



## Interventions

# Effect of personalized nutrition on health-related behaviour change: evidence from the Food4Me European randomized controlled trial

Carlos Celis-Morales,<sup>1,†</sup> Katherine M Livingstone,<sup>1,†</sup>  
Cyril FM Marsaux,<sup>2</sup> Anna L Macready,<sup>3</sup> Rosalind Fallaize,<sup>3</sup>  
Clare B O'Donovan,<sup>4</sup> Clara Woolhead,<sup>4</sup> Hannah Forster,<sup>4</sup>  
Marianne C Walsh,<sup>4</sup> Santiago Navas-Carretero,<sup>5</sup>  
Rodrigo San-Cristobal,<sup>5</sup> Lydia Tsirigoti,<sup>6</sup> Christina P Lambrinou,<sup>6</sup>  
Christina Mavrogianni,<sup>6</sup> George Moschonis,<sup>6</sup> Silvia Kolossa,<sup>7</sup>  
Jacqueline Hallmann,<sup>7</sup> Magdalena Godlewska,<sup>8</sup> Agnieszka Surwitto,<sup>8</sup>  
Iwona Traczyk,<sup>8</sup> Christian A Drevon,<sup>9</sup> Jildau Bouwman,<sup>10</sup>  
Ben van Ommen,<sup>10</sup> Keith Grimaldi,<sup>11</sup> Laurence D Parnell,<sup>12</sup>  
John NS Matthews,<sup>13</sup> Yannis Manios,<sup>6</sup> Hannelore Daniel,<sup>7</sup>  
J Alfredo Martinez,<sup>5</sup> Julie A Lovegrove,<sup>3</sup> Eileen R Gibney,<sup>4</sup>  
Lorraine Brennan,<sup>4</sup> Wim HM Saris,<sup>2</sup> Mike Gibney<sup>4</sup> and  
John C Mathers;<sup>1\*</sup> on behalf of the Food4Me Study

<sup>1</sup>Human Nutrition Research Centre, Newcastle University, Newcastle upon Tyne, UK, <sup>2</sup>Department of Human Biology, Maastricht University Medical Centre, Maastricht, The Netherlands, <sup>3</sup>Hugh Sinclair Unit of Human Nutrition and Institute for Cardiovascular and Metabolic Research, University of Reading, Reading, UK, <sup>4</sup>UCD Institute of Food and Health, University College Dublin, Dublin, Ireland, <sup>5</sup>Department of Nutrition and Physiology, University of Navarra, Navarra, and CIBER Fisiopatología Obesidad y Nutrición (CIBERObn), Instituto de Salud Carlos III, Madrid, Spain, <sup>6</sup>Department of Nutrition and Dietetics, Harokopio University, Athens, Greece, <sup>7</sup>ZIEL Research Center of Nutrition and Food Sciences, Munich Technical University, Munich, Germany, <sup>8</sup>National Food & Nutrition Institute (IZZ), Warsaw, Poland, <sup>9</sup>Institute of Basic Medical Sciences, Faculty of Medicine, University of Oslo, Oslo, Norway, <sup>10</sup>TNO, Microbiology and Systems Biology Group, Zeist, The Netherlands, <sup>11</sup>Eurogenetica Ltd, Burnham-on-Sea, UK, <sup>12</sup>Jean Mayer US Department of Agriculture Human Nutrition Research Center on Aging at Tufts University, Boston, MA, USA and <sup>13</sup>School of Mathematics and Statistics, Newcastle University, Newcastle upon Tyne, UK

\*Corresponding author. Human Nutrition Research Centre, Institute of Cellular Medicine, Newcastle University Biomedical Research Building, Campus for Ageing and Vitality, Newcastle upon Tyne NE4 5PL, UK. E-mail: john.mathers@newcastle.ac.uk

<sup>†</sup>C.C.M. and K.M.L. are joint first authors.

Accepted 7 June 2016

## Abstract

**Background:** Optimal nutritional choices are linked with better health, but many current interventions to improve diet have limited effect. We tested the hypothesis that providing personalized nutrition (PN) advice based on information on individual diet and lifestyle, phenotype and/or genotype would promote larger, more appropriate, and sustained changes in dietary behaviour.

**Methods:** Adults from seven European countries were recruited to an internet-delivered intervention (Food4Me) and randomized to: (i) conventional dietary advice (control) or to PN advice based on: (ii) individual baseline diet; (iii) individual baseline diet plus phenotype (anthropometry and blood biomarkers); or (iv) individual baseline diet plus phenotype plus genotype (five diet-responsive genetic variants). Outcomes were dietary intake, anthropometry and blood biomarkers measured at baseline and after 3 and 6 months' intervention.

**Results:** At baseline, mean age of participants was 39.8 years (range 18–79), 59% of participants were female and mean body mass index (BMI) was 25.5 kg/m<sup>2</sup>. From the enrolled participants, 1269 completed the study. Following a 6-month intervention, participants randomized to PN consumed less red meat [-5.48 g, (95% confidence interval: -10.8, -0.09),  $P=0.046$ ], salt [-0.65 g, (-1.1, -0.25),  $P=0.002$ ] and saturated fat [-1.14 % of energy, (-1.6, -0.67),  $P<0.0001$ ], increased folate [29.6 µg, (0.21, 59.0),  $P=0.048$ ] intake and had higher Healthy Eating Index scores [1.27, (0.30, 2.25),  $P=0.010$ ] than those randomized to the control arm. There was no evidence that including phenotypic and phenotypic plus genotypic information enhanced the effectiveness of the PN advice.

**Conclusions:** Among European adults, PN advice via internet-delivered intervention produced larger and more appropriate changes in dietary behaviour than a conventional approach.

**Key words:** Personalized nutrition, internet-based, randomized controlled trial, genotype, phenotype, obesity, diet, metabolic health

### Key Messages

- This study demonstrates clearly the value of personalization in improving key lifestyle factors relevant to a wide range of health outcomes.
- Personalized interventions can be delivered successfully to individuals across several countries using the internet.
- We demonstrate that there was no evidence that including phenotypic or phenotypic plus genotypic information enhanced the effectiveness of the PN advice.

## Introduction

Poor diet and lack of physical activity (PA) are major risk factors for non-communicable diseases (NCDs) including type 2 diabetes (T2D), cardiovascular diseases (CVDs) and many cancers.<sup>1,2</sup> Up to 80% of major CVDs, and over one-third of cancers, could be prevented by eliminating shared risk factors, including tobacco use, unhealthy diet, physical inactivity and excess alcohol consumption.<sup>3</sup> This emphasizes the importance of changing lifestyle in public health initiatives.

Most population strategies to reduce NCD burden have used 'one size fits all' public health recommendations, e.g. 'eat at least five portions of fruit and vegetables daily'.<sup>4</sup> However, the global burden of NCD continues to rise, underlining the need for more effective prevention.<sup>5</sup> Advances in the cost and time efficiency of genome sequencing and enhanced ability to extract information of interest, e.g. disease risk, have fuelled interest in the use of personal genetics.<sup>6,7</sup> However, the effectiveness of genetic-based information in facilitating behaviour change is

unclear. A systematic review recommended that more, and larger, randomized controlled trials (RCTs) are needed to determine whether DNA-based dietary advice motivates people to make appropriate behavioural changes.<sup>8</sup>

Personalized dietary interventions are designed according to key characteristics of the individual participants. The more tailored the intervention, the more sophisticated and potentially expensive it will be to acquire, analyse and act upon those participant characteristics. With conventional face-to-face interventions, the resource implications of the necessary information collection and processing could mean that such personalized nutrition (PN) interventions would be limited to the more affluent. Given that the prevalence and risk of death from NCDs are strongly socioeconomically patterned,<sup>9</sup> it is important that interventions reach all social groups. Use of the internet is rising rapidly in Europe.<sup>5,10</sup> Current data show that 76.5% of the population of the European Union use the internet and, increasingly, national governments and others use the internet to deliver a wide range of social, financial and health services.<sup>5,10</sup> Thus, digital-based technologies for delivering interventions may offer advantages including convenience, scalability, personalization/stratification, sustainability and cost effectiveness. Therefore, the aims of the Food4Me Study were to conduct a multi-centre, internet-based RCT of PN to determine whether providing more personalized dietary advice leads to larger and more appropriate changes in dietary behaviour than standard 'one size fits all' population advice.

## Methods

### Study design

The Food4Me 'Proof of Principle' study was a 6-month, four-arm RCT conducted across seven European countries to compare the effects of three levels of PN with standard population advice (control) on health-related outcomes. Full details of the study protocol have been described elsewhere.<sup>11</sup>

The intervention was designed to emulate an internet-based PN service [www.food4me.org], and the study aimed to answer the following primary questions: (i) does personalization of dietary advice improve diet in comparison with non-personalized, conventional healthy eating guidelines? and (ii) is personalization based on individualized phenotypic or phenotypic plus genotypic information more effective in assisting and/or motivating study participants to make and to sustain appropriate health-promoting changes, than personalization based on analysis of baseline diet alone? To answer these questions participants were randomized to a Control group (Level 0) or to

one of three PN intervention groups with increasingly more detailed personalized dietary advice (Levels 1–3) for a 6-month period:

- Level 0 (L0): non-personalized dietary, body weight and physical activity advice based on (European) population guidelines;
- Level 1 (L1): personalized dietary advice based on individual dietary intake data alone;
- Level 2 (L2): personalized dietary advice based on individual dietary intake and phenotypic data;
- Level 3 (L3): personalized dietary advice based on individual dietary intake and phenotypic and genotypic data.

### Outcomes

The primary outcome was dietary intake following 6 months' intervention, and the secondary outcomes included anthropometric measures (i.e. body weight, body mass index (BMI) and waist circumference) and blood biomarkers (i.e. total cholesterol, carotenoids and fatty acids). Outcomes were also measured at 3 months.

### Recruitment and randomization

Participants were recruited in seven European countries (Ireland, The Netherlands, Spain, Greece, the UK, Poland and Germany) as described elsewhere.<sup>11</sup> We aimed to recruit a total of 1540 study participants aged  $\geq 18$  years.<sup>11</sup> Participants were randomized to the intervention groups (L0–L3), stratified by country, sex and age ( $< 45$  or  $\geq 45$  years) using an automated server designed for the study using an urn randomization scheme.<sup>12</sup>

### Eligibility criteria

Participants aged  $\geq 18$  years of age were included in the study. To keep the cohort as representative as possible of the adult population, the following minimal 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 past 3 months; (iv) diabetes, coeliac disease, Crohn's disease or any metabolic disease or condition altering nutritional requirements such as thyroid disorders (if condition was not controlled), allergies or food intolerances.

### Ethics approval and participant consent

The research ethics committees at each university or research centre delivering the intervention granted approval for the study. Before participation, potential volunteers

completed an informed consent form online before submitting personal data (see [Supplementary Methods](#), available as [Supplementary data](#) at *IJE* online).

### Personalized feedback report

Participants randomized to L1, L2 and L3 received personalized feedback. Personalized feedback reports were derived manually from decision trees which were developed specifically for the Food4Me project. These decision trees were implemented by trained nutritionists and dietitians in the research centres leading the intervention in each of the seven countries. To ensure uniformity in delivery of the intervention across countries, the same decision trees were used in each country and these PN messages were translated into the local language. At baseline, 3 months and 6 months, dietary intakes were assessed using a validated online Food Frequency Questionnaire (FFQ)<sup>13,14</sup> and intakes of food groups and nutrients categorized as too high or too low were identified and ranked. Contributing foods were identified and specific messages were developed according to standardized algorithms to advise change in intake of those foods.<sup>11,13,14</sup> For participants randomized to L2 and L3, the feedback also included and referred to phenotypic measures (L2) and phenotypic plus genotypic data (L3). Details of these feedback reports are described in [Supplementary Methods \(Figures S1 and S3\)](#), available as [Supplementary data](#) at *IJE* online), and elsewhere.<sup>11</sup>

### Study measurements

To ensure that procedures were similar in all recruiting centres, standardized operating procedures were implemented for all study procedures by the local researchers.<sup>11</sup> Time points for each measurement are summarized in [Table S1](#), available as [Supplementary data](#) at *IJE* online.

Participants provided socio-demographic, health and anthropometric data online at screening, and detailed information on dietary intake and food preferences.<sup>11</sup> Anthropometric measures were made and reported by participants via the internet. Habitual dietary intake was quantified using an online-FFQ, developed and validated for this study,<sup>13,14</sup> and evaluated using the updated (2010) Healthy Eating Index (HEI).<sup>15</sup> Physical activity (PA) patterns were determined using a PA monitor (TracmorD) and self-reported Baecke PA questionnaire.<sup>16</sup> Dried blood spot filters were collected for measurements of total cholesterol, carotenoids, n-3 fatty acid index, 32 individual fatty acids and vitamin D (25-OH D<sub>2</sub> and 25-OH D<sub>3</sub>). Buccal cell samples were collected for DNA extraction and genotyping of five selected loci used for personalized advice

([Figure S2](#)). Further details are provided elsewhere<sup>11</sup> and in [Supplementary Methods](#).

### Statistical analysis

Data were analysed on an intention-to-treat basis. To answer our primary research question ('Is personalized nutritional advice more effective than the conventional one size fits all?'), intervention effects on major food groups and targeted personalized nutrients were assessed. We used an analysis of covariance with baseline intake as covariate. The principal assessment of treatment used Contrast 1 comparing L0 (Control) with the mean of L1-L3. First, generic dietary targets set for L0 (energy intake, fruit and vegetables, whole grains, dairy products, oily fish, red meat, salt and fats) were used as outcome measures. Second, analysis was restricted to participants who received advice for the top five targeted nutrients (salt, saturated fat, dietary fibre, folate and polyunsaturated fat) and phenotypic characteristics (body weight, BMI, waist circumference (WC) and blood markers), which were used as outcome measures. For this second part of the analysis, outcomes for those who received PN targeting these nutrients were compared with the subset of matched Level 0 (Control) participants who would have benefited from the same personalized advice and who were selected by applying the algorithm used to identify their PN counterparts in L1.

Our secondary research question ('Is personalization based on individualized phenotypic or phenotypic plus genotypic information more effective in assisting and/or motivating participants to make and to sustain appropriate healthy changes, than personalization based on diet alone?') was tested using two further contrasts. 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. The outcomes for these analyses were the same food groups, target nutrients and phenotypic characteristics as for Contrast 1. STATA v13 was used for analyses.

## Results

### Study participants

A total of 5562 participants were screened online between August 2012 and August 2013; the characteristics of these individuals have been reported elsewhere.<sup>17</sup> The first 1607

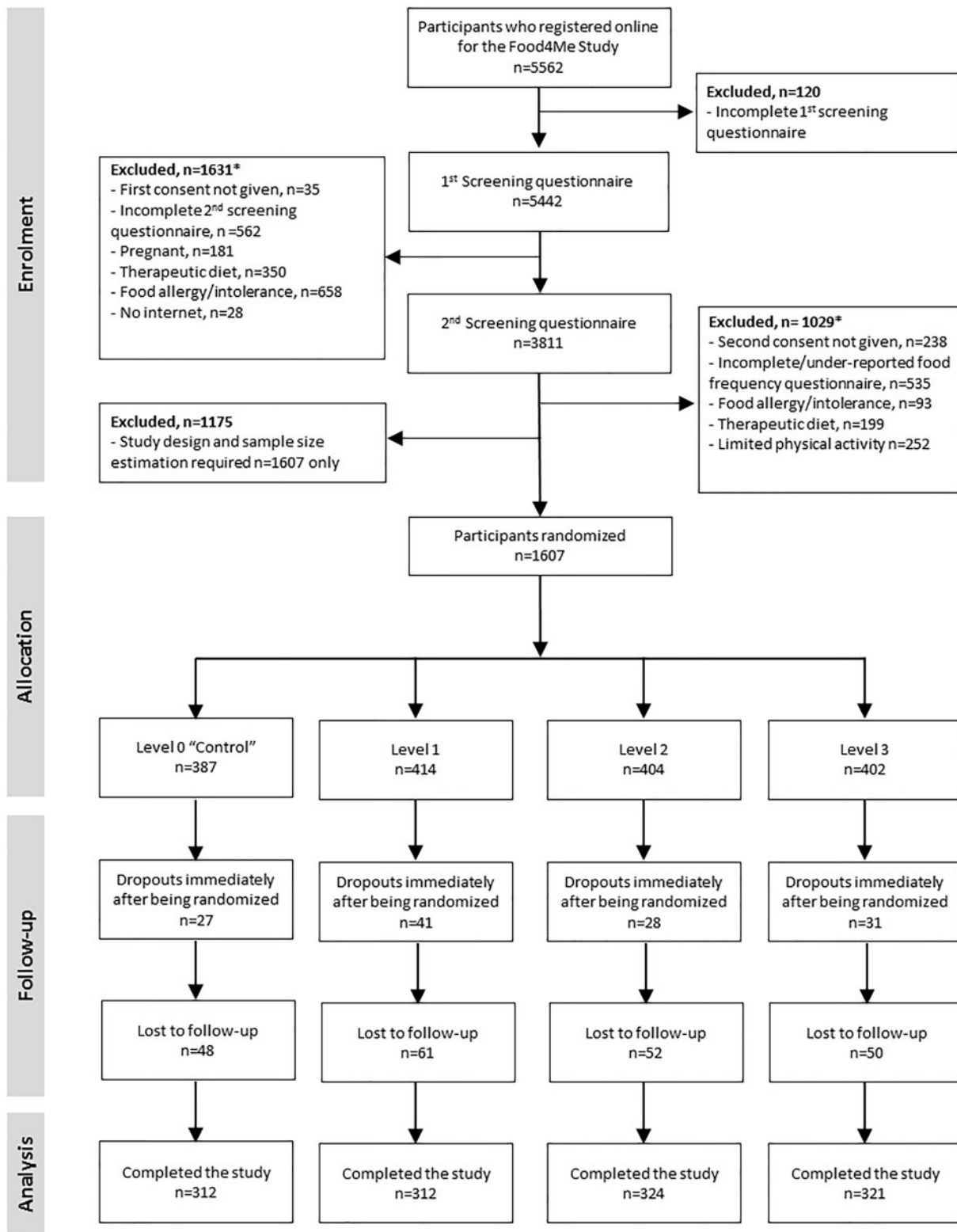


Figure 1. CONSORT diagram for the Food4Me Study.

volunteers meeting the inclusion criteria were recruited to the RCT and randomized to one of the four intervention arms (Figure 1).<sup>11</sup> Baseline characteristics of the participants by intervention arm are shown in Table 1 and in the

supplementary material (Tables S3 and S4, available as Supplementary data at *IJE* online). In summary, 59% of the participants were female, mean age was 39.8 (range 18 to 79) years, 46% were overweight or obese and 24%

**Table 1.** Baseline characteristics of the Food4Me Study participants

Variables	Control (Level 0)	Level 1	Level 2	Level 3
Total, <i>n</i> (%)	363 (24.4)	376 (25.3)	377 (25.3)	372 (25.0)
Sex, female, <i>n</i> (%)	214 (58.9)	216 (57.5)	220 (58.3)	220 (59.1)
Age (years)	39.4 (13.3)	39.7 (12.9)	40.2 (12.8)	40.2 (13.1)
Age range (years)	18 to 72	18 to 79	18 to 68	18 to 73
Ethnicity, <i>n</i> (%)				
White	347 (95.6)	366 (97.3)	369 (98.0)	356 (95.8)
Other ethnic groups	16 (4.4)	10 (2.7)	8 (2.0)	16 (4.2)
Anthropometrics				
Height (cm)	171.2 (9.3)	171.3 (9.4)	170.7 (9.3)	171.2 (9.5)
Weight (kg)	74.3 (15.2)	74.1 (16.6)	74.8 (15.9)	75.4 (15.4)
BMI (kg.m <sup>-2</sup> )	25.4 (4.7)	25.2 (5.0)	25.6 (17.6)	25.7 (4.8)
Waist circumference (cm)	85.6 (13.9)	84.5 (13.8)	86.1 (14.0)	86.5 (13.4)
Weight status, <i>n</i> (%)				
Underweight	8 (2.2)	10 (2.7)	12 (3.2)	9 (2.4)
Normal weight	181 (50.3)	210 (56.3)	192 (51.1)	176 (47.5)
Overweight	119 (33.1)	96 (25.7)	102 (27.1)	131 (35.3)
Obese	52 (14.4)	57 (15.3)	70 (18.6)	55 (14.8)
Central obesity	84 (23.4)	82 (22.1)	96 (25.6)	98 (26.4)
Smoking behaviour, <i>n</i> (%)				
Current smokers	50 (13.7)	46 (12.3)	35 (9.2)	50 (13.5)
Ex-smokers	89 (24.6)	99 (26.3)	100 (26.7)	88 (23.6)
Non-smokers	224 (61.7)	231 (61.4)	242 (64.1)	234 (62.9)
Physical activity				
Physical Activity Level (PAL)	1.71 (0.2)	1.75 (0.2)	1.73 (0.2)	1.74 (0.2)
Medical history, <i>n</i> (%)				
Disease history <sup>a</sup>	171 (47.0)	152 (40.3)	173 (46.0)	154 (41.5)
Medication <sup>b</sup>	113 (31.0)	98 (26.1)	120 (31.7)	115 (30.9)

Data are presented as means (standard deviation) or as % for categorical variables. Levels 1–3 received personalized nutrition advice.

<sup>a</sup>Disease history includes cancer, high blood pressure, heart disease, liver disease, kidney disease, arthritis, osteoporosis, ulcers, fibromyalgia, diabetes, lung disease, allergies, epilepsy, thyroid disease, anaemia, blood disorders, alcohol abuse, drug addiction and depression.

<sup>b</sup>Medication includes prescribed medication use only. Central obesity was determined using waist circumference cut-off point of 88 cm and 102 cm for females and males, respectively.

were centrally obese. Regarding health parameters, 44% and 30% reported the existence of a disease and medication use, respectively, and 12% were current smokers (Table 1). Further details of participants are described elsewhere.<sup>11</sup> After 6 months, 21% of participants randomized to the intervention were lost to follow-up with 8% dropping out immediately after randomization (Figure 1).

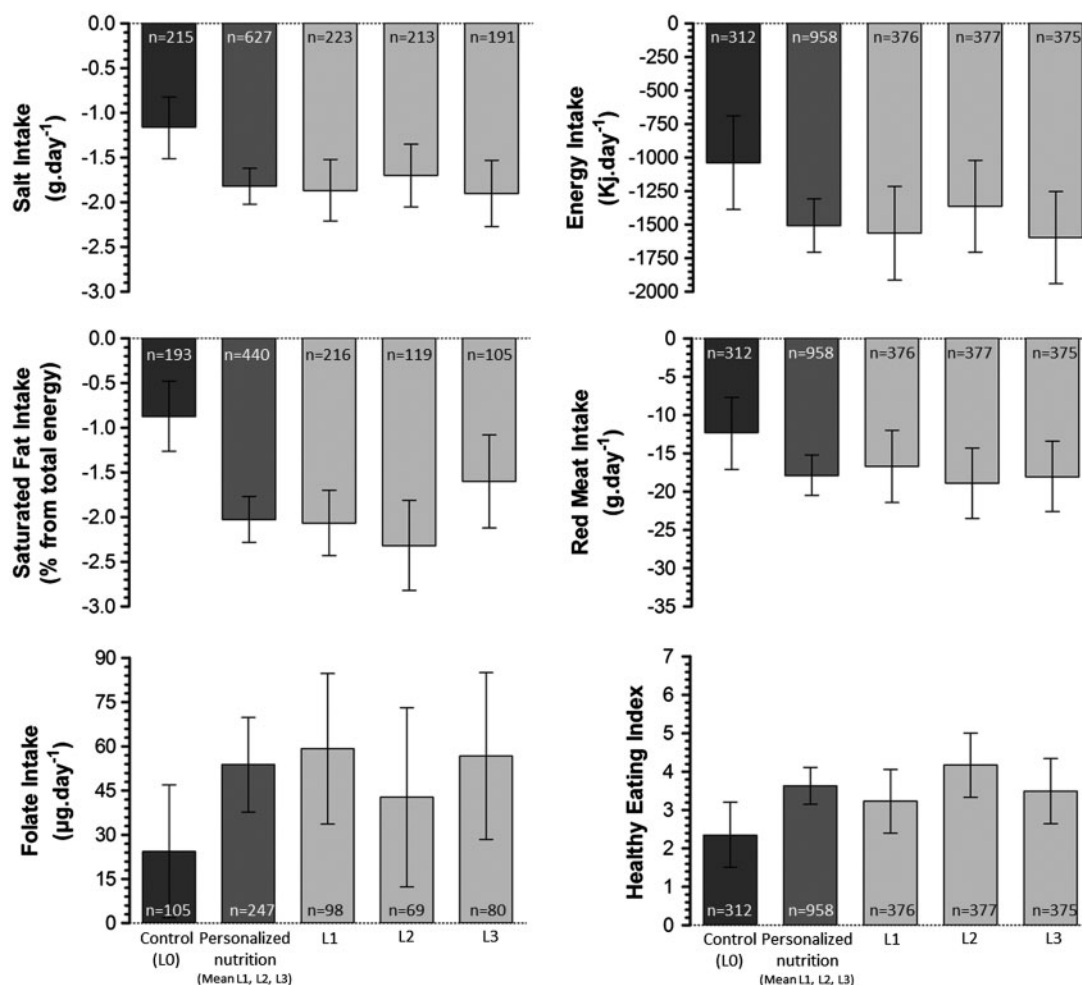
### Effect of different levels of personalized nutritional advice on intakes of major food groups

Overall, participants in the Food4Me study improved their diet over the 6-month intervention period (Figure 2). Individuals receiving PN advice consumed less red meat (8.5%) and less salt (6.3%), had lower energy intake (4.4%) and higher HEI scores (2.6%) when compared with the Control group (Table 2; Figure 2; Table S3 and Table S6, available as Supplementary data at IJE online).

Similar results were found at month 3 (Table S5, available as Supplementary data at IJE online). Changes in dietary outcomes did not differ between Levels 1, 2 and 3 of PN (Table 2; Tables S5 and S6, available as Supplementary data at IJE online). No evidence of differences was observed for other food groups (Table 2; Tables S5 and S6). Similar results were found when dietary misreporters were excluded (data not shown).

### Effects of different levels of personalized nutrition advice on intakes of target nutrients and on anthropometric markers

To determine effects on targeted nutrients, we assessed changes in the top five most common targets for personalized advice. i.e. salt, saturated fat, dietary fibre, folate and polyunsaturated fats. Baseline data for these subgroups are presented in Table S4. Each participant also received personalized advice concerning body weight and WC



**Figure 2.** Changes from baseline to month 6 in dietary intakes after receiving personalized advice. Data are presented as adjusted changes from baseline (95% CI). Panels on the left refer only to participants receiving PN advice for the specified target nutrients and the matched control (L0) participants. Panels on the right include all participants in each of the intervention groups. The Healthy Eating Index was calculated as described by Guenther *et al.*(15).

**Table 2.** Effect of intervention on intakes of major food groups at month 6

	Control Mean (L0)	Personalized nutrition Mean (L1, L2, L3)	Treatment effects $\Delta$ (Mean L1, L2, L3)–L0	P-value L0 vs (L1+L2+L3)
n	312	958		
Fruits (g/day <sup>-1</sup> )	381	412	31.4 (–0.70 to 63.7)	0.054
Vegetables (g/day <sup>-1</sup> )	232	234	2.02 (–14.9 to 18.9)	0.814
Fruits and vegetables (g/day <sup>-1</sup> )	613	647	33.9 (–8.0 to 75.7)	0.113
Whole grains (g/day <sup>-1</sup> )	164	165	0.95 (–15.2 to 17.1)	0.908
Oily fish (g/day <sup>-1</sup> )	26.7	24.9	–1.76 (–5.2 to 1.6)	0.312
Red meat (g/day <sup>-1</sup> )	64.7	59.3	–5.48 (–10.8 to –0.09)	0.046
Low-fat dairy (g/day <sup>-1</sup> )	226	230	3.45 (–19.7 to 26.6)	0.769
Salt (g/day <sup>-1</sup> )	6.50	6.09	–0.41 (–0.71 to –0.10)	0.008
Healthy Eating Index	51.8	53.1	1.27 (0.30 to 2.25)	0.010

Data are presented as adjusted means and as the difference between personalized nutrition (PN; mean Levels 1–3) and control (Level 0) with the corresponding 95% CI. All analyses were adjusted for baseline values. Differences between levels of PN are presented in Tables S5 and S6, available as Supplementary data at IJE online.

**Table 3.** Effect of targeted intervention on dietary and anthropometric outcomes at month 6

Targets of personalized advice	Matched controls (L0)		Personalized nutrition		Intervention effects $\Delta$ (Mean L1, L2, L3)–L0	P-value L0 vs (L1+L2+L3)
	n	Mean	n	Mean (L1, L2, L3)		
Salt (g/day <sup>-1</sup> ) <sup>a</sup>	215	7.29	627	6.64	–0.65 (–1.1 to –0.25)	0.002
Saturated fat (% total energy)	193	14.6	440	13.5	–1.14 (–1.6 to –0.67)	<0.0001
Dietary fibre (g/day <sup>-1</sup> )	97	23.0	268	23.3	–0.25 (–1.9 to 2.4)	0.821
Folate ( $\mu$ g/day <sup>-1</sup> )	105	2.58	247	2.87	29.6 (0.21 to 59.0)	0.048
Polyunsaturated fat (% total energy)	66	4.94	148	5.27	0.33 (–0.02 to 0.69)	0.069
Energy intake (MJ.day <sup>-1</sup> )	146	9.66	437	9.49	–0.17 (–0.7 to 0.5)	0.834
Body weight (kg)	146	84.6	437	83.9	–0.61 (–1.4 to 0.17)	0.128
BMI (kg.m <sup>2</sup> )	146	28.9	437	28.6	–0.24 (–0.52 to 0.4)	0.097
Waist circumference (cm)	72	100	235	99.2	–0.9 (–2.1 to 0.39)	0.173

Analysis is restricted to participants randomized to Levels 1–3 receiving personalized advice targeting the specified dietary and anthropometric outcomes. For this analysis, matched control group (Level 0) participants were selected by applying the algorithm used for Level 1 participants to identify those who would have benefited from the personalized advice for these nutrients. Data are presented as adjusted means and as the difference between personalized nutrition (PN; mean levels 1–3) and control with the corresponding 95% CI. Differences between levels of PN are presented in Tables S7 and S8, available as Supplementary data at *IJE* online. All analyses were adjusted for baseline values.

(Table 3). Outcomes were analysed for those who received PN targeting these nutrients compared with the subset of matched L0 (Control) participants who would have benefited from personalized advice and who were selected by applying the same algorithm used to identify their PN counterparts in L1. After 6 months, participants receiving PN advice consumed less salt (8.9%) and saturated fat (7.8%) and had higher folate intake (11.5%) compared with the Control group (Table 3 and Figure 2). At month 3, there were improvements for salt, saturated fat, blood carotenoids, body weight and BMI made by participants receiving PN (Table S7). Changes in these outcomes at both 3 and 6 months were similar for all three types of PN advice (comparisons between Levels 1–3 are presented in Tables S7 and S8, available as Supplementary data at *IJE* online). Similar results were found when dietary misreporters were excluded (data not shown).

### Adverse events

There were no reports of adverse events directly related to the trial.

### Discussion

The main findings of this study were that, overall, PN advice was more effective in improving dietary behaviours when compared with conventional ‘one size fits all’ population-based advice. However, we found no evidence that including phenotypic or phenotypic plus genotypic information in the derivation and communication of PN advice enhanced the effectiveness of the intervention compared with personalization of nutrition advice based

on evaluation of current individual dietary intake alone. Our findings also showed that the internet was an effective vehicle for recruiting and retaining participants, and for delivering PN interventions, over 6 months across seven European countries.

Our results are in line with findings from a recent review and meta-analysis of RCTs evaluating the effectiveness of personalized e-Health lifestyle-based interventions on weight loss and dietary intake.<sup>5,18</sup> Internet-based personalized interventions were more effective in reducing body weight (–1.00 kg,  $P < 0.001$ )<sup>18</sup> and in increasing fruit and vegetable consumption (0.35 servings/day<sup>-1</sup>,  $P < 0.001$ )<sup>5</sup> than non-personalized advice. The effect sizes among participants receiving PN advice for body weight and fruit and vegetable intake were similar to those observed in the Food4Me Study (Table 2 and Figure 2).

Sequencing of the human genome, combined with the recognition that interactions between genotype and environment influence health, brings new opportunities for personalization of medicine and of dietary or lifestyle advice.<sup>7,19</sup> Despite suggestions that genotype-based interventions would have greater efficacy, few studies have tested this hypothesis.<sup>20,21</sup> In 2010, a systematic review reported that evidence was weak because of the small number of studies and their limited quality, and concluded that ‘claims that receiving DNA-based test results motivates people to change their behaviour are not supported by the evidence’.<sup>8</sup> Disclosing the outcomes of genomic testing in 2240 participants was not associated with changes in behavioural outcomes (fat intake or exercise) after 3 or 12 months.<sup>22</sup> In contrast, a recent Canadian RCT in young adults, comparing the effectiveness of four pieces of personalized genotype-based dietary advice with conventional



dietary advice, reported that genotype-based advice produced greater reductions in sodium intake ( $-287 \text{ mg/day}^{-1}$  versus  $-129 \text{ mg/day}^{-1}$ ) among participants who carried the risk version of the *ACE* gene compared with the control group.<sup>23</sup> No effects of personalized genotype-based dietary advice were found for three other outcomes (caffeine, vitamin C and added sugar), which may be explained by the fact that intakes of these nutrients by intervention participants were in line with current recommendations. Meisel *et al.* (2015) reported that adding information about *FTO* status (a major variant influencing adiposity<sup>24</sup>) to weight control advice enhanced readiness to control weight but had no effect on actual behaviour change.<sup>25</sup> Moreover, an intervention conducted in 107 participants using information on *APOE* genotype as a tool for promoting lifestyle changes, found that provision of personalized genetic information, based on *APOE* genotype, may improve dietary fat quality in the short term.<sup>21</sup>

### Strengths and limitations

The Food4Me study is the largest internet-based, PN intervention study to date and provides robust evidence for the impact of PN on dietary intake and phenotypic outcomes. Other innovative aspects of the Food4Me study include the creation of algorithms for delivering tailored lifestyle advice based on participant characteristics including behavioural, phenotypic and genotypic information. A second strength of the study was the delivery of the intervention across seven European countries via the internet and the application of a remote system for data and biological sample collection. An internet-based platform to deliver the intervention was effective in retaining participants; 79% completed follow-up after 6 months' intervention and there was > 98% compliance for blood and DNA testing, which is high compared with previous web-based survey research<sup>26</sup> and web-based<sup>22</sup> or face-to-face<sup>25</sup> genetic-based interventions. A recent study of direct-to-consumer genomic testing by Bloss *et al.* reported 44% and 63% drop-outs at months 3 and 12, respectively.<sup>22,27</sup>

Moreover, the profile of those interested in participating in the Food4Me intervention study was similar to that of European adults,<sup>11,17</sup> most of whom would benefit from improved diet and more physical activity. At the end of the study, we collected feedback from 139 respondents across the seven countries. Overall, 92% of the participants agreed or strongly agreed with the statement that 'the Food4me website was easy to use'. In addition, 76% of the participants agreed or strongly agreed with the statement that 'you were satisfied with the detail of information that you received in your nutrition feedback report'. Further, 80% of the participants agreed or strongly agreed with the

statement that 'the dietary advice in the feedback reports you received was relevant to you'.

Compared with conventional face-to-face interventions, the internet-based design of our present study limited the number of measures collected. Although participants were well characterized and phenotyped, some key health biomarkers, such as blood pressure, were not measured. Furthermore, all data collected during the study were self-reported or derived from biological samples collected remotely. Thus, there is the potential for measurement errors. To minimize such errors, all protocols were standardized across centres, delivered in the language of each country and supported by online advice and video clips. Our validation study of 10% of participants found strong agreement between self-reported and measured height and weight, and a perfect match for identity and key socio-demographic factors (age and sex).<sup>28</sup> Furthermore, our study was designed to test the additive effects of PN intervention using diet, phenotypic and genomic information and future studies are needed to test whether providing PN advice based on genotypic information alone leads to more substantial improvements in lifestyle behaviours than conventional approaches.

### Implications

Our results provide strong evidence for the effectiveness of a personalized approach, compared with a conventional 'one size fits all' approach in achieving dietary change to improve health. Specifically, we demonstrate that personalization of dietary advice based on analysis of current eating patterns influences individuals to make bigger changes towards a healthier diet than non-personalized, conventional dietary advice. Adding phenotypic or genotypic data to the information did not enhance the effectiveness of the intervention. Moreover, PN intervention via the internet was highly effective in recruiting and retaining participants, and offers promise as a scalable and sustainable route to improving dietary behaviours, with important public health benefits.<sup>5</sup>

### Conclusion

After 6 months' intervention, participants who received personalized nutrition advice had a healthier diet compared with controls, regardless of whether this personalization was based on their diet alone, diet and phenotype or diet, phenotype and genotype. These results demonstrate a lack of added value from using phenotypic or phenotypic + genotypic information to personalize lifestyle interventions.

## Supplementary Data

Supplementary data are available at *IJE* online.

## Funding

This work was supported by the European Commission under the Food, Agriculture, Fisheries and Biotechnology Theme of the Seventh Framework Programme for Research and Technological Development [265494]. The sponsor had no role in the study's design or conduct, data collection, management, analysis or interpretation, manuscript preparation, review or approval.

## Author contributions

C.C.-M., K.M.L. and J.C.M. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. Study concept and design: J.C.M., M.G., H.D., J.A.M., J.A.L., E.R.G., L.B., W.H.M., Y.M. and C.A.D. Acquisition, analysis or interpretation of data: C.C.-M., K.M.L., C.F.M.M., A.L.M., R.F., C.B. O'D., C.W., H.F., M.C.W., S.N.-C.-C., R.S.-C., L.T., C.P.L., C.M., G.M., S.K., J.H., M.G., A.S., I.T., C.A.D., J.B., B.vO., K.G., L.D. P., H.D., J.A.M., J.A.L., E.R.G., L.B., W.H.M.S., Y.M., C.A.D., M.G. and J.C.M. Drafting of the manuscript: C.C.-M., K.M.L. and J.C.M. Statistical analysis: C.C.-M., J.N.S.M. and J.C.M. Critical revision and final approval of the manuscript: C.C.-M., K.M.L., C.F.M.M., A.L.M., R.F., C.B.O'D., C.W., H.F., M.C.W., S.N.-C., R.S.-C., L.T., C.P.L., C.M., G.M., S.K., J.H., M.G., A.S., I.T., C.A.D., J.B., B.vO., K.G., L.D.P., J.N.S.M., H.D., J.A.M., J.A.L., E.R.G., L.B., W.H.M.S., Y.M., C.A.D., M.G. and J.C.M. Obtained funding: J.C.M., M.G., H.D., J.A.M., J.A.L., E.R.G., L.B., W.H.M.S., Y.M. and C.A.D. Management of the trial: M.C.W., J.C.M. and M.G.

**Conflict of interest:** K.G. reports personal fees from Eurogenetica Limited, outside the submitted work. C.A.D. reports personal fees from Vitas Ltd, during the conduct of the study; other from Vitas Ltd, outside the submitted work; no other conflict of interests. W.H.M.S. has received research support from several food companies such as Nestle, DSM, Unilever, Nutrition et Sante and Danone as well as pharmaceutical companies such as GSK, Novartis and Novo Nordisk. He is medical consultant for N&S and is an unpaid scientific adviser for the International Life Science Institute, ILSI Europe. J.N.S.M. reports grants from European Union, during the conduct of the study. M.G. reports that he is a non-remunerated member of the Google Food Innovation Lab Community of Practice on Personalized Nutrition. J.C.M. reports grants from European Union, during the conduct of the study; grants and personal fees from Medical

Research Council, grants and personal fees from Biotechnology and Biological Sciences Research Council, personal fees and non-financial support from Waltham Pet Nutrition, personal fees and non-financial support from University of Wageningen, The Netherlands, non-financial support from Technical University Munich, non-financial support from University College Dublin, non-financial support from University of Groningen, The Netherlands, non-financial support from University of Maastricht, The Netherlands, outside the submitted work.

## References

1. WHO. *Global Health Risk: Mortality and Burden of Disease Attributable to Selected Major Risks*. Geneva: World Health Organization, 2009.
2. Ezzati M, Riboli E. Global health behavioural and dietary risk factors for noncommunicable diseases. *N Engl J Med* 2013; **369**:954–64.
3. WHO. *Primary Health Care: Now More Than Ever*. Geneva: World Health Organization, 2008.
4. National Health Service. *Live Well*. 2014. <http://www.nhs.uk/Livewell/Goodfood/Pages/Healthyeating.aspx> (6 March 2015, date last accessed).
5. Celis-Morales C, Lara J, Mathers JC. Personalising nutritional guidance for more effective behaviour change. *Proc Nutr Soc* 2015;**74**:130–38.
6. Fallaize R, Macready AL, Butler LT, Ellis JA, Lovegrove JA. An insight into the public acceptance of nutrigenomic-based personalised nutrition. *Nutr Res Rev* 2013;**26**:39–48.
7. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med* 2015;**30**:3.
8. Marteau TM, French DP, Griffin SJ *et al*. Effects of communicating DNA-based disease risk estimates on risk-reducing behaviours. *Cochrane Database Syst Rev* 2010;**10**:CD007275.
9. Di Cesare M, Khang Y-H, Asaria P *et al*. Inequalities in non-communicable diseases and effective responses. *Lancet* 2013;**381**:585–97.
10. Seybert H, Loof A. *Internet Usage in 2010 – Households and Individuals*. Eurostat 2010. [ec.europa.eu/eurostat/product?lang=en&mode=view&code=KS](http://ec.europa.eu/eurostat/product?lang=en&mode=view&code=KS) (20 January 2016, date last accessed).
11. Celis-Morales C, Livingstone KM, Marsaux CFM *et al*. Design and baseline characteristics of the Food4Me study: a web-based randomised controlled trial of personalised nutrition in seven European countries. *Genes Nutr* 2014;**10**:1–13.
12. Wei LJ, Lachin JM. Properties of the urn randomization in clinical-trials. *Control Clin Trials* 1988;**9**:345–64.
13. Forster H, Fallaize R, Gallagher C *et al*. Online dietary intake estimation: the Food4Me food frequency questionnaire. *J Med Internet Res* 2014;**16**:e150–e.
14. Fallaize R, Forster H, Macready AL *et al*. Online dietary intake estimation: reproducibility and validity of the Food4Me Food Frequency Questionnaire against a 4-day weighed food record. *J Med Internet Res* 2014;**16**(18):e190.
15. Guenther PM, Casavale KO, Reedy J *et al*. Update of the Healthy Eating Index: HEI-2010. *J Acad Nutr Dietet* 2013;**113**:569–80.

16. Baecke JAH, Burema J, Frijters JER. A short questionnaire for the measurement of habitual physical activity in epidemiological-studies. *Am J Clin Nutr* 1982;**36**:936–42.
17. Livingstone K, Celis-Morales C, Navas-Carretero S *et al*. Profile of European adults interested in internet-based personalised nutrition: the Food4Me study. *Eur J Nutr* 2016;**55**:759–69.
18. Kodama S, Saito K, Tanaka S *et al*. Effect of web-based lifestyle modification on weight control: a meta-analysis. *Int J Obes (Lond)* 2012;**36**:675–85.
19. McBride CM, Bryan AD, Bray MS, Swan GE, Green ED. Health behaviour change: can genomics improve behavioural adherence?. *Am J Public Health* 2012;**102**:401–05.
20. Joost H-G, Gibney MJ, Cashman KD *et al*. Personalised nutrition: status and perspectives. *Br J Nutr* 2007;**98**:26–31.
21. Hietaranta-Luoma H-L, Tahvonen R, Iso-Touru T, Puolijoki H, Hopia A. An intervention study of individual, apoE genotype-based dietary and physical activity advice: impact on health behaviour. *J Nutrigenet Nutrigenom* 2014;**7**:161–74.
22. Bloss CS, Wineinger NE, Darst BF, Schork NJ, Topol EJ. Impact of direct-to-consumer genomic testing at long term follow-up. *J Med Genet* 2013;**50**:393–400.
23. Nielsen DE, El-Sohemy A. Disclosure of genetic information and change in dietary intake: a randomized controlled trial. *Plos One* 2014;**9**:e112665.
24. Frayling TM, Timpson NJ, Weedon MN *et al*. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* 2007;**316**:889–94.
25. Meisel SF, Beeken RJ, van Jaarsveld CH, Wardle J. Genetic susceptibility testing and readiness to control weight: Results from a randomized controlled trial. *Obesity (Silver Spring)* 2015;**23**:305–12.
26. Yetter G, Capaccioli K. Differences in responses to Web and paper surveys among school professionals. *Behav Res Methods* 2010;**42**:266–72.
27. Bloss CS, Schork NJ, Topol EJ. Effect of direct-to-consumer genomewide profiling to assess disease risk. *N Engl J Med* 2011;**364**:524–34.
28. Celis-Morales C, Livingstone KM, Woolhead C *et al*. How reliable is internet-based self-reported identity, socio-demographic and obesity measures in European adults?. *Genes Nutr* 2015;**10**:476.