0.03	0.34 ± 0.03	0.87	0.75	0.55
Legumes	0.14 ± 0.01	0.12 ± 0.02	0.13 ± 0.02	0.11 ± 0.02	0.13 ± 0.02	0.29	0.55	0.50
Nuts	0.16 ± 0.01	0.14 ± 0.02	0.15 ± 0.02	0.11 ± 0.02	0.16 ± 0.02	0.26	0.55	0.08
Sweets and pastries	0.17 ± 0.01	0.22 ± 0.02	0.26 ± 0.03	0.19 ± 0.02	0.20 ± 0.02	0.06	0.014	0.64
White meat	0.29 ± 0.01	0.32 ± 0.02	0.33 ± 0.03	0.29 ± 0.03	0.34 ± 0.03	0.42	0.63	0.15
Tomato sauce	0.097 ± 0.003	0.018 ± 0.004	0.020 ± 0.005	0.020 ± 0.005	0.013 ± 0.005	0.11	0.50	0.27

1, Values represent adjusted means ± SE; contrast analyses were used to test for significant differences between groups; linear mixed models were adjusted for baseline age, sex and country. L0, Level 0 - Control, generalized advice; L1, Level 1 – personalized advice based on diet alone; L2, Level 2 – personalized advice based on diet and phenotype; L3, Level 3 – personalized advice based on diet, phenotype and genotype.

Supplemental Table 4 Effect of personalized nutrition intervention on Mediterranean diet (MD) score at month 6 by country¹

	Control Mean (L0)	Personalized nutrition Mean (L1, L2, L3)	Personalized nutrition			P L0 vs (L1+L2+L3) ¹	P L1 vs (L2+L3) ¹	P L2 vs L3 ¹
			L1	L2	L3			
UK (n=207)	5.60	5.77	5.47	5.83	5.99	0.53	0.12	0.62
Ireland (n=217)	5.05	5.48	5.33	5.43	5.67	0.10	0.45	0.46
The Netherlands (n=220)	5.24	5.45	5.38	5.18	5.79	0.29	0.62	0.013
Germany (n=208)	4.68	5.06	5.13	5.00	5.05	0.12	0.67	0.87
Spain (n=214)	6.06	6.41	6.37	6.15	6.71	0.19	0.81	0.08
Greece (n=210)	5.25	5.38	5.70	5.28	5.19	0.58	0.06	0.73
Poland (n=204)	4.47	4.78	4.57	4.84	4.96	0.21	0.21	0.70

1, Values represent adjusted means ± SE; linear mixed models were used, with contrast analyses to test for significant differences between groups. Analyses were adjusted for baseline age and sex; L0, Level 0 - Control, generalized advice; L1, Level 1 – personalized advice based on diet alone; L2, Level 2 – personalized advice based on diet and phenotype; L3, Level 3 – personalized advice based on diet, phenotype and genotype

Online Supplemental Material

Supplemental Table 5 Comparison of a liner mixed model (LMM), last observation carrier forward (LOCF) and a complete case analysis (CC) on the effect of personalized nutrition intervention on Mediterranean diet (MD) score components at baseline and month 6¹

	Control Mean (L0)	Personalized nutrition Mean (L1, L2, L3)	Personalized nutrition			P L0 vs (L1+L2+L3)	P L1 vs (L2+L3)	P L2 vs L3
			L1	L2	L3			
n at baseline	360	1120	373	376	371			
MD score at baseline	5.17 ± 0.09	5.10 ± 0.05	5.16 ± 0.09	5.05 ± 0.09	5.09 ± 0.09	0.49	0.36	0.75
LMM (n=1480)								
MD score at month 6	5.20 ± 0.05	5.48 ± 0.07	5.43 ± 0.10	5.38 ± 0.10	5.63 ± 0.10	0.002	0.46	0.029
LOCF (n=1480)								
MD score at month 6	5.26 ± 0.07	5.49 ± 0.04	5.44 ± 0.07	5.39 ± 0.07	5.64 ± 0.07	0.004	0.41	0.011
CC (n=1270)								
MD score at month 6	5.31 ± 0.08	5.59 ± 0.05	5.54 ± 0.08	5.49 ± 0.08	5.73 ± 0.08	0.003	0.46	0.029

1, Values represent adjusted means ± SE; contrast analyses were used to test for significant differences between groups; models were adjusted for baseline age, sex and country. L0, Level 0 - Control, generalized advice; L1, Level 1 – personalized advice based on diet alone; L2, Level 2 – personalized advice based on diet and phenotype; L3, Level 3 – personalized advice based on diet, phenotype and genotype.

Supplemental Table 6 Effect of PN intervention on MD score at month 6 in participants stratified by risk vs non-risk genetic variants¹

	Control Mean (L0)	Personalized nutrition Mean (L1, L2, L3)	Personalized nutrition			P	P	P
			L1	L2	L3	L0 vs (L1+L2+L3)	L1 vs (L2+L3)	L2 vs L3
<i>FTO</i> (rs9939609)								
Non-risk (n=468)	5.18 ± 0.08	5.30 ± 0.12	5.38 ± 0.16	5.19 ± 0.16	5.32 ± 0.17	0.45	0.41	0.51
Risk (n=1002)	5.21 ± 0.06	5.57 ± 0.09	5.46 ± 0.12	5.48 ± 0.12	5.74 ± 0.12	0.002	0.21	0.06
<i>MTHFR</i> (rs1801133)								
Non-risk (n=661)	5.13 ± 0.08	5.34 ± 0.11	5.33 ± 0.14	5.24 ± 0.15	5.46 ± 0.14	0.13	0.88	0.19
Risk (n=809)	5.59 ± 0.10	5.59 ± 0.10	5.52 ± 0.13	5.50 ± 0.13	5.75 ± 0.13	0.006	0.47	0.10
<i>ApoE</i> (rs429358 & rs7412)								
Non-risk (n=1078)	5.15 ± 0.06	5.38 ± 0.08	5.38 ± 0.11	5.34 ± 0.11	5.43 ± 0.11	0.028	0.94	0.48
Risk (n=386)	5.33 ± 0.10	5.72 ± 0.15	5.56 ± 0.19	5.47 ± 0.20	6.13 ± 0.20	0.040	0.24	0.006
<i>TCF7L2</i> (rs7903146)								
Non-risk (n=742)	5.20 ± 0.07	5.49 ± 0.10	5.52 ± 0.14	5.32 ± 0.14	5.64 ± 0.14	0.036	0.75	0.044
Risk (n=725)	5.19 ± 0.07	5.49 ± 0.10	5.38 ± 0.14	5.49 ± 0.14	5.61 ± 0.13	0.016	0.23	0.45
<i>FADS1</i> (rs174546)								
Non-risk (n=839)	5.24 ± 0.07	5.62 ± 0.10	5.59 ± 0.13	5.54 ± 0.13	5.73 ± 0.13	0.019	0.75	0.21
Risk (n=631)	5.14 ± 0.08	5.30 ± 0.11	5.25 ± 0.15	5.19 ± 0.15	5.47 ± 0.14	0.24	0.61	0.10

1, Values represent adjusted means ± SE; linear mixed models were used, with contrast analyses to test for significant differences between groups. Analyses were adjusted for baseline age, sex and country; L0, Level 0 - Control, generalized advice; L1, Level 1 – personalized advice based on diet alone; L2, Level 2 – personalized advice based on diet and phenotype; L3, Level 3 – personalized advice based on diet, phenotype and genotype. Risk carriers were defined as carrying one or two copies of the risk allele, while non-risk carriers carried no copies of the risk allele.

Supplemental Table 7 Effect of disclosing genetic information on MD score at month 6 participants classified as risk and non-risk carriers of genetic variants in L3

	Control Mean (L0)	L2	Disclosure of genetic information		L0 vs L3 risk	L0 vs L3 non-risk	L2 vs L3 risk	L2 vs L3 non-risk
			L3-risk carriers	L3-non-risk carriers				
<i>FTO</i> , rs9939609	5.20 ± 0.05	5.39 ± 0.10	5.70 ± 0.10	5.41 ± 0.16	<0.001	0.022	0.012	0.88
<i>MTHFR</i> , rs1801133	5.20 ± 0.05	5.39 ± 0.10	5.68 ± 0.12	5.55 ± 0.13	<0.001	0.016	0.030	0.26
<i>ApoE</i> , rs429358 & rs7412	5.23 ± 0.05	5.41 ± 0.10	5.84 ± 0.17	5.53 ± 0.11	<0.001	0.004	0.016	0.16
<i>TCF7L2</i> , rs7903146	5.18 ± 0.05	5.37 ± 0.10	5.68 ± 0.13	5.57 ± 0.13	<0.001	0.013	0.025	0.24
<i>FADS1</i> , rs174546	5.19 ± 0.05	5.37 ± 0.10	5.61 ± 0.13	5.63 ± 0.11	0.003	0.002	0.10	0.09

1, Values represent adjusted means ± SE; contrast analyses were used to test for significant differences between groups and were adjusted for baseline values; L0, Level 0 - Control, generalized advice; L1, Level 1 – personalized advice based on diet alone; L2, Level 2 – personalized advice based on diet and phenotype; L3, Level 3 – personalized advice based on diet, phenotype and genotype. Risk carriers were defined as carrying one or two copies of the risk allele, while non-risk carriers carried no copies of the risk allele.