Supplemental Table 1. Screening questionnaire on dietary habits and reasons for interest in the study

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| --- | --- | --- |
| **Question** | **Response options** | **Aggregated response** |
| How often do you eat your main meal away from home? | Never or up to once/ month  Two to three times/ month  Once per week Twice or more/ week | Rarely  Often |
| How many hot or cooked meals do you normally eat per day? |
| How often do you prepare a meal "from scratch"? | Every day 4-6 times per week 1-3 times per week  (Almost) never | Often  Rarely |
| Do you skip meals and replace them with snacks? | Often  Rarely |
| How much time on average do you spend preparing a main meal? | Less than 10 min  10-20 min  20-30 min  Up to an hour  Over an hour | Less than 30 min  More than 30 min |
| I can be as healthy as I want to be | Completely disagree Disagree  Neither disagree nor agree Agree  Completely agree | Disagree  Neither disagree nor agree  Agree  Note that the option 'Neither disagree nor agree' was excluded in the data analysis |
| I am in control of my health |
| I can pretty much stay healthy by taking care of myself |
| Efforts to improve your health are a waste of time |
| I am bored by all the attention that is paid to health and disease prevention |
| What's the use of concerning yourself about your health - you'll only worry yourself to death |
| Eating healthily is something I do frequently |
| I eat healthily without having to consciously think about it |
| I feel weird if I don't eat healthily |
|  |
| I'm interested in personalised nutrition | No  Yes | No Yes |
| I want to know what foods are best for me |
| I want to lose weight |
| I want to gain weight |
| I want to improve my family's health |
| I want to improve my health |
| I want to improve my wellbeing |
| I want to improve my sports performance |
| I want to prevent a future illness |
| I have a family history of diet-related illness |
| I think it is important to help academic studies |
| I am curious to find out what happens in these studies |
| I can manage to stick to healthful foods: even if I need a long time to develop the necessary routines | Very uncertain  Rather uncertain Rather certain Very certain | Not certain  Certain |
| I can manage to stick to healthful foods: even if I have to try several times until it works |
| I can manage to stick to healthful foods: even if I have to rethink my entire way of nutrition |
| I can manage to stick to healthful foods: even if I do not receive a great deal of support from others when making my first attempts |
| I can manage to stick to healthful foods: even if I have to make a detailed plan |

Supplemental Table 2.Odds ratio of participants dropping out by dietary habits and reasons for interest in the study

|  |  |  |  |
| --- | --- | --- | --- |
| **Question** | **Odds ratio** | **95% CI** | **P\*** |
| Eat your main meal away from home often (ref rarely) | 1.33 | 1.04-1.72 | **0.023** |
| Normally eat many hot or cooked meals eat per day (ref rarely) | 1.06 | 0.82-1.37 | 0.67 |
| How often do you prepare a meal "from scratch" (ref often) | 1.03 | 0.79-1.34 | 0.82 |
| Do you skip meals and replace them with snacks (ref rarely) | 1.75 | 1.16-2.65 | **0.008** |
| Time spent preparing a main meal (ref less than 30 min) | 0.96 | 0.75-1.24 | 0.78 |
| I can be as healthy as I want to be (ref disagree) | 0.95 | 0.62-1.44 | 0.79 |
| I am in control of my health (ref disagree) | 0.87 | 0.58-1.29 | 0.48 |
| I can pretty much stay healthy by taking care of myself (ref disagree) | 0.91 | 0.50-1.65 | 0.75 |
| Efforts to improve your health are a waste of time (ref disagree) | 1.65 | 0.78-3.48 | 0.19 |
| I am bored by all the attention that is paid to health and disease prevention (ref disagree) | 1.30 | 0.58-2.94 | 0.53 |
| What's the use of concerning yourself about your health - you'll only worry yourself to death (ref disagree) | 1.31 | 0.74-2.33 | 0.35 |
| Eating healthily is something I do frequently (ref disagree) | 0.62 | 0.45-0.86 | **0.003** |
| I eat healthily without having to consciously think about It (ref disagree) | 0.74 | 0.56-0.97 | **0.031** |
| I feel weird if I don't eat healthily (ref disagree) | 1.04 | 0.77-1.41 | 0.81 |
| I'm interested in personalised nutrition (ref no) | 0.94 | 0.71-1.24 | 0.65 |
| I want to know what foods are best for me (ref no) | 0.86 | 0.64-1.15 | 0.31 |
| I want to lose weight (ref no) | 1.53 | 1.18-1.97 | **0.001** |
| I want to gain weight (ref no) | 1.32 | 0.60-2.95 | 0.49 |
| I want to improve my family's health (ref no) | 0.96 | 0.72-1.28 | 0.77 |
| I want to improve my health (ref no) | 0.99 | 0.77-1.28 | 0.97 |
| I want to improve my wellbeing (ref no) | 1.23 | 0.96-1.6 | 0.11 |
| I want to improve my sports performance (ref no) | 1.09 | 0.85-1.41 | 0.49 |
| I want to prevent a future illness (ref no) | 1.08 | 0.84-1.39 | 0.55 |
| I have a family history of diet-related illness (ref no) | 0.81 | 0.52-1.25 | 0.34 |
| I think it is important to help academic studies (ref no) | 0.80 | 0.62-1.03 | 0.09 |
| I am curious to find out what happens in these studies (ref no) | 0.82 | 0.64-1.05 | 0.11 |
| I can manage to stick to healthful foods: even if I need a long time to develop the necessary routines (ref no) | 0.99 | 0.61-1.62 | 0.98 |
| I can manage to stick to healthful foods: even if I have to try several times until it works (ref no) | 0.76 | 0.45-1.30 | 0.31 |
| I can manage to stick to healthful foods: even if I have to rethink my entire way of nutrition (ref no) | 1.16 | 0.80-1.68 | 0.43 |
| I can manage to stick to healthful foods: even if I do not receive a great deal of support from others when making my first attempts (ref no) | 0.76 | 0.55-1.05 | 0.10 |
| I can manage to stick to healthful foods: even if I have to make a detailed plan (ref no) | 0.81 | 0.56-1.15 | 0.24 |

Values represent the adjusted OR, 95% CI and their corresponding P value.

\*, Logistic regression was used to test for significant differences between groups. Models were adjusted for age, sex and country. Variables are dichotomous.

**Supplementary Methods**

The following text is an excerpt from the full manuscript detailing the study design and baseline characteristics of the Food4Me randomized controlled trial (RCT) (1) and has been republished with the kind permission of Springer-Verlag.

**Study design**

The Food4Me Proof of Principle (PoP) study was a four-arm, web-based RCT conducted across seven European countries, which compared the effects of different levels of personalised nutrition (PN) on health-related outcomes. The intervention was designed to emulate a real-life web-based PN service, and the study aimed to answer the following primary research questions:

• Does personalisation of dietary advice assist and/or motivate participants to eat a healthier diet in comparison with non-personalised, conventional healthy eating guidelines?

• Is personalisation based on individualised phenotypic or genotypic information more effective in assisting and/or motivating study participants to make, and to sustain, appropriate healthy changes, than personalisation based on diet alone?

To answer these research questions, we used an hierarchical study design in participants randomised to a control group (Level 0) or to one of 3 PN interventions with increasingly complex bases for personalised dietary advice (Levels 1–3), i.e. randomisation was to one of the following treatment groups for a 6-month period:

• Level 0 (L0): (control group): non-personalised dietary advice based on (European) population healthy eating guidelines.

• Level 1 (L1): personalised dietary advice based on individual dietary intake data alone.

• Level 2 (L2): personalised dietary advice based on individual dietary intake and phenotypic data.

• Level 3 (L3): personalised dietary advice based on individual dietary intake, phenotypic and genotypic data.

The secondary research question of the study was as follows:

• Does more frequent feedback help participants to improve their compliance and motivate them to eat a healthier diet and follow a healthier lifestyle in comparison with those receiving less frequent feedback?

To answer this secondary research question, participants randomised to Levels 1, 2 or 3 were further randomised into “low-intensity” or “high-intensity” intervention groups:

• Low intensity: personalised feedback given three times during the intervention (at baseline, month 3 and month 6).

• High intensity: personalised feedback given five times during the intervention (at baseline and months 1, 2, 3 and 6). In addition, the “high-intensity” group had access to an online forum for discussion of topics related to the intervention, had access to personalised recipes and had more personalised physical activity (PA) feedback.

**Primary and secondary outcomes**

The primary outcome of the study was dietary intake at months 3 and 6. The secondary outcomes included PA and phenotypic biomarkers at months 3 and 6. The latter included obesity-related measures (i.e. body weight, body mass index (BMI) and waist circumference) and blood-based biomarkers (i.e. blood glucose, total cholesterol, carotenoids and fatty acids).

**Recruitment**

Participants were recruited via the Internet to emulate a web-based PN service. This was aided by local and national advertising of the study via the Internet, radio, newspapers, posters, e-flyers, social media and word of mouth.

Recruitment into the Food4Me intervention trial was carried out using identical standardised protocols in seven European recruitment centres. Based on sample size calculations (see below for further details), we aimed to recruit a total of 1,540 study participants (i.e. 220 participants per country). The PoP study recruitment sites were as follows: University College Dublin, Ireland; Maastricht University, the Netherlands; University of Navarra, Spain; Harokopio University, Greece; University of Reading, UK; National Food and Nutrition Institute, Poland; and Technische Universität München, Germany.

**Eligibility criteria**

Participants aged ≥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:

• Pregnant or lactating;

• No or limited access to the Internet;

• Following a prescribed diet for any reason, including weight loss, in the last 3 months;

• 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.

Exclusion based on prescribed diet or specific diseases was to avoid the theoretical risk that participating in the study could be disadvantageous to the individual.

Ethical approval and participant consent

The Research Ethics Committees at each University or Research Centre delivering the intervention granted ethical approval for the study. An application for the Norwegian arm of the study administered by the University of Oslo was not approved by the local ethics committee.

Prior to participation, an information sheet was provided to all potential volunteers who completed an online informed consent form before submitting personal data. This signed online consent form was automatically directed to the study coordinator to be counter-signed and archived. A second online informed consent form was completed before randomisation to the intervention study only for participants who met the inclusion criteria. A two-step consenting process was applied to permit collection of socio-demographic and dietary information for those interested in participating in PN even if they were ineligible for enrolment in this study, e.g. because of prescribed diets or food allergies. All Ethical Committees accepted an online informed consent procedure, except for the Netherlands and Germany whose ethics committees requested an additional written informed consent form for each participant recruited into the study. This hard copy consent form was returned by the participant to the respective recruitment centre.

**Intervention design**

Eligible and consenting participants were allocated to one of the four arms of the study, which included three intervention groups receiving different levels of personalised nutritional advice (L1: dietary data only; L2: dietary and phenotypic data; and L3: dietary, phenotypic and genotypic data) and the control group (L0), receiving conventional, non-personalised advice. To address our secondary research question, participants in levels L1, L2 and L3 were allocated into “low-” or “high-”intensity groups (see next section for details of the randomisation methods). At the end of the study (month 6), all participants received a personalised report which contained dietary, phenotypic and genotypic information and which summarised changes in their individual dietary intake and phenotypic measures between baseline and month 6 of the intervention.

**Randomisation**

Participants were randomised to one of the seven treatment groups (control group (L0), L1 high intensity, L1 low intensity, L2 high intensity, L2 low intensity, L3 high intensity and L3 low intensity) in combination with stratified randomisation by country (UK, Greece, Spain, Poland, Ireland, Germany and the Netherlands), sex (female or male) and age (<45 or ≥45 years) equally allocated to each treatment using an urn randomisation scheme (2).

Intervention groups

Level 0 (“control group”)

Following baseline measures, participants randomised to the control group (L0) received non-personalised dietary advice based on conventional population healthy eating guidelines. This non-personalised dietary advice was based on national dietary recommendations in each of the seven European countries participating in the Food4Me PoP Study which were integrated to produce a coherent set of recommendations suitable for Europe-wide use. These “standardised” recommendations included advice on energy intake to optimise BMI and on the consumption of fruits and vegetables, whole-grain products, fish, dairy products, meat, type of fat and salt. In addition, these recommendations included a generic PA recommendation. An advice leaflet was delivered via the web and also attached to an e-mail, which was sent to participants at baseline and at month 3 of the study.

Level 1 (“diet group”)

Following baseline measures, participants randomised to L1 received feedback on how their intakes of specific food groups (fruits and vegetables, whole-grain products, fish, dairy products and meat) compared with guideline amounts. In addition, personalised dietary advice based on their reported dietary intake at baseline and month 3.

Level 2 (“diet + phenotype group”)

Following baseline measures, participants randomised to L2 received personalised dietary advice based on their dietary intake (as for L1) and also on their baseline phenotypic data. The phenotypic feedback was based on anthropometric measurements and nutrient- and metabolic-related biomarkers.

Level 3 (“diet + phenotype + genotype group”)

Participants randomised to L3 received personalised dietary advice based on their dietary intake plus phenotypic and genotypic data collected at baseline. The genotypic feedback was based on specific variants in five nutrient-responsive genes selected specifically for the study.

**Personalised feedback report**

Participants randomised to L1, L2 and L3 received personalised feedback based on decision trees developed to provide a structured, evidence-based protocol for delivering tailored advice. This advice was based on dietary, PA, phenotypic and genotypic information as appropriate for each intervention group. In each case, intakes were compared with recommended intakes and determined to be adequate, high or low. If intakes were categorised as too high or too low, contributing foods were identified and specific messages were developed to advise change in intake of those foods. Full details of these decision trees will be published elsewhere. Protocols for the decision trees were standardised across the seven recruitment centres and translated into the language of each country. Nutritionists and dietitians implementing the decision trees were trained to ensure consistency in the PN advice given throughout the study, and, across all seven countries, these staff participated in frequent teleconferences (every 1–2 weeks) to resolve issues and to share best practice.

The participants’ reports contained information on how their health-related characteristics compared with recommendations. Estimations of healthy behaviours were explained using a three-colour sliding scale: green representing “Good, no change recommended”, amber representing “Improvement recommended” and red representing “Improvement strongly recommended”. For the genotype-based information, risk was indicated using “Yes” or “No” according to whether the participant did, or did not, carry the higher risk variant for each of the five nutrient-related genes. Finally, each report contained a personalised message from the dietitian/nutritionist to the participant. This message provided tailored advice for body weight and PA, and included specific nutrition-related goals derived from dietary, phenotypic and/or genotypic markers (according to the participants’ intervention group). Based on patient-centred counselling models for facilitating dietary change (3), a total of three nutrient-related goals were provided. These goals were selected by ranking all dietary, phenotypic and genotypic markers (as appropriate for the intervention group) based on their risk status (red, amber or green). The cut-off points for each of the nutritional and phenotypic variables were used to derive personalised goals and advice.

**Behavioural change techniques**

Explicit behaviour change techniques (BCT) were integrated into several aspects of the intervention and used to support, encourage and enhance dietary and lifestyle changes. The BCT and their conceptual framework were derived from work by Michie et al. on smoking cessation and dietary behaviour change (4, 5). The BCT categories used in the Food4Me PoP study were as follows: (1) behaviour and motivation, (2) behaviour and self-regulatory capacity/skills, (3) interaction and delivery, (4) interaction and information gathering and (5) interaction and communication.

**Study measures**

Participants consented to self-report all their measures via the Internet and to send requested biological samples (Dry Blood Spot cards and buccal swabs) by conventional mail, using prepaid, stamped addressed envelopes provided by the research team. To ensure that procedures were similar in all recruiting centres, standardised operating procedures were prepared for all study procedures (see below), and researchers underwent centralised training. In addition, to enable participants to collect and report the required information and to collect, process and dispatch the necessary biological samples correctly, participants were provided with detailed instructions online, including pictures and video demonstrations of all procedures, in their native language.

First screening questionnaire

Participants who consented to take part in the study completed an online screening questionnaire that included basic socio-demographic and health statistics, and information about Internet access, pregnancy and lactation, prescribed diets, food intolerance and allergies (used as exclusion criteria). Persons who were deemed unsuitable for the study, e.g. because of inadequate Internet access, pregnancy or use of a therapeutic diet, received formal e-mail notification that they did not match the inclusion criteria for the study and were thanked for their time.

Second screening questionnaire

Eligible participants for inclusion in the RCT completed a second online questionnaire, which collected more detailed socio-demographic, health and anthropometric data, as well as detailed information on food choices and dietary habits using a Food Frequency Questionnaire (FFQ) developed and validated specifically for this study (see below). Following assessment of this information, participants considered suitable for inclusion in the intervention study were asked to complete a second online consent form, which was sent to the study coordinator to be signed and archived. Potential participants considered unsuitable for the intervention study, e.g. through non-compliance in completion of the screening FFQ, received formal notification that they did not match the inclusion criteria for the study and were thanked for their time.

Anthropometric measurements

Body weight, height and upper thigh, waist and hip circumferences were self-measured and self-reported by participants via the Internet. Standardised instructions on how to perform these measurements were provided in printed and digital format (i.e. a video clip available on the Food4Me website in the languages of each of the seven recruitment countries). Participants were instructed to measure body weight without shoes and wear light clothing using a home or commercial scale and to measure height barefoot using a standardised measuring tape provided by Food4Me. Waist circumference was measured at the mid-point between the lower rib and the iliac crest using the same tape measure. Hip circumference was measured at the widest point around the greater trochanters, while the upper thigh circumference was measured midway between the iliac crest and the knee.

Food Frequency Questionnaire (FFQ)

Habitual dietary intake was quantified using an online-FFQ, developed for this study which included food items consumed frequently in each of the seven recruitment countries. The Food4Me online-FFQ has been validated against a 4-day weighed food record, and the agreement between methods varied, with correlations ranging from .23 (vitamin D) to .65 (protein, % total energy) for nutrient intakes and .11 (soups, sauces and miscellaneous foods) to .73 (yogurts) for food group intake (6, 7). Intakes of foods and nutrients were computed in real time using a food composition database based on McCance & Widdowson’s “The composition of foods” (8).

Metabolic markers

Finger-prick blood samples were collected by participants using a collection pack provided by Vitas Ltd, Oslo, Norway. To help with blood collection, participants had access to an online video demonstration with instructions and frequently asked questions. Each participant was asked to fill two Dry Blood Spot cards (equivalent to five drops of blood or to 150 µl of blood per card) at each collection time point. When the ten blood spots were filled, participants were instructed to dry the cards at room temperature for at least 2 h, but not longer than 4 h, before samples were put in an airtight aluminium bag with drying sachet and returned by post to the corresponding recruiting centre. The centres shipped the samples to Vitas (Vitas Ltd, Norway) and DSM (DSM Nutritional Products Ltd, Switzerland) for measurements of glucose, total cholesterol, carotenoids, n-3 fatty acid index and 32 other fatty acids (by Vitas), and vitamin D (25-OH D2 and 25-OH D3) (by DSM).

Genotypic analyses

Buccal cell samples were collected by participants at baseline using Isohelix SK-1 DNA buccal swabs and Isohelix Dri-capsules and returned by post to each recruiting centre for shipment to LCG Genomics (Hertfordshire, UK). LCG Genomics undertook DNA extraction and genotyping of the five loci used for derived personalised advice. These loci were analysed using KASPTM genotyping assays to provide bi-allelic scoring of single nucleotide polymorphisms (SNPs) and insertions and deletions at specific loci.

Physical activity

PA patterns were determined using a PA monitor—the DirectLife triaxial accelerometer for movement registration (TracmorD) (Philips Consumer Lifestyle, the Netherlands)—and a self-reported Baecke PA questionnaire (9) which was completed online. The accelerometer-based monitor (Philips DirectLife Activity Monitor, the Netherlands) was posted to each participant. Online video demonstrations as well as digital and printed instructions were provided at baseline. Participants were instructed to wear the monitor throughout the six-month intervention and to upload their PA data fortnightly via an online interface.

Sample size consideration

A power calculation was conducted a priori using Minitab® (version 16.1.0) and data for n-3 fatty acids and glucose concentrations in adult European populations. To address our primary research questions, and based on the resources available for the intervention, a sample size of n = 326 participants for each of the four intervention arms was planned. This allows us to detect differences of 0.22 SD in our main outcomes with 80 % power and alpha = 0.05. Assuming that the population standard deviation (SD) for n-3 fatty acid index is 1.5 units and for glucose is 1.05 mmol l−1, a total sample of n = 1,280 participants was estimated as sufficient to detect a real differences of 0.33 units for n-3 PUFA and 0.23 mmol l−1 glucose post-intervention. Allowing for a potential 20 % drop out, we aimed to recruit 1,540 participants into the study (220 participants per centre).

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