# *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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**Author names**

Katherine M. Livingstone*[1], Carlos Celis-Morales*[1], Santiago Navas-Carretero[2], Rodrigo San-Cristobal[2], Anna L. Macready[3], Rosalind Fallaize[3], Hannah Forster[4], Clara Woolhead[4], Clare B. O’Donovan[4], Cyril F.M. Marsaux[5], Silvia Kolossa[6], Lydia Tsirigoti[7], Christina P. Lambrinou[7], George Moschonis[7], Magdalena Godlewska[8], Agnieszka Surwiłło[8], Christian A. Drevon[9], Yannis Manios[7], Iwona Traczyk[8], Eileen R. Gibney[4], Lorraine Brennan[4], Marianne C. Walsh[4], Julie A. Lovegrove[3], Wim H. Saris[5], Hannelore Daniel[6], Mike Gibney[4], J. Alfredo Martinez[2], John C. Mathers[1], on behalf of the Food4Me Study.

**Author affiliations**

1, Human Nutrition Research Centre, Institute of Cellular Medicine, Newcastle University, Newcastle Upon Tyne, UK (KML, katherine.livingstone@newcastle.ac.uk, CCM, carlos.celis@newcastle.ac.uk; JCM, john.mathers@newcastle.ac.uk)

2, Center for Nutrition Research, University of Navarra, Pamplona, Spain; CIBER Fisiopatología Obesidad y Nutrición (CIBERobn), Instituto de Salud Carlos III, Madrid, Spain (SNC, snavas@unav.es; RSC, rsan.1@alumni.unav.es; JAM, jalfmtz@unav.es)

3, Hugh Sinclair Unit of Human Nutrition and Institute for Cardiovascular and Metabolic Research, University of Reading, Reading, UK (ALM, a.l.macready@reading.ac.uk; RF, r.fallaize@reading.ac.uk; JAL, j.a.lovegrove@reading.ac.uk)

4, UCD Institute of Food and Health, University College Dublin, Belfield, Dublin 4, Republic of Ireland (CBD, clare.odonovan@ucdconnect.ie; HF, hannah.forster@ucdconnect.ie; CW, clara.woolhead@ucdconnect.ie; EG, eileen.gibney@ucd.ie; LB, lorraine.brennan@ucd.ie; MCW, marianne.walsh@ucd.ie; MG, mike.gibney@ucd.ie)

5, Department of Human Biology, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre, Maastricht, The Netherlands (CFMM, c.marsaux@maastrichtuniversity.nl; WHS, w.saris@maastrichtuniversity.nl)

6, ZIEL Research Center of Nutrition and Food Sciences, Biochemistry Unit, Technical University of Munich, Germany (SK, silvia.kolossa@tum.de; HD, hannelore.daniel@tum.de)

7, Department of Nutrition and Dietetics, Harokopio University, Athens, Greece (LT, tsirigoti.lydia@gmail.com; CPL, cplambrinos@gmail.com; GM, gmoschi@hua.gr; YM, manios@hua.gr)

8, National Food & Nutrition Institute (IZZ), Poland (MG, mgodlewska@izz.waw.pl; AS, asurwillo@izz.waw.pl; IT, itraczyk@izz.waw.pl)

9, Department of Nutrition, Institute of Basic Medical Sciences, Faculty of Medicine, University of Oslo, Oslo, Norway (CAD, c.a.drevon@medisin.uio.no)

*KML and CCM contributed equally are joint first-authors

**Corresponding author; request for reprints**

Professor John C. Mathers

Human Nutrition Research Centre

Institute of Cellular Medicine

Newcastle University

Biomedical Research Building

Campus for Ageing and Vitality

Newcastle upon Tyne

NE4 5PL

UK

john.mathers@newcastle.ac.uk

Tel: +44 (0) 1912081133 Fax: +44 (0) 1912081101

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

**Abstract (words count=286)**

**Background**

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

**Objective**

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

**Design**

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

**Results**

At baseline, high MD scorers had 0.5 kg/m$^2$ lower BMI (*P*=0.007) and 0.03 higher PAL (*P*=0.003) than low scorers. MD scores at month 6 were greater in individuals randomized to PN (L1, L2 and L3) compared with Control (PN: 5.20 ± 0.05 vs. Control: 5.48 ± 0.07 respectively; *P*=0.002). There was no significant difference in MD scores at month 6

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

**Conclusions**

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

## INTRODUCTION

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

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

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

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

## METHODS

### Study design

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

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

**Ethical approval and participant consent**

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

**Eligibility criteria**

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

**Intervention arms**

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

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

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

**Personalized feedback report**

Participants randomized to L1, L2 and L3 received personalized feedback reports via email at baseline, month 3 and month 6 of the intervention. For those randomized to PN, algorithms were used to provide participants with 3 specific dietary goals according to the individual's intakes of nutrients. For participants randomized to L2 and L3, the dietary advice was also 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).

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

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

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

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

**Statistical analyses**

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

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

## RESULTS

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

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

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

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

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 cm lower WC (*P*<0.001) than low scorers (Table 1). High MD scorers spent less time in sedentary behaviors (*P*=0.005), had higher PAL (*P*=0.003) and MVPA (*P*<0.001) and met more PA recommendations (*P*=0.022) than low scorers (Table 1). More low MD scorers wanted to lose weight than high scorers (49 vs. 45%; *P*=0.041; Table 1), whereas more high scorers reported being on a restricted diet (9 vs. 6%; *P*=0.014; Table 1).

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

**Dietary intakes by MD score**

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

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

**Differences in MD scores following intervention**

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

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

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

**Sensitivity analyses**

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

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

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

## DISCUSSION

### Main findings

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

### Comparison with other studies

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

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

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

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

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

**Strengths and limitations**

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

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

**Implications of findings**

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

## Conclusions

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

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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

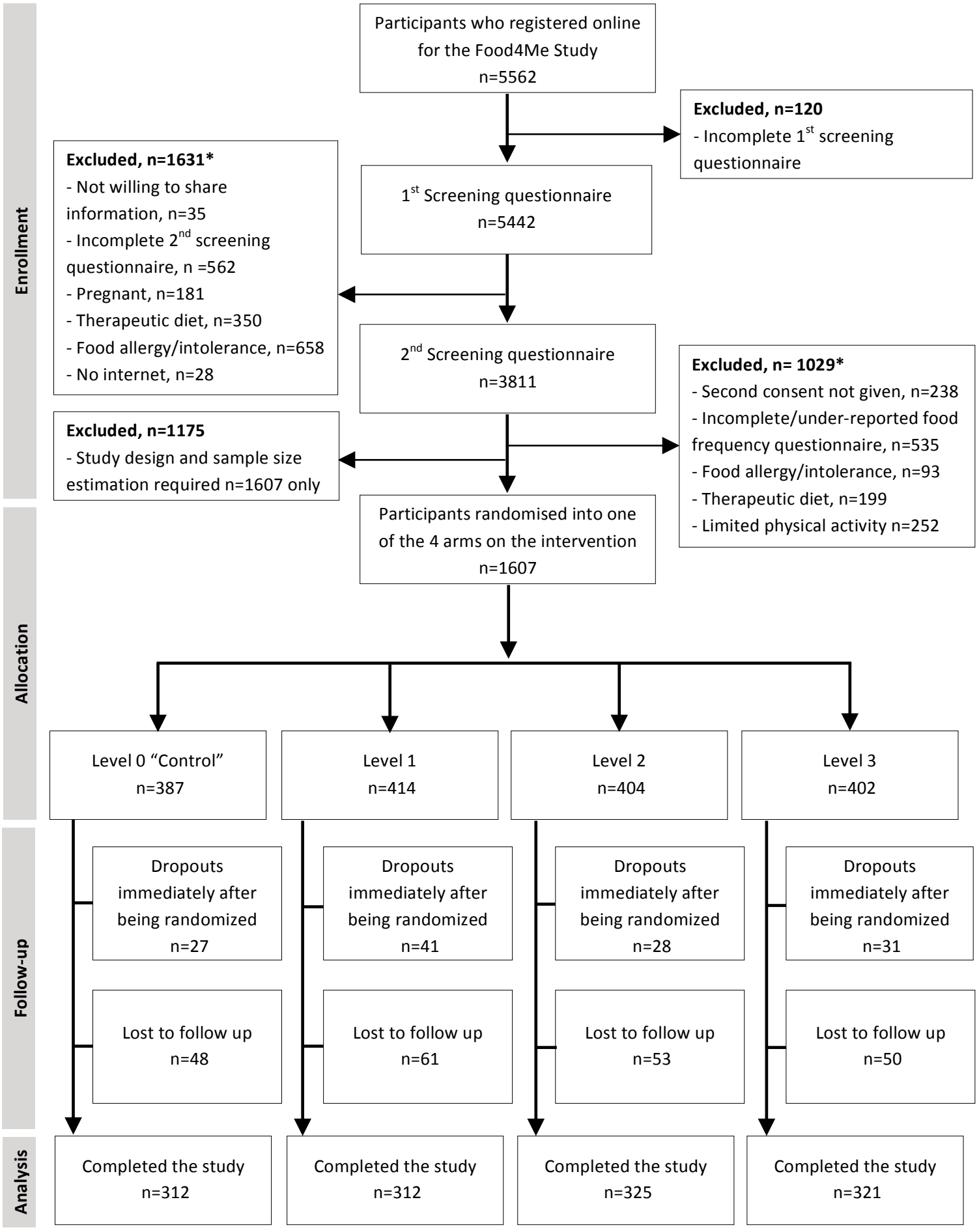
Enrollment
Allocation
Follow-up
Analysis
Participants who registered online for the Food4Me Study n=5562
Excluded, n=120
- Incomplete 1st screening questionnaire
1st Screening questionnaire n=5442
Excluded, n=1631*
- Not willing to share information, n=35
- Incomplete 2nd screening questionnaire, n =562
- Pregnant, n=181
- Therapeutic diet, n=350
- Food allergy/intolerance, n=658
- No internet, n=28
2nd Screening questionnaire n=3811
Excluded, n= 1029*
- Second consent not given, n=238
- Incomplete/under-reported food frequency questionnaire, n=535
- Food allergy/intolerance, n=93
- Therapeutic diet, n=199
- Limited physical activity n=252
Excluded, n=1175
- Study design and sample size estimation required n=1607 only
Participants randomised into one of the 4 arms on the intervention n=1607
Level 0 "Control" n=387
Level 1 n=414
Level 2 n=404
Level 3 n=402
Dropouts immediately after being randomized n=27
Dropouts immediately after being randomized n=41
Dropouts immediately after being randomized n=28
Dropouts immediately after being randomized n=31
Lost to follow up n=48
Lost to follow up n=61
Lost to follow up n=53
Lost to follow up n=50
Completed the study n=312
Completed the study n=312
Completed the study n=325
Completed the study n=321

**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

**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.