Effect of an Internet-based, personalized nutrition randomized trial on dietary changes associated with the Mediterranean diet: the Food4Me Study[1,2]

Katherine M Livingstone,[3,13] Carlos Celis-Morales,[3,13] Santiago Navas-Carretero,[4,5] Rodrigo San-Cristobal,[5] Anna L Macready,[6] Rosalind Fallaize,[6] Hannah Forster,[7] Clara Woolhead,[7] Clare B O'Donovan,[7] Cyril FM Marsaux,[8] Silvia Kolossa,[9] Lydia Tsirigoti,[10] Christina P Lambrinou,[10] George Moschonis,[10] Magdalena Godlewska,[11] Agnieszka Surwiłło,[11] Christian A Drevon,[12] Yannis Manios,[10] Iwona Traczyk,[11] Eileen R Gibney,[7] Lorraine Brennan,[7] Marianne C Walsh,[7] Julie A Lovegrove,[6] Wim H Saris,[8] Hannelore Daniel,[9] Mike Gibney,[7] J Alfredo Martinez,[5] and John C Mathers[3] on behalf of the Food4Me Study*

[3]Human Nutrition Research Centre, Institute of Cellular Medicine, Newcastle University, Newcastle Upon Tyne, United Kingdom; [4]Center for Nutrition Research, University of Navarra, Pamplona, Spain; [5]CIBER Fisiopatología Obesidad y Nutrición (CIBERobn), Instituto de Salud Carlos III, Madrid, Spain; [6]Hugh Sinclair Unit of Human Nutrition and Institute for Cardiovascular and Metabolic Research, University of Reading, Reading, United Kingdom; [7]UCD Institute of Food and Health, University College Dublin, Belfield, Dublin, Republic of Ireland; [8]Department of Human Biology, School of Nutrition and Translational Research in Metabolism (NUTRIM), Maastricht University Medical Center, Maastricht, Netherlands; [9]Research Center of Nutrition and Food Sciences (ZIEL), Biochemistry Unit, Technical University of Munich, Munich, Germany; [10]Department of Nutrition and Dietetics, Harokopio University, Athens, Greece; [11]National Food and Nutrition Institute, Poland; and [12]Department of Nutrition, Institute of Basic Medical Sciences, Faculty of Medicine, University of Oslo, Oslo, Norway

ABSTRACT

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

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

Design: Participants (n = 1607) were recruited into a 6-mo, Internet-based, PN randomized controlled trial (Food4Me) designed to evaluate the effect of PN on dietary change. Participants were randomly assigned to receive conventional dietary advice [control; level 0 (L0)] or PN advice on the basis of current diet [level 1 (L1)], diet and phenotype [level 2 (L2)], or diet, phenotype, and genotype [level 3 (L3)]. Dietary intakes from food-frequency questionnaires at baseline and at 6 mo were converted to a MedDiet score. Linear regression compared participant characteristics between high (>5) and low (≤5) MedDiet scores. Differences in MedDiet scores between treatment arms at month 6 were evaluated by using contrast analyses.

Results: At baseline, high MedDiet scorers had a 0.5 lower body mass index (in kg/m^2; P = 0.007) and a 0.03 higher physical activity level (P = 0.003) than did low scorers. MedDiet scores at month 6 were greater in individuals randomly assigned to receive PN (L1, L2, and L3) than in controls (PN compared with controls: 5.20 ± 0.05 and 5.48 ± 0.07, respectively; P = 0.002). There was no significant difference in MedDiet scores at month 6 between PN advice on the basis of L1 compared with L2 and L3. However, differences in MedDiet scores at month 6 were greater in L3 than in L2 (L3 compared with L2: 5.63 ± 0.10 and 5.38 ± 0.10, respectively; P = 0.029).

Conclusions: Higher MedDiet scores at baseline were associated with healthier lifestyles and lower adiposity. After the intervention, MedDiet scores were greater in individuals randomly assigned to receive PN than in controls, with the addition of DNA-based dietary advice resulting in the largest differences in MedDiet scores. Although differences were significant, their clinical relevance is modest. This trial was registered at clinicaltrials.gov as NCT01530139. *Am J Clin Nutr* 2016;104:288–97.

Keywords: Mediterranean diet, Food4Me, personalized nutrition, Internet-based, European adults

INTRODUCTION

The burden of noncommunicable diseases and obesity has grown rapidly in the past 30 y (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 highly refined carbohydrate foods are associated with obesity and type 2 diabetes (3, 4). In contrast, the Mediterranean diet (MedDiet),[14]

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[2] Supplemental Tables 1–7 are available from the ''Online Supporting Material'' link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

[13] These authors contributed equally to this work and are joint first authors.

*To whom correspondence should be addressed. E-mail: john.mathers@newcastle.ac.uk.

[14] Abbreviations used: *APOE*, apolipoprotein E; BMR, basal metabolic rate; CC, complete case; *FADS1*, fatty acid desaturase 1; FFQ, food-frequency questionnaire; *FTO*, fat mass and obesity–associated; ITT, intention-to-treat; 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; LOCF, last observation carried forward; LMM, linear mixed model; MedDiet, Mediterranean diet; *MTHFR*, methylenetetrahydrofolate reductase; PA, physical activity; PN, personalized nutrition; PoP, proof-of-principle; PREDIMED, Prevención con Dieta Mediterránea; RCT, randomized controlled trial; *TCF7L2*, transcription factor 7-like 2; WC, waist circumference.

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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 noncommunicable diseases (6, 7) and obesity (8–10). In addition, randomized controlled trials (RCTs) showed that MedDiet-based interventions reduced the risk of cardiovascular disease in both primary and secondary prevention studies (11, 12).

Several approaches for scoring the MedDiet have been developed (13, 14), including the PREDIMED (Prevención con Dieta Mediterránea) 14-point score (15, 16). The latter identified 14 dietary components that best characterized the MedDiet and showed that higher MedDiet scores were associated with ≤30% lower incidence of cardiovascular events (15, 17). On the basis of such evidence, there is strong reason to believe that changing dietary intakes so that they align better with the MedDiet would produce substantial public health benefit (18). However, achieving such changes may be challenging with current intervention strategies that use "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 genetics-based PN interventions have shown 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 (NCT01530139) was the first Internet-based study, to our knowledge, to show that PN advice was more effective in improving dietary intakes, including lowering intakes of red meat and improving diet quality, than conventional "one size fits all" population-based advice (24). Given that the MedDiet is widely recognized as a healthy eating pattern, in this analysis we used the MedDiet score as an external (objective) reference to investigate whether Internet-based PN advice improved the "healthfulness" of participants' diets.

The Food4Me PoP study was a 6-mo, Internet-based, PN intervention across 7 European countries designed to improve dietary intakes. The present article aimed to evaluate the effect of this PN intervention by comparing differences in MedDiet scores at month 6 between treatment arms.

METHODS

Study design

The Food4Me PoP study (25) was a 6-mo, 4-arm, Internet-based RCT conducted across 7 European countries and was designed to compare the effects of personalized dietary and physical activity (PA) advice with generalized advice in changing dietary and lifestyle behaviors (26). The intervention was intended to emulate a "real life" Internet-based PN service, in which all advice was delivered via the Internet. Participants were recruited to the intervention study via the Food4Me website (25) and were asked via e-mail to complete online questionnaires and provide biological samples at 3 fixed time points (i.e., after baseline and at 3 and 6 mo). Online information about the study was available to participants, which included, for example, video clips describing how to make anthropometric measurements and collect biological samples. This design was complemented by an online interface through which participants could interact via e-mail with the dietitians, nutritionists, and researchers at each center during the 6-mo intervention. The primary aims of the Food4Me study were as follows: *1*) to determine whether personalization of dietary advice assisted and/or motivated participants to choose a healthier diet in comparison with nonpersonalized conventional healthy eating guidelines and *2*) 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 randomly assigned to 1 of 4 intervention arms by using an urn randomization scheme (27) and received either nonpersonalized general dietary advice [control; level 0 (L0)] or 1 of 3 levels of PN. To encourage dietary and lifestyle change, behavioral change techniques derived from work by Michie et al. (28, 29) on smoking cessation and dietary behavior change were used. Participants were asked to complete an online food-frequency questionnaire (FFQ) and the 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

A total of 1607 participants were randomly assigned to the study and were recruited between August 2012 and August 2013 from the following centers: University College Dublin (Ireland), Maastricht University (Netherlands), University of Navarra (Spain), Harokopio University (Greece), University of Reading (United Kingdom), National Food and Nutrition Institute (Poland), and Technical University of Munich (Germany). The research ethics committees at each university or research center delivering the intervention granted ethical approval for the study. All participants who expressed an interest in the study were asked to sign online consent forms at 2 stages in the screening process. These consent forms were automatically directed to the local study investigators to be countersigned and archived (26).

Eligibility criteria

On the basis of sample size calculations we aimed to recruit a total of 1540 study participants. As per the eligibility criteria, participants aged ≥18 y were included in the study. The following sets of exclusion criteria were applied: *1*) pregnant or lactating; *2*) no or limited access to the Internet; *3*) adhering to a prescribed diet for any reason, including weight loss, in the past 3 mo; and *4*) presence of diabetes, celiac disease, Crohn 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 by using an urn randomization scheme. Those randomly assigned to level 1 (L1) received personalized dietary advice on the basis of current diet and PA alone; level 2 (L2) received personalized dietary advice

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on the basis of dietary, PA, and phenotypic data; and level 3 (L3) received personalized dietary advice on the basis of dietary, PA, and 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 (fruit and vegetables, wholegrain products, fish, dairy products, and meat). Personalized phenotypic feedback used anthropometric measurements and nutrient- and metabolic-related biomarkers to derive personalized feedback, and specific variants in 5 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 randomly assigned to the control arm (L0) received dietary advice on the basis of population-level healthy eating guidelines. This nonpersonalized dietary advice was derived from national dietary recommendations in each of the 7 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 who were randomly assigned to L1, L2, and L3 received personalized feedback reports via e-mail at baseline, month 3, and month 6 of the intervention. For those randomly assigned to PN, algorithms were used to provide participants with 3 specific dietary goals according to the individual's intakes of nutrients. For participants randomly assigned to L2 and L3, the dietary advice was also based on phenotypic data (L2) and phenotypic plus genotypic data (L3). Reported intakes were compared with recommended intakes and determined to be adequate, high, or low. If intakes were too high or too low, contributing foods were identified and specific messages developed to advise change in the intake of those foods. Estimations of healthy behaviors were explained by using a 3-color sliding scale: green represented "good, no change recommended," amber represented "improvement recommended," and red represented "improvement strongly recommended." For the genotype-based information, risk was indicated by using "yes" or "no" according to whether the participant did, or did not, carry the higher risk variant for each of the 5 nutrient-related genes included in the study. In addition, each report contained a personalized message from the dietitian/nutritionist to the participant. Further details of the protocol are provided elsewhere (26).

Participant characteristics and dietary intakes

After being randomly assigned, participants completed online questionnaires on sociodemographic, health, and anthropometric characteristics at baseline. Participants also completed an online FFQ to estimate usual dietary intakes at baseline and at months 3 and 6 of the intervention. This FFQ, which was developed and validated for the Food4Me Study (30, 31), included 157 food items consumed frequently in each of the 7 recruitment countries. Intakes of foods and nutrients were computed in real time by using a food-composition database based on McCance and Widdowson's *The Composition of Foods* (32). Intakes were assessed by using a standardized set of recommendations (26) for foods and food groups that were integrated and harmonized across 8 European countries (United Kingdom, Ireland, Germany, Netherlands, Spain, Greece, Poland, and Norway) (33–36). Further details are provided elsewhere (30).

Adherence to the MedDiet was estimated on the basis of the PREDIMED 14-point criteria (11, 16) (**Supplemental Table 1**). FFQs at baseline and at month 6 were used to derive each of the following criteria: a higher intake of olive oil than other cooking fat; a higher intake of white meat than red meat; and a 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 criteria they met and 0 for each they did not meet; points were summed to create an overall MedDiet score, ranging from 0 to 14 (16). A dichotomous variable for MedDiet score was created ["low" (operationalized as a score $\leq$5) and "high" (score $>$5)] on the basis of a median MedDiet score of 5 at baseline.

Anthropometric, sociodemographic, and PA measures

Body weight (in kg), height (in m), and waist circumference (WC; in 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. BMI (in kg/m^2) was estimated from body weight and height. Self-reported measurements were validated in a subsample of participants (n = 140) and showed a high degree of reliability (37). PA level [ratio between total energy expenditure and basal metabolic rate (BMR)], moderate and vigorous PA [the percentage of individuals meeting PA recommendations ($>$150 min of moderate PA or $>$75 min of vigorous PA or an equivalent combination of moderate and vigorous PA/wk (38)], and time spent in sedentary behaviors were estimated from triaxial accelerometers (TracmorD; Philips Consumer Lifestyle).

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 salary for each occupation was $>$0.5 SDs from the mean European salary, these participants were placed in group 1, salaries between 0.5 to $-$0.5 SDs were placed into group 2, and those $<-$0.5 SDs were placed into group 3. The following groups and group names were generated: group 1, "professional or managerial"; group 2, "intermediate"; and group 3, "routine or manual" (39, 40). Categories for "students" and "retired or unemployed" were added.

Statistical analyses

Data were analyzed by using Stata (version 13; StataCorp) on the basis of intention-to-treat (ITT) analysis of all individuals randomly assigned into the intervention with baseline data (n = 1480). Logistic and multiple linear regressions were used to test for significant differences between groups at baseline for categorical and continuous variables, respectively. Comparisons between low and high MedDiet scores at baseline were adjusted

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for baseline age, sex, and country. PA outcomes were further adjusted for time spent wearing the accelerometer at baseline and season. To answer our primary research question—"What effect does a PN intervention have on dietary changes associated with the MedDiet?"—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 variable estimates (treatment arms) were specified at month 6 only. Contrast analyses were used to compare treatment arms. The principal assessment of differences in MedDiet scores used contrast 1, which compared L0 (control) with the mean of L1–L3 (mean of all 3 PN arms). Contrast 2, which compared 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, which compared L2 with L3, tested whether the addition of genotypic information promoted changes that differed from those that used phenotypic and dietary information only.

On the basis of 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 on the basis of the last observation carried forward (LOCF) method (n = 1480) and a complete case (CC) analysis (n = 1270). Additional sensitivity analyses adjusted for over- and underreporters of total energy intake: underreporting was operationalized as an energy intake less than the BMR × 1.1 (42), where BMR was calculated according to the Oxford equation (43) and overreporting as an intake >4500 kcal/d (44). Furthermore, analyses in individuals who were randomly assigned to L3 were stratified by carriage of the risk genotype for methylenetetrahydrofolate reductase (*MTHFR*), fat mass and obesity–associated (*FTO*), transcription factor 7-like 2 (*TCF7L2*), apolipoprotein E [*APOE(e4)*], and fatty acid desaturase 1 (*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 1 copy of the risk allele, and "2" if they had 2 copies of the risk allele for each gene. A second variable was generated to indicate if an individual had no copies (0), 1 copy (1), or 2 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 randomly assigned into the intervention. One hundred twenty-seven participants dropped out immediately after randomization, which left a total of 1480 participants who provided dietary data at baseline and for the 6-mo intervention. An additional 210 participants were lost to follow-up; therefore, 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**.

Sociodemographic, anthropometric, and health-related characteristics by MedDiet score

The mean ± SD age of participants was 39.9 ± 13.0 y, 59% were female, and 97% were white (**Table 1**). Participants with a high MedDiet score at baseline were, on average, 1.5 y older than those with a low score (P = 0.005). There were no differences in sex or ethnicity between high and low scorers. Thirty-nine percent 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 MedDiet scorers (Table 1).

High MedDiet scorers weighed 2.3 kg less (P = 0.003), had a 0.5-unit lower BMI (P = 0.007), and a 1.9-cm lower WC ($P <$ 0.001) than low scorers (Table 1). High MedDiet scorers spent less time in sedentary behaviors (P = 0.005), had a higher PA level (P = 0.003) and moderate and vigorous PA ($P < 0.001$), and met more PA recommendations (P = 0.022) than low scorers (Table 1). More low MedDiet scorers wanted to lose weight than did high scorers (49% compared with 45%; P = 0.041; Table 1), whereas more high scorers reported adhering to a restricted diet (9% compared with 6%; P = 0.014; Table 1).

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

Dietary intakes by MedDiet score

Although energy intakes did not differ, the energy intake-to-BMR ratio was higher in high MedDiet scorers than in low MedDiet scorers (1.72 ± 0.70 compared with 1.62 ± 0.63; P = 0.012; **Table 2**). As expected, high MedDiet scorers had a lower percentage of energy intakes from total fat ($P < 0.001$) and SFAs ($P < 0.001$) and a higher percentage of energy intakes from MUFAs (P = 0.009) and PUFAs ($P < 0.001$) than did low scorers (Table 2). Percentages of energy intakes from protein and sugars were 1.2% and 1.7% higher in high MedDiet scorers than in low scorers, respectively ($P < 0.001$), whereas percentages of energy intakes from carbohydrates were 0.8% lower (P = 0.042). Salt intake did not differ significantly between high and low MedDiet scorers (Table 2).

More high MedDiet scorers met the recommendations for consumption of oily fish (+36%; $P < 0.001$), red meat (+7%; P = 0.006), and fruit and vegetables (+41%; $P < 0.001$) than did low scorers (Table 2). No significant differences in intakes of whole grains or low-fat dairy products were observed between MedDiet scorers (Table 2).

Differences in MedDiet scores after the intervention

After the 6-mo intervention, improvements in MedDiet scores were greater in individuals randomly assigned to PN (mean L1, L2 and L3) than in controls (L0) (PN compared with control arms: 5.20 ± 0.05 and 5.48 ± 0.07, respectively; P = 0.002; **Table 3**). MedDiet scores at month 6 in participants who received PN advice on the basis of current diet alone (L1) were not significantly different from those randomly assigned to L2 and L3 [who received advice on the basis of current diet + phenotype (L2) and diet + phenotype + genotype (L3)] (Table 3). However, MedDiet scores at month 6 for participants who received PN advice in L3 (diet + phenotype + genotype) were greater than in participants in L2 at month 6 (L3 compared with L2: 5.63 ± 0.10 and 5.38 ± 0.10, respectively; P = 0.029; Table 3).

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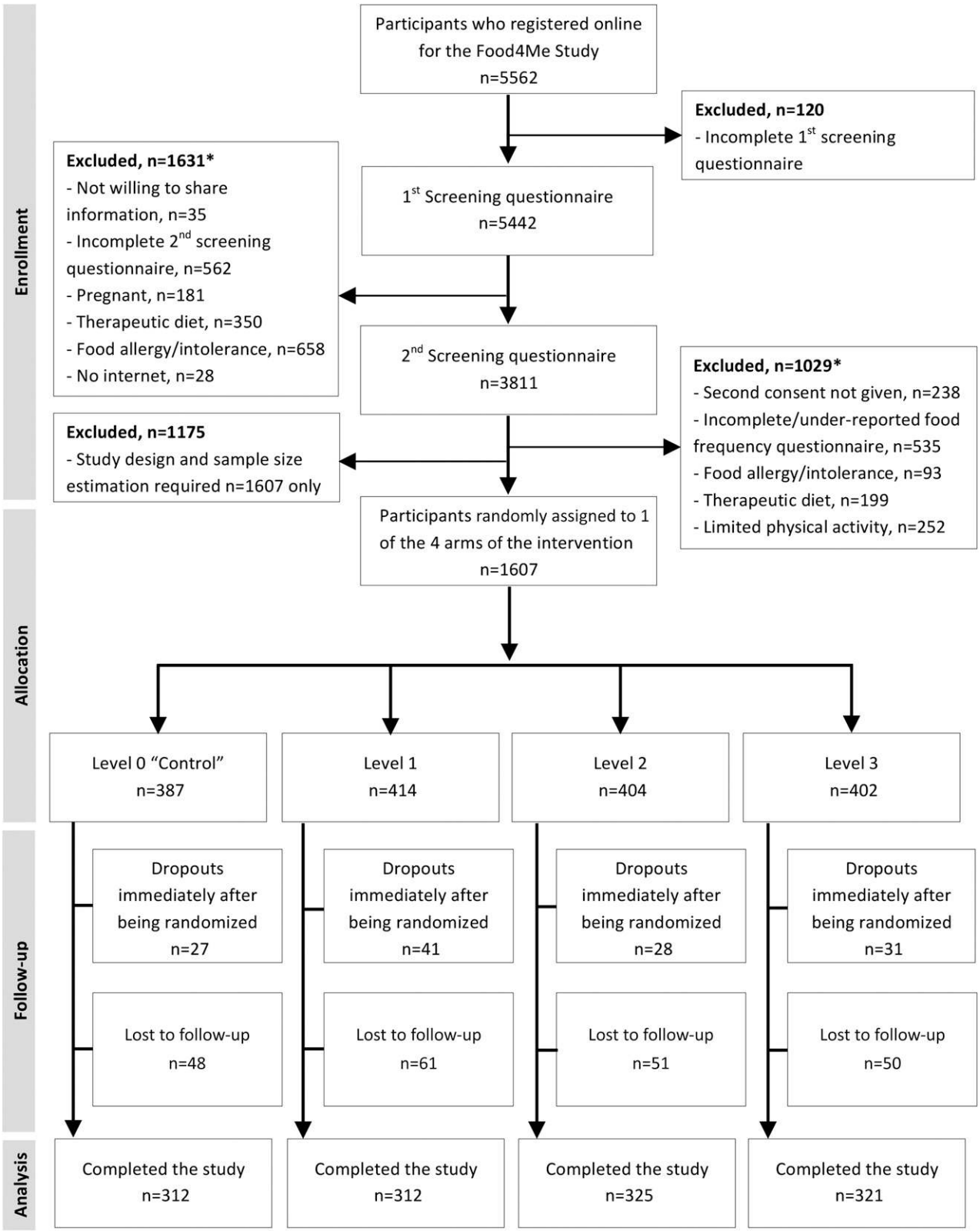

FIGURE 1 CONSORT (Consolidated Standard of Reporting Trials) diagram showing participants who were randomly assigned to the Food4Me proof-of-principle study. *Total number of participants who reported ≥1 exclusion criteria.

MedDiet scores at month 3 between intervention arms were lower in those randomly assigned to L2 than those in L3 (P = 0.010) (**Supplemental Table 3**).

MedDiet scores at month 6 when stratified by country were not significantly different between the control and PN arms (mean L1, L2, and L3). For the Netherlands only, MedDiet

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TABLE 1
Sociodemographic characteristics of participants according to MedDiet score at baseline[1]

	All	Low MedDiet score (≤5)	High MedDiet score (>5)	*P*
n	1480	880	600	
MedDiet score	5.12 ± 1.68[2]	3.99 ± 1.02	6.77 ± 0.92	<0.001
Age, y	39.9 ± 13.0	39.3 ± 12.9	40.8 ± 13.1	0.005
Female, %	58.5	57.2	60.3	0.21
Ethnicity, %				
White	96.8	97.3	96.0	0.42
Occupation, %				
Professional or managerial	39.2	38.1	40.9	0.39
Intermediate occupations	26.1	26.3	25.7	0.39
Routine or 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
Anthropometric measurements				
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[3]				
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
Meets physical activity 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, %				
Wants 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]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. MedDiet, Mediterranean diet; MVPA, moderate and vigorous physical activity; PAL, physical activity level.
[2]Mean ± SD (all such values).
[3]Physical activity measures were available for 1285 participants only.

scores were higher for L3 participants than for L2 participants (P = 0.013) (**Supplemental Table 4**). When Mediterranean (Greece and Spain) and non-Mediterranean countries (United Kingdom, Ireland, Netherlands, Germany, and Poland) were grouped, the effect of PN (mean L1, L2, and L3) compared with the control on MedDiet scores at month 6 was significant in non-Mediterranean countries only (PN compared with control: 5.31 ± 0.09 and 5.02 ± 0.06, respectively; 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 was consistent across LMM, LOCF, and CC analyses and that the use of LMM produced the most conservative estimate of MedDiet score at month 6 (**Supplemental Table 5**).

To understand the influence of genetic risk on MedDiet score at month 6, analyses were stratified by nonrisk and risk carriers for each of the 5 genes. For *FTO* and *MTHFR* genes, MedDiet score at month 6 was higher in individuals randomly assigned to PN than in those in the control arm in risk carriers only. The effect of PN on MedDiet score at month 6 was similar for risk and nonrisk carriers for *APOE* and *TCF7L2* but was only significant for nonrisk carriers of *FADS1* (**Supplemental Table 6**). As summarized in **Supplemental Table 7**, disclosure of genetic information made little difference in MedDiet score at month 6 for individuals randomly assigned to PN compared with controls, although differences were apparent between L2 and L3.

Adjustment for under- and overreporters did not change the pattern of results (data not shown). Stratifying analyses by carriage of a risk allele for any 1 of the 5 genes studied showed that in participants with 2 copies of a risk allele of any of the 5 genes, MedDiet scores at month 6 were greater in participants randomly assigned to PN (mean L1, L2, and L3) than in those randomly assigned to the control (5.69 ± 0.11 compared with 5.14 ± 0.08; $P < 0.001$; data not shown). However, no significant differences in MedDiet between the PN and control arms were observed in individuals carrying 1 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).

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TABLE 2
Dietary intakes of participants according to MedDiet score at baseline[1]

	All	Low MedDiet score (≤5)	High MedDiet score (>5)	*P*
n	1480	880	600	
MedDiet score	5.12 ± 1.68[2]	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 to BMR ratio	1.66 ± 0.66	1.62 ± 0.63	1.72 ± 0.70	0.012
Total fat, % of energy	35.9 ± 5.91	36.4 ± 5.71	35.2 ± 6.12	<0.001
SFAs, % of energy	14.1 ± 3.14	14.9 ± 3.16	13.0 ± 2.73	<0.001
MUFAs, % of energy	13.7 ± 3.12	13.6 ± 2.85	13.9 ± 3.48	0.009
PUFAs, % of energy	5.7 ± 1.44	5.6 ± 1.38	5.9 ± 1.52	<0.001
Protein, % of energy	17.1 ± 3.71	16.6 ± 3.49	17.8 ± 3.91	<0.001
Carbohydrate, % of energy	46.0 ± 7.60	46.3 ± 7.28	45.5 ± 8.03	0.042
Sugars, % of 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
Whole grains	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]Multiple linear regression was used to test for significant differences between groups adjusted for age, sex, and country. BMR, basal metabolic rate; EI, energy intake; MedDiet, Mediterranean diet.
[2]Mean ± SD (all such values).

DISCUSSION

Main findings

The main findings from our secondary analysis of 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 MedDiet. We observed that PN was more effective than generalized dietary advice (control) in improving MedDiet scores. Furthermore, the addition of genotypic information to PN advice improved MedDiet

TABLE 3
Effect of PN intervention on MedDiet score components at baseline and month 6[1]

			PN			*P*		
	Control mean (L0)	PN (mean L1, L2, L3)	L1	L2	L3	L0 vs (L1+L2+L3)	L1 vs (L2+L3)	L2 vs L3
Baseline, *n*	360	1120	373	376	371			
MedDiet 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
MedDiet 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
Carbonated 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 are adjusted means ± SEs unless otherwise indicated. Contrast analyses were used to test for significant differences between arms; 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); MedDiet, Mediterranean diet; PN, personalized nutrition.

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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 nutrients (26), and findings from this intervention showed that PN (mean L1, L2, and L3) was more effective than "one size fits all" generalized dietary advice for lowering red meat (8.5%; $P = 0.046$) and salt (6.3%; $P = 0.008$) intakes and improving Healthy Eating Index score (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 MedDiet score. In contrast to the main analysis of the PN intervention, our secondary analysis of differences in MedDiet scores between treatment arms suggests that the provision of genotype-based advice offers added benefit compared with 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 whether 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 the MedDiet score in particular, and thus the present findings should not be considered in isolation.

Previous studies evaluated the associations between adherence to the MedDiet and health outcomes, including obesity, metabolic syndrome, and type 2 diabetes. We confirmed findings from the PREDIMED study that showed that individuals with low MedDiet adherence were more likely to be current smokers, have a higher BMI and WC, and lower PA (10, 18). The PREDIMED study found that low socioeconomic status was associated with low MedDiet adherence and, although not significant in the Food4Me study, we observed higher percentages of individuals in routine or manual occupations in the low MedDiet score group than in 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 of a MedDiet on dietary quality, as evidenced by lower intakes of SFAs and higher intakes of MUFAs and PUFAs and more individuals meeting food-based dietary recommendations. In the Food4Me Study, a higher MedDiet 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 differences in MedDiet score. In the PREDIMED study, 1551 individuals were randomly assigned to receive either leaflets providing generalized dietary advice on the basis of American Heart Association guidelines (control) or personalized advice in 1 of 2 MedDiet groups (45). Participants randomly assigned to receive personalized advice received motivational interviews every 3 mo to negotiate nutritional goals, as well as group educational sessions on a quarterly basis. Participants exposed to the MedDiet-based intervention increased consumption of olive oil, nuts, vegetables, legumes, and fruit and reduced consumption of meat, pastries, cakes, and sweets, thus improving overall dietary patterns and supporting the use of PN in facilitating change toward a Mediterranean-style diet. Previous PN interventions have achieved improvements in sodium intake in individuals at higher genotype-based risk (20); however, the Food4Me PoP study was the first, to our knowledge, 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 MedDiet scores between treatment arms were only evident in non-Mediterranean countries. Baseline MedDiet scores were low in Greece compared with Spain, and changes after the intervention were smaller than in all other countries, which warrants further investigation.

Strengths and limitations

The present study has a number of strengths. Our participants were drawn from 7 European countries, facilitating the comparison of MedDiet scores between Mediterranean and non-Mediterranean countries. Our estimation of the MedDiet was based on the PREDIMED 14-point score, which is a validated and widely used MedDiet score. We estimated changes in MedDiet 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 3 recommended analytic 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 measurements has been confirmed in our study (37). Dietary intakes were estimated by an FFQ, which is subject to misreporting error (46), but this was minimized by previous validation against a 4-d weighed food record (31). The small sample size limited our power to investigate the effect of individual genes in the present study. In addition, 97% of our study participants were white 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 an improved diet and PA (47). Furthermore, the Food4Me PoP study did not aim to change MedDiet scores specifically, rather the overall diet, which may indirectly have improved MedDiet scores.

Implications of findings

PN is a more effective approach for improving MedDiet score than generalized dietary advice. A systematic review and meta-analysis of observational evidence by Sofi et al. (5) found that a 2-point increase (10-point scale) in adherence to the MedDiet was associated with a significant reduction in overall mortality (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). There is also accumulating evidence from intervention studies that randomization to the MedDiet reduced cardiovascular disease 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

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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 on the basis of a combination of their diet, phenotype, and genotype is advantageous. In addition, Internet-based approaches offer important opportunities for scaling up PN interventions in a cost-effective manner.

Conclusions

After a 6-mo RCT, MedDiet scores were greater in individuals who received PN advice than in those who received nonpersonalized advice. Furthermore, improvements in MedDiet score were greater in individuals who received PN on the basis of diet, phenotype, and genotype compared with advice based on diet and phenotype alone.

The authors' responsibilities were as follows—CAD, YM, IT, ERG, LB, JAL, WHS, HD, M Gibney, JAM, and JCM: contributed to the research design; JCM: was the Food4Me PoP study leader; CC-M, SN-C, RS-C, RF, HF, CW, CBO, CFMM, SK, LT, CPL, GM, M Godlewska, AS, ERG, LB, MCW, JAM, and JCM: contributed to developing the standardized operating procedures for the study; CC-M, SN-C, RS-C, RF, HF, CW, CBO, CFMM, SK, LT, CPL, GM, M Godlewska, AS, MCW, JAM, and JCM: conducted the intervention; CC-M, CFMM, and WHS: contributed to PA measurements; KML and CC-M: wrote the manuscript and performed the statistical analysis and are joint first authors; and all authors: contributed to a critical review of the manuscript during the writing process and approved the final manuscript. None of the authors had a personal or financial conflict of interest.

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