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The effect of the apolipoprotein E genotype on response to personalized dietary advice intervention: findings from the Food4Me randomized controlled trial[1]

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ABSTRACT

Background: The apolipoprotein E (*APOE*) risk allele (ε4) is associated with higher total cholesterol (TC), amplified response to saturated fatty acid (SFA) reduction, and increased cardiovascular disease. Although knowledge of gene risk may enhance dietary change, it is unclear whether ε4 carriers would benefit from gene-based personalized nutrition (PN).

Objectives: The aims of this study were to *1*) investigate interactions between *APOE* genotype and habitual dietary fat intake and modulations of fat intake on metabolic outcomes; *2*) determine whether gene-based PN results in greater dietary change than do standard dietary advice (level 0) and nongene-based PN (levels 1–2); and *3*) assess the impact of knowledge of *APOE* risk (risk: E4+, nonrisk: E4−) on dietary change after gene-based PN (level 3).

Design: Individuals (n = 1466) recruited into the Food4Me pan-European PN dietary intervention study were randomly assigned to 4 treatment arms and genotyped for *APOE* (rs429358 and rs7412). Diet and dried blood spot TC and ω-3 (n–3) index were determined at baseline and after a 6-mo intervention. Data were analyzed with the use of adjusted general linear models.

Results: Significantly higher TC concentrations were observed in E4+ participants than in E4− ($P < 0.05$). Although there were no significant differences in *APOE* response to gene-based PN (E4+ compared with E4−), both groups had a greater reduction in SFA (percentage of total energy) intake than at level 0 (mean ± SD: E4+, −0.72% ± 0.35% compared with −1.95% ± 0.45%, P = 0.035; E4−, −0.31% ± 0.20% compared with −1.68% ± 0.35%, P = 0.029). Gene-based PN was associated with a smaller reduction in SFA intake than in nongene-based PN (level 2) for E4− participants (−1.68% ± 0.35% compared with −2.56% ± 0.27%, P = 0.025).

Conclusions: The *APOE* ε4 allele was associated with higher TC. Although gene-based PN targeted to *APOE* was more effective in reducing SFA intake than standard dietary advice, there was no difference between *APOE* "risk" and "nonrisk" groups. Furthermore, disclosure of *APOE* nonrisk may have weakened dietary response to PN. This trial was registered at clinicaltrials.gov as NCT01530139. *Am J Clin Nutr* doi: 10.3945/ajcn.116.135012.

Keywords: *APOE*, nutrigenomics, Food4Me, dietary fat, personalized nutrition

INTRODUCTION

Coronary artery disease (CAD)[15] is the leading cause of global mortality, accounting for 1 of 5 deaths in Europe (1). Recent estimates suggest that up to 80% of CHD and cerebrovascular disease could be avoided by improving diet and lifestyle (2).

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[15] Abbreviations used: *ACE*, angiotensin-converting enzyme; *APOE*, apolipoprotein E; BCT, behavioral change technique; CAD, coronary artery disease; DBS, dried blood spot; *FADS*, fatty acid desaturase; *FTO*, fat mass and obesity-associated; GLM, general linear model; *MTHFR*, methylene tetrahydrofolate reductase; PA, physical activity; PN, personalized nutrition; RCT, randomized controlled trial; TC, total cholesterol; *TCF7L2*, transcription factor 7-like 2; %TE, percentage of total energy.

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Although intervention strategies traditionally have used a one-size-fits-all approach to changing dietary behavior, evidence suggests that a personalized approach may be more effective (3, 4). Moreover, there has been much interest in the use of genetic information to tailor dietary advice, yet further randomized controlled trials (RCTs) are needed to establish the benefit of such advice on sustained dietary changes (5, 6). Of particular interest in relation to CHD risk is the apolipoprotein E (*APOE*) genotype.

The *APOE* gene is a key regulator of cholesterol and lipid metabolism. *APOE* is polymorphic, with the common missense polymorphisms (rs429358 and rs7412) resulting in 3 alleles, ε2, ε3, and ε4, combining to form 6 haplotypes, E2/E2, E2/E3, E2/E4, E3/E3, E3/E4, and E4/E4. In a sample of 5805 Caucasians, the *APOE* allele frequency for ε2, ε3, and ε4 was 0.08, 0.77, and 0.15 respectively (7). The ε4 allele is associated with increased serum total cholesterol (TC) and LDL cholesterol, as well as coronary artery disease and mortality (8–12). Estimates of the CHD HR for E4+ (E3/E4 and E4/E4), compared with E4− (E3/E3), range from 1.06 to 1.42 (8, 9, 11, 13). There is also a growing body of evidence showing that the *APOE* genotype may influence lipid response to dietary fat; data from intervention studies suggest that E4+ participants may be more sensitive to dietary cholesterol, total fat, and, in particular, SFA modulation (14, 15). Given their predisposition to CHD, ε4 carriers might benefit from lower dietary SFAs and blood cholesterol (16) and gene-based personalized nutrition (PN) intervention. However, there is a concern that gene-based PN may reduce motivation for dietary change in individuals without risky genes and undermine current healthy eating messages (17).

The Food4Me study is a pan-European, 6-mo, Web-based RCT designed to assess the impact of personalizing dietary advice on change in dietary behavior. Participants were allocated to 1 of 4 intervention groups on the basis of standard guidelines (level 0, control); dietary intake (level 1); dietary intake and phenotype (level 2); and dietary intake, phenotype, and genotype (level 3). Level 3 participants received feedback on 5 genes: methylene tetrahydrofolate reductase (*MTHFR*), fatty acid desaturase (*FADS1*), transcription factor 7-like 2 (*TCF7L2*), fat mass and obesity-associated (*FTO*), and *APOE*.

The aim of the present analysis was to *1*) investigate interactions between *APOE* genotype and habitual dietary fat intake and modulations of fat intake on metabolic outcomes in the Food4Me study; *2*) assess whether gene-based PN led to greater changes in diet than did standard dietary advice (control) and nongene-based PN for E4− and E4+ participants; and *3*) assess the impact of knowledge of *APOE* risk on changes in diet and metabolic outcomes after gene-based PN.

METHODS

The Food4Me proof-of-principle study (NCT01530139) is a 6-mo randomized controlled dietary advice intervention study conducted in 7 European research centers: University College Dublin, Ireland; University of Reading, United Kingdom; Maastricht University, Netherlands; University of Navarra, Spain; Harokopio University, Greece; National Food and Nutrition Institute, Poland; and Technische Universität München, Germany. The study had a parallel design with 4 intervention arms and was conducted via the Web to emulate a Web-delivered PN service (www.food4me.org) (18). Ethics approval was granted at each center and digital informed consent was obtained before participation. The study was developed while following international regulations and the Helsinki Declaration.

Participants

A total of 1607 participants (aged ≥18 y) were recruited to the Food4Me study, as detailed elsewhere (19). Exclusion criteria were no or limited access to the Internet, following a medically prescribed diet in the previous 3 mo, or presence of a condition likely to alter dietary requirements, e.g., Crohn disease, celiac disease, food allergy/intolerance, pregnancy, or lactation.

Study design

A randomization scheme that incorporated both sex and age categories (<45 y and >45 y) was used to allocate participants to 1 of the 4 Food4Me intervention groups, as follows—level 0: standard nonpersonalized dietary and physical activity (PA) advice; level 1: advice based on dietary intake and PA; level 2: advice based on dietary intake, PA, and phenotype (blood biomarkers); and level 3: advice based on dietary intake, PA, phenotype, and genotype. Detailed recruitment and study procedures are reported elsewhere (19).

Interaction with study participants was conducted remotely via the Food4Me website, by e-mail and post, with the use of standardized operating procedures. A study welcome pack was sent to the participants via post containing a dried blood spot (DBS) collection kit (Vitas), an Isohelix SK-1 DNA buccal swab kit (LCG Genomics), a TracmorD triaxial accelerometer (Philips Consumer Lifestyle), measuring tape, and standardized instructions for completion of baseline measurements (month 0). On the allocated study day and after an 8-h overnight fast, participants collected DBS and buccal swab samples, and measured their height, weight, and waist circumference. Questionnaires to be completed on the same day included the validated Food4Me food-frequency questionnaire (20, 21) and the validated Baecke PA questionnaire (22–24). Participants repeated these measurements, excluding the buccal cell sample, at 3 and 6 mo. The TracmorD triaxial accelerometer (25) was worn for the entire duration of the study, and data were uploaded on a biweekly basis.

Dietary feedback

After analysis of data collected at months 0 and 3, participants received tailored dietary feedback (in their native language) according to their study allocation group. The dietary feedback provided was based on a predefined set of algorithms that incorporated dietary, anthropometric, PA, phenotypic, and genotypic data when appropriate. The system was designed to ensure consistent feedback across centers and has since been successfully automatized (26). *APOE* gene variants were coded as "risk" [a genetic variation that can be modified by diet, i.e., E3/E4 or E4/E4 (E4+)] or "nonrisk" [E2/E2, E2/E3, E3/E3 (E4−)]. Along with the risk result, level 3 participants received the following basic information about the *APOE* genotype: "A specific variation of this gene is associated with a greater need to maintain healthy cholesterol concentrations. Decreasing saturated fat intake has been associated with an improvement in cholesterol and factors relating to cardiovascular health in these individuals." For level 3 E4+ participants with high dietary SFA intake and/or high blood

TC who were being advised to lower dietary SFAs, reference to gene risk was also included in the advice message, i.e., "You have a genetic variation that can benefit by keeping a healthy intake of saturated fat and a normal level of blood cholesterol."

Biochemical analysis

Participants were asked to complete 2 DBS cards, each containing 5 blood spots, at months 0, 3, and 6 ($\sim$150 μL blood/card). After the blood spots were dried at room temperature for 2–4 h, the cards were placed in a sealed aluminum bag (Whatman Foil Bags, item no. 10534321) containing a drying sachet (Sorb-it, item no. 10548234; Süd-Chemie) and posted back to the research center in their country. Researchers subsequently shipped the DBS cards to Vitas for analysis of whole-blood TC (liquid chromatography–UV) and ω-3 index [EPA (20:5n–3) + DHA (22:6n–3)/total fatty acids) × 100] (27). Fatty acids were measured with the use of gas chromatography–flame ionization detector.

DNA extraction and genotyping

Participants were instructed to rub the Isohelix SK-1 DNA buccal swab against the inside of their cheek for 1 min before returning it to a plastic tube containing an Isohelix Dri-Capsule. On return to the center, swabs were shipped to LCG Genomics for genotypic analysis. After DNA extraction, KASP genotyping assays were used to provide biallelic scoring of polymorphisms in the *APOE* gene (rs429358 and rs7412). Hardy-Weinberg equilibrium for multiple alleles was analyzed, with no significant deviation observed for rs7412 (0.91; $P = 1.00$), whereas rs429358 displayed linkage disequilibrium (0.005; $P = 0.008$).

Statistical analyses

Data are presented as means ± SEMs. Data were checked for normality of distribution, and skewed variables were normalized with the use of $\log_{10}$ (ω-3 index) and square root (TC) transformations. General linear models (GLMs), adjusted for center, sex, age, and BMI, were used to assess differences in baseline anthropometric and biochemical values between genotype groups. Habitual nutrient intake–gene interactions were assessed with the use of the same GLM, but with the addition of a dietary fat × genotype interaction term; fat was dichotomized by median intake to assess the impact of the *APOE* genotype on TC and ω-3 index in participants with a similar habitual intake. Post hoc Bonferroni tests were used to detect specific differences between groups.

Interactions between genotype and dietary fat on TC and ω-3 index after dietary advice intervention were assessed by measuring percentage change in dietary fat intake, with 0% used as a reference to dichotomize participants (i.e., reduction compared with increase in fat intake), and then using the resulting groups as fixed factors in the GLM. The interaction term genotype × change in fat was then added to the GLM, with the change in biomarker as the response variable and the respective preintervention/baseline biomarker value as a covariate. The model was adjusted for baseline variables, age, sex, center, and weight change [postintervention weight (kilograms) – preintervention weight (kilograms)].

The impact of knowledge of *APOE* risk (risk: E4+, E3/E4, and E4/E4; and nonrisk: E4−, E2/E2, E2/E3, and E3/E3) on change in diet and TC and ω-3 index (month 6 − month 0) for level 3 participants advised to lower their SFAs at baseline (with high dietary SFAs and/or high blood TC) was assessed with the use of GLMs. Models were adjusted for baseline variables, age, sex, center, and weight change. To assess whether gene-based PN led to greater changes in diet, TC, and ω-3 index (month 6 − month 0) than did standard dietary advice (level 0) and nongene-based PN (levels 1–2), a contrast analysis was performed. Separate analyses were conducted for E4+ (risk) and E4− (nonrisk), with level 3 as the reference group and levels 0, 1, and 2 as the comparison groups. As previously, participants with high dietary SFAs and/or high blood TC who were advised to lower their SFAs at baseline were included and analyses were adjusted for baseline variables, age, sex, center, and weight change. Statistical analyses were performed with the use of Stata version 13.0.

RESULTS

Subject characteristics

A total of 1466 of the 1607 participants randomly assigned to the Food4Me study were genotyped for *APOE* and included in the baseline analysis. Frequency of *APOE* genotype and *APOE* allele according to Food4Me country are presented in **Table 1**. *APOE* E2/E4 participants ($n = 27$) were removed from subsequent analysis because of their low population frequency. Subject characteristics, including anthropometric measurements and fasting biomarkers, are presented according to *APOE* genotype in **Table 2**. There was no evidence of a genotype-dependent difference in baseline anthropometric measurements, although E4+ participants had higher TC than did E4− subjects ($P = 0.040$ for E3/E3 and $P = 0.002$ for E2 carriers).

Habitual dietary and genotype effects at baseline

The associations between dietary fat (total fat, SFAs, MUFAs, PUFAs, and ω-3), *APOE* genotype, dietary fat × genotype interactions, and TC and ω-3 index are reported in **Table 3**. Dietary intake was dichotomized at the median (total fat, 35.8%; SFAs, 14.0%; MUFAs, 13.5%; PUFAs, 5.6; and ω-3, 0.67%) to determine the effect of specific genotypes in participants with similar habitual dietary fat intake; this is presented in Table 3 according to genotype group.

An independent effect of genotype was observed for dietary fat and TC concentrations at baseline (total fat, $P = 0.002$; SFAs, $P = 0.002$; MUFAs, $P = 0.002$; PUFAs, $P = 0.003$; and ω-3, $P = 0.004$), with the highest TC concentrations seen in carriers of the ε4 allele (E4+). Overall diet effects (SFAs, $P = 0.008$; MUFAs, $P = 0.025$; PUFAs, $P = 0.007$; and ω-3, $P < 0.001$) were observed for the ω-3 index, with lower dietary SFAs (11.7% ± 0.1%) and higher PUFAs (6.80% ± 0.05%) and ω-3 (0.89% ± 0.01%) fat intake associated with a higher ω-3 index. Although a significant MUFA × *APOE* interaction was observed for the ω-3 index ($P = 0.025$), no differences between genotype groups and fat intake were observed after post hoc analyses.

Dietary and genotype effects of the intervention (irrespective of group allocation)

The associations between change in dietary fat intake (total fat, SFAs, MUFAs, PUFAs, and ω-3), *APOE* genotype, and change

TABLE 1
Frequency of *APOE* genotype and *APOE* allele by Food4Me center[1]

	All	Ireland	United Kingdom	Netherlands	Germany	Poland	Spain	Greece
Genotype								
E2/E2	6 (0.4)	1 (0.5)	0 (0.0)	3 (1.4)	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)
E2/E3	152 (10.4)	14 (6.5)	22 (10.6)	28 (12.7)	21 (10.2)	29 (14.4)	22 (10.4)	16 (7.7)
E2/E4	27 (1.8)	3 (1.4)	6 (2.9)	3 (1.4)	7 (3.4)	4 (2.0)	1 (0.5)	3 (1.4)
E3/E3	922 (62.9)	133 (62.1)	132 (64.1)	124 (56.4)	125 (61.0)	125 (62.1)	139 (65.6)	144 (69.2)
E3/E4	330 (22.5)	57 (26.6)	43 (20.8)	58 (26.4)	48 (23.4)	38 (18.9)	46 (21.7)	40 (19.2)
E4/E4	29 (2.0)	6 (2.8)	3 (1.5)	4 (1.8)	4 (2.0)	3 (1.5)	4 (1.9)	5 (2.4)
Total	1466 (100)	214 (100)	206 (100)	220 (100)	205 (100)	201 (100)	212 (100)	208 (100)
E2 carriers[2]	158 (10.8)	15 (7.0)	22 (10.7)	31 (14.1)	21 (10.2)	31 (15.4)	22 (10.4)	16 (7.7)
E4 carriers[2]	359 (24.5)	63 (29.4)	46 (22.3)	62 (28.2)	52 (25.4)	41 (20.4)	50 (23.6)	45 (21.6)
Allele frequency								
ε2	6.5	4.4	6.5	8.4	6.8	8.9	5.4	4.6
ε3	79.3	78.7	76.2	75.9	77.8	76.0	81.6	82.7
ε4	14.2	16.8	17.4	15.7	15.3	15.1	13.0	12.7

[1]Values are *n* (%) or percentages, *n* = 1466. *APOE*, apolipoprotein E.
[2]Genotype groups combined; E2 carriers represent E2/E2 and E2/E3, and E4 carriers represent E4/E3 and E4/E4.

in fat × *APOE* interactions on TC and ω-3 index after intervention (month 6 − month 0) are reported in **Table 4**. Dietary intake was split into participants who reduced fat intake and those who increased fat intake. Mean reductions and increases in dietary fat intake are presented according to genotype group.

There was a significant impact of genotype on change in TC concentrations after dietary advice intervention (total fat, $P = 0.016$; SFAs, $P = 0.025$; MUFAs, $P = 0.019$; PUFAs, $P = 0.024$; and ω-3, $P = 0.027$). There were no independent effects of diet on lipid biomarkers after dietary advice intervention, although trends were observed for change in PUFA ($P = 0.068$) and ω-3 fat ($P = 0.087$) intake on ω-3 index. A trend was also observed for an ω-3 fat intake × *APOE* interaction on ω-3 index ($P = 0.087$).

Effect of knowledge of *APOE* gene risk on dietary change compared with other levels of personalization

The allocation of *APOE* risk according to intervention level is shown in **Figure 1**. Participants (levels 1–3) advised to lower dietary SFAs at baseline were selected for subsequent analysis. The effects of knowledge of *APOE* risk (E4+) in participants advised to reduce SFA intake at baseline on changes in diet, TC, and ω-3 index (month 6 − month 0) compared with other levels of personalization are reported in **Table 5**. A significantly greater reduction in total fat and SFAs [percentage of total energy (%TE)] was observed in E4+ participants receiving gene-based PN (level 3) than in those in the control group ($P = 0.034$ and $P = 0.035$, respectively). However, there were no differences in change in diet or biomarkers between personalized intervention groups.

The effects of knowledge of *APOE* nonrisk (E4−) in participants advised to reduce SFA intake at baseline on changes in diet, TC, and ω-3 index (month 6 − month 0) compared with other levels of personalization are reported in **Table 6**. As previously, participants receiving gene-based PN had a significantly greater reduction in dietary SFAs (%TE) than did those in the control group ($P = 0.029$). For total fat, a slight increase in intake was observed for the control group (level 0) compared with a reduction

TABLE 2
Anthropometric characteristics and fasting blood biomarkers by *APOE* genotype in European adults in the Food4Me study[1]

	APOE genotype				
		E4−		E4+	
	All (*n* = 1439)	E2 carriers (*n* = 158)	E3/E3 (*n* = 922)	E4 carriers (*n* = 359)	P^2
Sex, M/F, *n*/*n*	611/846				
Age, y	40 ± 0.4	40 ± 1	40 ± 0.4	40 ± 0.7	0.630
BMI, kg/m^2	25.5 ± 0.13	25.7 ± 0.4	25.4 ± 0.2	25.5 ± 0.3	0.704
Weight, kg	74.6 ± 0.44	76.8 ± 1.4	74.3 ± 0.5	75.4 ± 0.8	0.608
Waist circumference, m	0.86 ± 0.004	0.87 ± 0.01	0.86 ± 0.005	0.85 ± 0.01	0.693
Height, m	1.71 ± 0.003	1.73 ± 0.01	1.71 ± 0.003	1.72 ± 0.005	0.252
Cholesterol, mmol/L	4.59 ± 0.03	4.42 ± 0.08[a]	4.55 ± 0.03[a]	4.70 ± 0.05[b]	0.002
ω-3 index	5.68 ± 0.03	5.81 ± 0.10	5.66 ± 0.04	5.74 ± 0.06	0.341

[1]Data are means ± SEMs. Means without a common superscript letter differ between genotype groups, $P < 0.05$. *APOE*, apolipoprotein E.
[2]Data were analyzed by general linear model with adjustment for age, sex, center, and BMI. Where P for genotype < 0.05, a Bonferroni post hoc test was applied to determine between-group effects.

TABLE 3
Effect of *APOE* genotype and dietary fat intake (total and fat classes) on metabolic markers measured in dried blood spots at baseline in the Food4Me intervention study[1]

	E4−				E4+				
	E2 carriers (n = 158)		E3/E3 (n = 922)		E4 carriers (n = 359)		P^2		
	Low intake	High intake	Low intake	High intake	Low intake	High intake	Diet	Genotype	Diet × genotype
Total fat									
n	80	78	452	470	188	171			
Total fat, %TE	31.7 ± 0.4	39.9 ± 0.4	31.3 ± 0.2	40.6 ± 0.2	31.3 ± 0.3	40.6 ± 0.3			
Cholesterol, mmol/L	4.37 ± 0.11	4.48 ± 0.11	4.45 ± 0.04	4.64 ± 0.04	4.66 ± 0.07	4.73 ± 0.07	0.251	0.002	0.435
ω-3 index	5.81 ± 0.10	5.81 ± 0.13	5.66 ± 0.06	5.64 ± 0.06	5.79 ± 0.09	5.68 ± 0.09	0.989	0.344	0.456
SFAs									
n	77	81	456	466	187	172			
SFAs, %TE	11.7 ± 0.2	16.7 ± 0.2	11.7 ± 0.1	16.7 ± 0.1	11.6 ± 0.1	16.4 ± 0.1			
Cholesterol, mmol/L	4.40 ± 0.11	4.44 ± 0.11	4.49 ± 0.04	4.61 ± 0.04	4.66 ± 0.07	4.73 ± 0.07	0.413	0.002	0.789
ω-3 index	5.86 ± 0.14	5.76 ± 0.13	5.72 ± 0.06	5.58 ± 0.06	5.88 ± 0.09	5.57 ± 0.09	0.008	0.343	0.573
MUFAs									
n	84	74	451	471	185	174			
MUFAs, %TE	11.7 ± 0.2	15.5 ± 0.2	11.4 ± 0.1	16.1 ± 0.1	11.5 ± 0.1	16.1 ± 0.2			
Cholesterol, mmol/L	4.40 ± 0.10	4.45 ± 0.11	4.49 ± 0.04	4.60 ± 0.04	4.98 ± 0.07	4.80 ± 0.07	0.078	0.002	0.470
ω-3 index	5.67 ± 0.13	5.97 ± 0.14	5.71 ± 0.06	5.60 ± 0.06	5.86 ± 0.09	5.60 ± 0.09	0.025	0.280	0.025
PUFAs									
n	86	72	460	462	174	185			
PUFAs, %TE	4.7 ± 0.1	6.8 ± 0.1	4.6 ± 0.1	6.8 ± 0.1	4.7 ± 0.1	6.7 ± 0.1			
Cholesterol, mmol/L	4.38 ± 0.10	4.47 ± 0.11	4.51 ± 0.04	4.59 ± 0.04	4.69 ± 0.07	4.69 ± 0.07	0.445	0.003	0.614
ω-3 index	5.65 ± 0.13	6.00 ± 0.14	5.52 ± 0.06	5.77 ± 0.06	5.62 ± 0.09	5.84 ± 0.09	0.007	0.291	0.803
ω-3									
n	80	78	485	437	155	204			
ω-3, %TE	0.55 ± 0.01	0.90 ± 0.03	0.55 ± 0.01	0.89 ± 0.01	0.55 ± 0.01	0.89 ± 0.02			
Cholesterol, mmol/L	4.43 ± 0.11	4.41 ± 0.11	4.50 ± 0.04	4.61 ± 0.05	4.64 ± 0.08	4.74 ± 0.07	0.068	0.004	0.820
ω-3 index	5.50 ± 0.13	6.12 ± 0.08	5.34 ± 0.05	5.99 ± 0.06	5.30 ± 0.09	6.07 ± 0.08	<0.001	0.546	0.463

[1]Values are means ± SEMs. Intake of fat was dichotomized at the median: total fat, 35.8% (low intake, 31.4% ± 0.1%; high intake, 40.5% ± 0.1%); SFAs, 14.0% (low intake, 11.7% ± 0.1%; high intake, 16.6% ± 0.1%); MUFAs, 13.5% (low intake, 11.5% ± 0.1%; high intake, 16.0% ± 0.1%); PUFAs, 5.6% (low intake, 4.67% ± 0.02%; high intake, 6.80% ± 0.05%); and ω-3, 0.67% (low intake, 0.55% ± 0.01%; high intake, 0.89% ± 0.01%). Genotype groups combined: E2 carriers represent E2/E2 and E2/E3; E4 carriers represent E4/3 and E4/E4. Low intake indicates less than median fat intake; high intake indicates greater than median fat intake. *APOE*, apolipoprotein E; %TE, percentage of total energy.

[2]Data were analyzed by general linear model with adjustment for center, sex, age, and BMI. Where P for diet × genotype < 0.05, a Bonferroni post hoc test was applied to determine between-group effects (significant differences were not detected post hoc).

in the level 3 group (difference 2.72%TE, P = 0.006). The opposite was observed for total carbohydrate, which was reduced in the control group (level 0) and increased in level 3 (difference 2.15% TE, P = 0.027).

When comparing levels of personalization, a 0.88% greater reduction in SFAs (%TE) was observed in E4− participants who received nongene-based PN (level 2; PN based on diet and phenotype) than in those E4− participants receiving gene-based PN (P = 0.025). There were no significant differences between change in total fat, PUFAs, MUFAs, ω-3, carbohydrate, and protein intake and TC and ω-3 index for E4− carriers according to whether they received gene-based or nongene-based PN (level 3 compared with levels 1–2).

Effect of knowledge of *APOE* genotype on dietary change after gene-based PN

The effect of knowledge of *APOE* risk (risk: E4+, E3/E4, and E4/E4, and nonrisk: E4−, E2/E2, E2/E3, and E3/E3) in participants advised to reduce SFA intake at baseline on changes in diet, TC, and ω-3 index (month 6 − month 0) after gene-based PN (L3) are reported in **Table 7**. Approximately 30% of E4− participants who received gene-based PN were advised to lower their SFA intake at baseline compared with 53% of E4+ carriers (Figure 1). After intervention, there were no significant differences in dietary response or change in biomarker between E4+ and E4− participants.

DISCUSSION

Key findings in the present analysis included higher TC concentrations in E4 carriers (E4+) and a nutrient intake–gene interaction between *APOE* genotype and MUFA intake for ω-3 index at baseline. After intervention, gene-based PN resulted in significantly greater reductions in total fat and SFAs (%TE) than did standard dietary advice (control), irrespective of gene risk. For E4− (nonrisk) participants advised to lower SFA intake, gene-based PN resulted in smaller changes in dietary SFA intake at month 6 than did nongene-based PN (level 2).

Although the *APOE* rs429358 distribution was not in Hardy-Weinberg equilibrium, the haplotype frequencies observed in the Food4Me cohort (ε2, 6.5; ε3, 79.3; ε4, 14.2) were similar to those

TABLE 4
Effect of *APOE* genotype and change in dietary fat intake (total and fat classes) on changes in metabolic markers measured in dried blood spots between baseline and month 6 for participants in the Food4Me intervention study[1]

	E4−				E4+				
	E2 carriers (n = 132)		E3/E3 (n = 794)		E4 carriers (n = 315)		P^2		
	Decreased intake	Increased intake	Decreased intake	Increased intake	Decreased intake	Increased intake	Diet	Genotype	Diet × genotype
Total fat									
n	72	60	424	370	178	137			
Total fat, %TE	−4.49 ± 0.42	3.90 ± 0.41	−4.91 ± 0.19	3.93 ± 0.18	−4.76 ± 0.29	4.16 ± 0.34			
Cholesterol, mmol/L	−0.26 ± 0.12	−0.24 ± 0.13	−0.18 ± 0.05	−0.21 ± 0.05	−0.26 ± 0.08	−0.03 ± 0.09	0.527	0.016	0.313
ω-3 index	0.24 ± 0.15	−0.08 ± 0.16	0.26 ± 0.06	0.25 ± 0.06	0.40 ± 0.09	0.15 ± 0.11	0.808	0.136	0.384
SFAs									
n	86	46	484	310	206	109			
SFAs, %TE	−2.56 ± 0.21	2.01 ± 0.23	−2.68 ± 0.10	1.75 ± 0.08	−2.48 ± 0.14	2.13 ± 0.19			
Cholesterol, mmol/L	−0.32 ± 0.11	−0.14 ± 0.14	−0.21 ± 0.05	−0.17 ± 0.06	−0.18 ± 0.07	−0.11 ± 0.10	0.982	0.025	0.941
ω-3 index	0.24 ± 0.14	−0.14 ± 0.17	0.33 ± 0.06	0.14 ± 0.07	0.39 ± 0.09	0.10 ± 0.12	0.986	0.069	0.377
MUFAs									
n	64	68	397	397	165	150			
MUFAs, %TE	−1.88 ± 0.18	1.65 ± 0.17	−2.10 ± 0.10	2.00 ± 0.10	−2.19 ± 0.15	2.13 ± 0.17			
Cholesterol, mmol/L	−0.29 ± 0.13	−0.21 ± 0.12	−0.21 ± 0.05	−0.19 ± 0.05	−0.29 ± 0.08	−0.01 ± 0.08	0.392	0.019	0.583
ω-3 index	0.25 ± 0.15	−0.04 ± 0.15	0.23 ± 0.06	0.28 ± 0.06	0.36 ± 0.10	0.21 ± 0.10	0.547	0.309	0.373
PUFAs									
n	58	74	357	437	153	162			
PUFAs, %TE	−0.83 ± 0.10	1.12 ± 0.11	−1.06 ± 0.06	1.13 ± 0.06	−0.93 ± 0.07	1.13 ± 0.09			
Cholesterol, mmol/L	−0.28 ± 0.13	−0.23 ± 0.12	−0.12 ± 0.05	−0.26 ± 0.05	−0.23 ± 0.08	−0.09 ± 0.08	0.611	0.024	0.148
ω-3 index	−0.004 ± 0.16	0.18 ± 0.14	0.18 ± 0.07	0.32 ± 0.06	0.41 ± 0.10	0.17 ± 0.10	0.068	0.467	0.303
ω-3									
n	53	79	294	500	129	186			
ω-3, %TE	−0.12 ± 0.02	0.18 ± 0.02	−0.14 ± 0.01	0.22 ± 0.02	−0.13 ± 0.01	0.15 ± 0.03			
Cholesterol, mmol/L	−0.15 ± 0.14	−0.32 ± 0.11	−0.23 ± 0.06	−0.18 ± 0.05	−0.18 ± 0.09	−0.14 ± 0.08	0.738	0.027	0.738
ω-3 index	0.02 ± 0.17	0.14 ± 0.14	0.02 ± 0.07	0.39 ± 0.06	0.24 ± 0.11	0.32 ± 0.09	0.087	0.412	0.087

[1]Values are mean changes ± SEMs (month 6 – month 0). Zero percent change in fat intake was used as a reference to dichotomize participants, i.e., comparison of reduction and increase in fat intake; total fat (decrease, −4.82% ± 0.15%; increase, 3.98% ± 0.15%), SFAs (decrease, −2.62% ± 0.08%; increase, 1.84% ± 0.08%), MUFAs (decrease, −2.10% ± 0.07%; increase, 1.99% ± 0.08%), PUFAs (decrease, −1.00% ± 0.04%; increase, 1.13% ± 0.04%), and ω-3 (decrease, −0.14% ± 0.01%; increase, 0.22% ± 0.02%). Genotype groups combined: E2 carriers represent E2/E2 and E2/E3; E4 carriers represent E4/3 and E4/E4. Increased intake indicates >0% change in fat intake; decreased intake indicates <0% change in fat intake. *APOE*, apolipoprotein E; %TE, percentage of total energy.

[2]Data were analyzed by general linear model with adjustment for baseline values, center, sex, age, and change in weight (month 6 – month 0).

reported in previous studies of European populations (28). In contrast to previous observations (29, 30), there was no clear geographic cline in ε4 frequency.

DBS TC differed according to *APOE* genotype, with significantly higher TC observed in E4+ participants than in E4− subjects. With respect to the difference in TC between E4+ and E4− subjects, E3/E3 in the present study (0.15 mmol/L) was similar to previous data (0.16–0.36 mmol/L) in a large meta-analysis of 54,377 participants (31).

At baseline, there was a significant nutrient intake–gene interaction between total MUFA intake and *APOE* on long-chain ω-3 index, a reliable biomarker of ω-3 status, and dietary ω-3 PUFA, EPA, and DHA intake (32, 33). Furthermore, there is a dose-dependent inverse association between ω-3 index and CHD mortality (33), with an index ≥8% offering the most cardioprotective effects and an index ≤4% being associated with the greatest risk of CHD mortality (27). Thus, the ω-3 index may be a risk factor for CHD (34). In the Food4Me study, a higher ω-3 index was associated with lower SFA and higher PUFA and dietary ω-3 intake. In a study investigating the determinants of ω-3 index in a Mediterranean population, there were significant associations between EPA and DHA intake and ω-3 index ($P < 0.001$) and a trend for an inverse association between dietary SFAs and ω-3 index ($P = 0.095$) (35).

It has been suggested that gene-based dietary information is more understandable and useful than general dietary guidelines (36), and may enhance motivation to change (37). In a 2010 systematic review, a beneficial effect of genome-based risk estimates on dietary behavior was reported (2 RCTs, pooled OR: 2.24; 95% CI: 1.17, 4.27; $P = 0.01$; $I^2 = 0\%$), but no benefit of genome-based risk estimates on intention to change dietary behavior was observed (5). Furthermore, in a Canadian RCT, knowledge of angiotensin-converting enzyme (*ACE*) gene risk resulted in a significantly greater reduction in sodium intake than with nongene-based advice (−287 ± 114 compared with 130 ± 118 mg/d, $P = 0.008$) at a 12-mo follow-up (38). Change in sodium intake by participants carrying the nonrisk *ACE* genotype (−244 mg/d) was not significantly different ($P = 0.11$) from the control group. In our present study, gene-based PN promoted significantly greater reductions in the intake of total

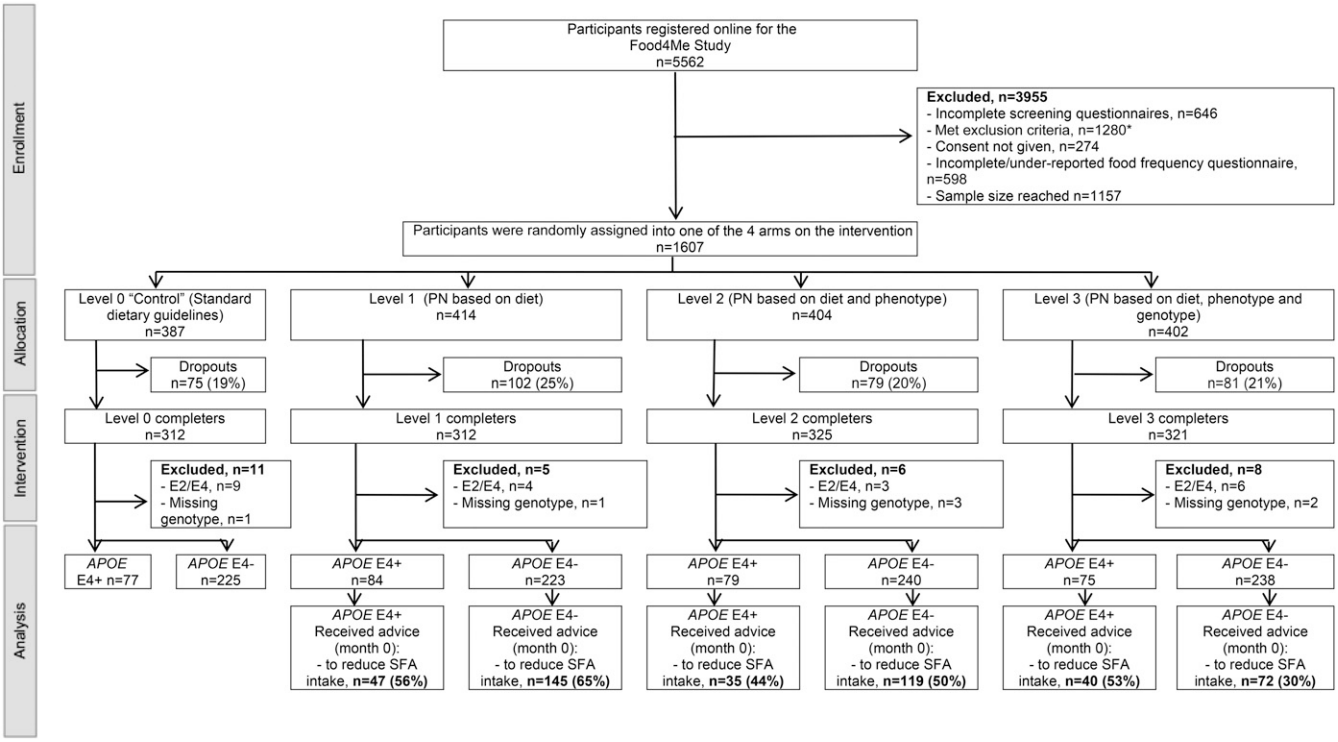

FIGURE 1 Consort diagram of participants randomly assigned to the Food4Me proof of principle study. *Total number of participants reporting ≥1 exclusion criteria. Parentheses in the analysis section (last row) indicate the percentage of each group who received advice to reduce SFA intake at month 0. *APOE*, apolipoprotein E; PN, personalized nutrition.

fat and SFAs than standard dietary advice (control), for both risk (E4+) and nonrisk (E4−) participants advised to lower SFAs. However, there were no significant differences in change of diet, TC, or ω-3 index between *APOE* risk groups (E4+ and E4−) receiving gene-based PN. In the REVEAL (Risk Evaluation and Education for Alzheimer's Disease) study, which investigated the impact of knowledge of Alzheimer disease risk (estimated with the use of *APOE* genotype and family history to generate a numerical risk) on dietary behaviors, E4+ participants were significantly more likely to endorse Alzheimer disease–specific health behavior change than E4− participants at a 12-mo follow-up (39). A similar result was observed in a study that investigated the impact of knowledge of *FTO* genotype on readiness to control weight, in which individuals with higher risk (AA or AT) displayed greater willingness to change than those with lower risk (TT) ($P = 0.051$) (40).

Although there was no additional benefit of gene-based PN for E4+ participants in the Food4Me study, knowledge of nonrisk

TABLE 5
Effect of knowledge of *APOE* risk (E4+) on change in dietary intake between baseline and month 6 for participants in the Food4Me intervention study[1]

	Control	Personalized intervention arms			P[2]		
	L0 *APOE* risk (n = 77)	L1 *APOE* risk (n = 47)	L2 *APOE* risk (n = 35)	L3 *APOE* risk (n = 40)	L3 vs. control (L0)	L3 vs. L1	L3 vs. L2
Total fat, %TE	0.37 ± 0.65	−3.03 ± 0.79	−1.63 ± 1.00	−3.07 ± 0.86	0.034	0.970	0.317
SFAs, %TE	−0.72 ± 0.35	−2.53 ± 0.37	−1.58 ± 0.56	−1.95 ± 0.45	0.035	0.335	0.537
MUFAs, %TE	0.37 ± 0.32	−0.71 ± 0.35	−0.41 ± 0.42	−1.05 ± 0.36	0.073	0.467	0.303
PUFAs, %TE	−0.04 ± 0.13	0.20 ± 0.19	0.30 ± 0.23	0.01 ± 0.23	0.718	0.965	0.720
ω-3, %TE	0.04 ± 0.03	0.08 ± 0.03	0.08 ± 0.03	0.08 ± 0.03	0.899	0.900	0.990
Carbohydrate, %TE	−0.89 ± 0.76	1.89 ± 0.85	0.11 ± 0.98	1.55 ± 0.92	0.127	0.945	0.130
Protein, %TE	0.38 ± 0.43	0.40 ± 0.43	0.49 ± 0.49	1.37 ± 0.40	0.392	0.245	0.226
BMI, kg/m^2	−0.25 ± 0.13	−0.35 ± 0.15	−0.04 ± 0.19	−0.44 ± 0.18	0.231	0.590	0.086
Cholesterol, mmol/L	−0.32 ± 0.11	−0.04 ± 0.16	−0.39 ± 0.15	−0.19 ± 0.16	0.240	0.663	0.228
ω-3 index	−0.04 ± 0.11	0.29 ± 0.16	0.38 ± 0.16	0.14 ± 0.16	0.545	0.610	0.240

[1]Values are mean changes ± SEMs (month 6 – month 0). E4− includes E2/E2, E2/E3, and E3/E3; E4+ includes E3/E4 and E4/E4. *APOE*, apolipoprotein E; L, level; %TE, percentage of total energy.

[2]Data were analyzed by general linear model with adjustment for baseline values, center, sex, age, and change in weight (month 6 – month 0).

TABLE 6
Effect of knowledge of *APOE* nonrisk (E4−) on change in dietary intake between baseline and month 6 for participants in the Food4Me intervention study[1]

	Control	Personalized intervention arms			P^2		
	L0 *APOE* nonrisk (n = 225)	L1 *APOE* nonrisk (n = 145)	L2 *APOE* nonrisk (n = 119)	L3 *APOE* nonrisk (n = 72)	L3 vs. control (L0)	L3 vs. L1	L3 vs. L2
Total fat, %TE	0.31 ± 0.37	−2.63 ± 0.47	−3.42 ± 0.51	−2.41 ± 0.66	0.006	0.280	0.381
SFAs, %TE	−0.31 ± 0.20	−1.88 ± 0.25	−2.56 ± 0.27	−1.68 ± 0.35	0.029	0.119	0.025
MUFAs, %TE	0.32 ± 0.17	−0.75 ± 0.22	−0.87 ± 0.24	−0.64 ± 0.31	0.012	0.382	0.601
PUFAs, %TE	0.25 ± 0.11	−0.01 ± 014	0.04 ± 0.15	−0.18 ± 0.19	0.053	0.273	0.119
ω-3, %TE	0.13 ± 0.03	0.02 ± 0.04	0.05 ± 0.05	0.06 ± 0.06	0.278	0.442	0.903
Carbohydrate, %TE	−1.22 ± 0.45	1.65 ± 0.55	1.92 ± 0.61	0.93 ± 0.79	0.027	0.211	0.558
Protein, %TE	0.85 ± 0.21	0.77 ± 0.26	0.80 ± 0.28	1.17 ± 0.36	0.997	0.346	0.634
BMI, kg/m^2	−0.28 ± 0.08	−0.44 ± 0.09	−0.41 ± 0.10	−0.51 ± 0.13	0.970	0.711	0.364
Cholesterol, mmol/L	−0.27 ± 0.07	−0.22 ± 0.08	−0.39 ± 0.09	−0.41 ± 0.12	0.855	0.959	0.560
ω-3 index	0.27 ± 0.07	0.11 ± 0.09	0.26 ± 0.09	0.18 ± 0.12	0.536	0.700	0.464

[1]Values are mean changes ± SEMs (month 6 – month 0). E4− includes E2/E2, E2/E3, and E3/E3; E4+ includes E3/E4 and E4/E4. *APOE*, apolipoprotein E; L, level; %TE, percentage of total energy.
[2]Data were analyzed by general linear model with adjustment for baseline values, center, sex, age, and change in weight (month 6 – month 0).

(E4−) resulted in a lower reduction in SFA intake at 6 mo than in E4− participants receiving nongene-based PN (level 2) who were not informed of their *APOE* risk (−1.68% compared with −2.56%). Providing no-risk genotypic results may reduce motivation to follow dietary advice (41). A potential reason for the lack of response in Food4Me E4 carriers is the absence of a specific behavioral change technique (BCT) involving information on the consequences of a specific behavior related to genotype. A key BCT in the Coventry, Aberdeen, and London—Refined taxonomy (a 40-item taxonomy to improve PA and healthy eating behaviors) is to "provide information of the consequences of the behavior to the individual." In the context of *APOE* genotype, a consequence of carrying the ε4 allele would be increased cardiovascular disease risk (31), and the corresponding risk-reducing behavior would be lowered SFA intake. In the present study, the *APOE* risk information conveyed to participants was framed positively, i.e., "you have a genetic variation that can benefit by keeping a healthy intake of saturated fat and a normal level of blood cholesterol." The lack of an explicit link to an adverse consequence of E4+ status, e.g., higher cardiovascular disease risk, may have reduced the efficacy of this advice. In the REVEAL study, participants were informed that the E4 allele was associated with an increased risk of Alzheimer disease before gene disclosure (39). Although genotypic testing for polygenic disease risk may result in a fatalistic attitude (37), information on consequences of personal characteristics (e.g., genotype) and fear arousal can be useful aids in enhancing behavior change (42). In a meta-analysis of fear arousal techniques, stronger fear messages promoted greater intention and behavior change in public health campaigns, provided that the threat was perceived to be severe and personally relevant, and that individuals could take specific action to mitigate their risks (43). In a Finnish RCT, knowledge of personal *APOE* risk resulted in greater short-term improvements in dietary quality, waist circumference, and serum triglyceride when participants were informed of the link between dietary fat, cholesterol, and cardiovascular disease risk in an oral communication session (44). Furthermore, E4+ individuals significantly improved fat quality at 6 mo ($P < 0.01$), whereas there was no difference in fat quality in the E4− or control groups (44).

TABLE 7
Effect of knowledge of *APOE* genotype on change in dietary intake between baseline and month 6 for participants receiving gene-based personalized nutrition (level 3) in the Food4Me intervention study[1]

	Level 3		
	APOE nonrisk (E4−) (n = 72)	*APOE* risk (E4+) (n = 40)	P^2
Total fat, %TE	−2.41 ± 0.64	−3.07 ± 0.86	0.433
SFAs, %TE	−1.68 ± 0.33	−1.95 ± 0.45	0.348
MUFAs, %TE	−0.64 ± 0.28	−1.05 ± 0.36	0.307
PUFAs, %TE	−0.18 ± 0.17	0.01 ± 0.23	0.223
ω-3, %TE	0.06 ± 0.02	0.08 ± 0.03	0.392
Carbohydrate, %TE	0.93 ± 0.68	1.55 ± 0.92	0.421
Protein, %TE	1.17 ± 0.30	1.37 ± 0.40	0.502
BMI, kg/m^2	−0.51 ± 0.13	−0.44 ± 0.18	0.229
Cholesterol, mmol/L	−0.41 ± 0.12	−0.19 ± 0.16	0.203
ω-3 index	0.18 ± 0.12	0.14 ± 0.16	0.777

[1]Values are mean changes ± SEMs (month 6 – month 0). E4− includes E2/E2, E2/E3, and E3/E3; E4+ includes E3/E4 and E4/E4. *APOE*, apolipoprotein E; %TE, percentage of total energy.
[2]Data were analyzed by general linear model with adjustment for baseline values, center, sex, age, and change in weight (month 6 – month 0).

A limitation of Internet-delivered PN (as used in our Food4Me study) is the reduced opportunity to use BCT in response to verbal and nonverbal cues (e.g., body-language and facial expressions). Recent focus group data also revealed a lack of understanding in consumers of the use of genetic information to tailor dietary advice, and opinions regarding gene-based PN were mostly negative (45). Given that understanding and knowledge of specific gene-based PN advice was not evaluated in the Food4Me study, it is not possible to ascertain whether this contributed to the lack of effect observed. The Food4Me study was designed to assess the impact of 3 levels of personalization on dietary change, and was not specifically targeted to the *APOE* genotype. Furthermore, although participants were informed that they had a risky gene variant that would benefit from dietary change, advice was not stratified according to specific genotype groups (e.g., differing advice for E2/E3 and E3/E3). Strengths of this study include making use of the Internet to assess and deliver dietary advice, prospective genotyping, a larger sample size than reported previously (39, 44, 46), the measurement of actual dietary

change as distinct from intention to change, and the availability of relevant blood-based biomarkers of fat status (obtained from unsupervised sampling). As such, the Food4Me study provides robust evidence of the impact of knowledge of *APOE* risk on adherence to dietary advice.

In conclusion, *APOE* status was significantly associated with TC at baseline, with highest concentrations in E4+ participants. Whereas gene-based PN targeted to *APOE* was more effective in reducing SFA intake than standard dietary advice, there was no added benefit of knowledge of *APOE* risk on dietary change. Furthermore, it appears that disclosure of genotypic nonrisk status may have weakened the dietary response to PN. Future research should explore ways in which this detrimental response to gene-based PN can be mitigated.

The authors' responsibilities were as follows—ERG, LB, YM, IT, CAD, JAM, HD, WHMS, MJG, JCM, and JAL: contributed to the research design; RF, CC-M, ALM, CFMM, HF, CO, CW, RS-C, SK, CM, AS, SN-C, MCW, and JCM: conducted the intervention; RF and CC-M: performed the statistical analysis for the manuscript; RF and JAL: drafted the paper; and all authors: contributed to the development of standard operating procedures for the study design and data analysis, critically reviewed the manuscript during the writing process, and read and approved the final manuscript. CAD is a founder, board member, stockowner, and consultant for Vitas Ltd. None of the other authors reported a conflict of interest related to the study.

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