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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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Key Words: Mediterranean diet; Food4Me; personalized nutrition; internet-based; European adults

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 (≤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/m^2 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*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/m^2 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

415   **ACKNOWLEDGMENTS**

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Table 1 Socio-demographic characteristics of participants according to Mediterranean diet (MD) score at baseline[1]

	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 baseline[1]

	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 6[1]

	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
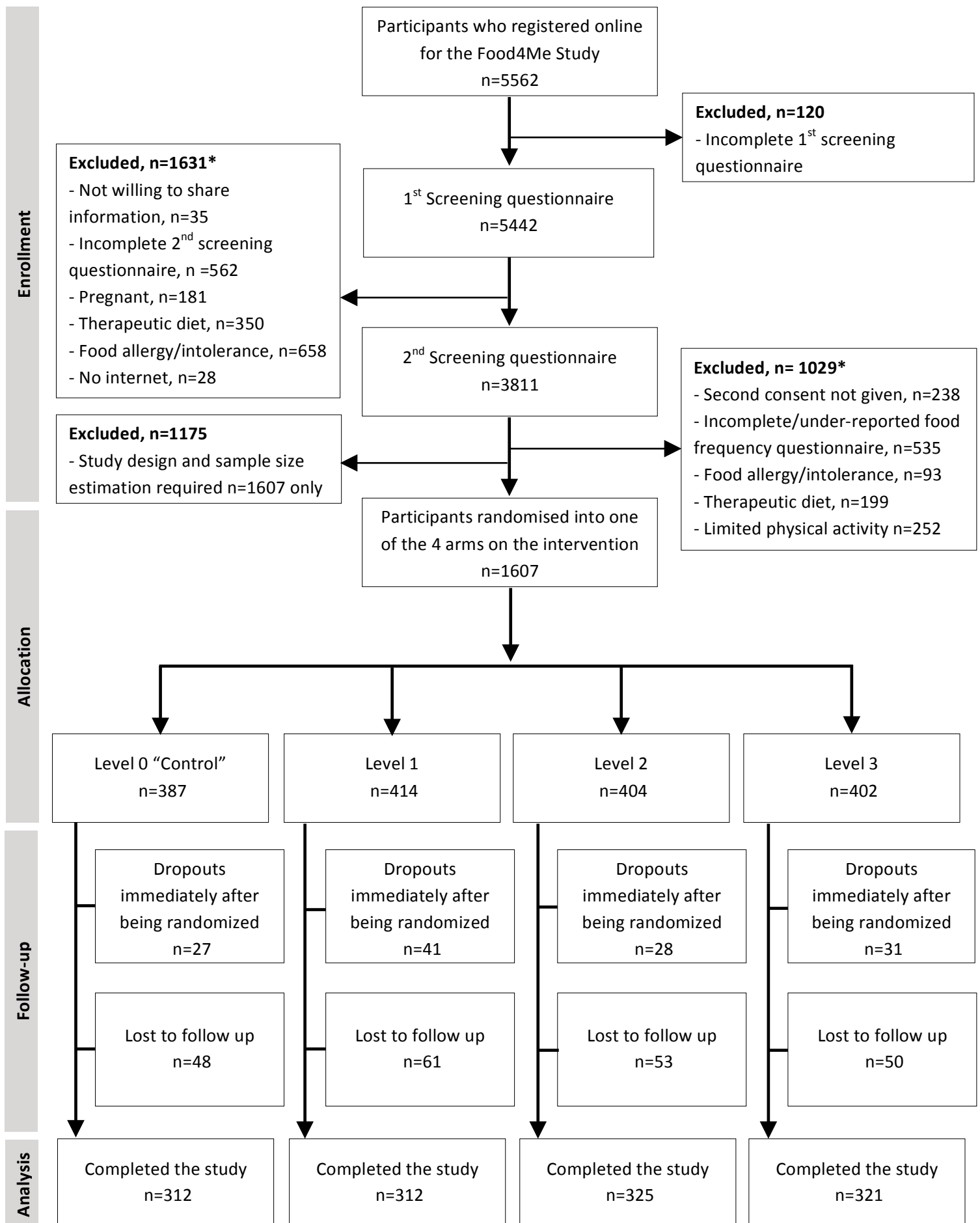
Figure 1

Title
Effect of an internet-based personalized nutrition intervention on dietary changes

associated with the Mediterranean diet: the Food4Me study

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 6[1]

	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 3[1]

	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 country[1]

	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

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 6[1]

	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 variants[1]

	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			
FTO (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
MTHFR (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
ApoE (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**
TCF7L2 (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
FADS1 (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				
FTO, 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
MTHFR, 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
ApoE, 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
TCF7L2, 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
FADS1, 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.