Title

Characteristics of participants who benefit most from personalised nutrition: findings from the pan-European Food4Me randomized controlled trial

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Sources of support

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 design or conduct, data collection, management, analysis or interpretation, manuscript preparation, review or approval

Short running head: Participants who benefits from personalisation
Abbreviations: Body mass index (BMI), Food frequency questionnaire (FFQ), Healthy eating index (HEI), Linear mixed model (LMM), Mediterranean diet (MD); Physical activity level (PAL), Personalised Nutrition (PN), Randomized controlled trial (RCT), Waist circumference (WC)
Trial registration: Clinicaltrials.gov NCT01530139
Number of Figures: 2
Number of Tables: 3
OSM available

Abstract

Little is known about who would benefit from internet-based personalised nutrition (PN) interventions. This study aimed to evaluate the characteristics of participants who achieved greatest improvements (i.e. benefit) in diet, adiposity and biomarkers following an internet-based PN intervention. Adults (n=1607) from seven European countries were recruited into a 6-month, randomized controlled trial (Food4Me) and randomized to receive conventional dietary advice (control) or PN advice. Information on dietary intake, adiposity, physical activity, blood biomarkers and participant characteristics was collected at baseline and month 6. Benefit from the intervention was defined as ≥5% change in the primary outcome (Healthy Eating Index) and secondary outcomes (waist circumference and BMI, physical activity, sedentary time and plasma concentrations of cholesterol, carotenoids and omega-3 index) at month 6. For our primary outcome, benefit from the intervention was greater in older participants and women. Benefit was greater for individuals reporting greater self-efficacy for "sticking to healthful foods" and who "felt weird if [they] didn't eat healthily". Participants benefited more if they reported wanting to improve their health and wellbeing. The characteristics of individuals benefiting did not differ by other demographic, health-related, anthropometric or genotypic characteristics. Findings were similar for secondary outcomes. Older individuals, women and individuals with less healthy diets at baseline benefitted more from PN advice. The odds of benefiting did not differ by weight status, genetic risk or socio-economic position. These findings have implications for the design of more effective future PN intervention studies and for tailored nutritional advice in public health and clinical settings.

Key Words: Food4Me; personalised nutrition; internet-based; intervention; European; adults

INTRODUCTION

Personalised nutrition (PN) approaches offer an alternative and potentially more effective strategy to improve dietary intake. [1; 2] PN interventions are tailored to key characteristics of the participant such as current diet, phenotype and genotype. [3] Although genotype-based personalised interventions designed to change risk behaviours (e.g. smoking and diet) have shown mixed results, [4] recent PN interventions have demonstrated encouraging improvements in dietary behaviours. [2; 5; 6; 7] Furthermore, internet-based interventions have the advantage of being scalable and more cost-effective than face-to-face interventions. Evidence from internet-based nutrition interventions suggests that participants who are most likely to benefit from a nutrition-related intervention are older, female and more highly educated. [8] These are also the characteristics of those who are interested in internet-based PN interventions. [9] These findings raise the possibility that other population groups may benefit less from internet-based PN interventions. However, this hypothesis is yet to be examined in a randomized controlled trial (RCT) and the characteristics of participants who benefit most from internet-based PN interventions are unknown. With the use of internet-based PN interventions increasing, [10; 11] understanding the characteristics of individuals who would benefit most from such interventions is an imperative for improving the design of PN interventions that are intended to improve diet and health outcomes across the population.

The Food4Me Study was a 6-month, internet-based, PN intervention conducted in seven European countries that showed that PN advice improved dietary intakes more than generalised dietary advice. [6; 10; 12; 13] The present paper examines the socio-demographic, anthropometric, physical activity-related, health-related, genotypic and behavioural characteristics of participants who benefited most from this PN intervention based on change in diet quality and adiposity following the intervention.

PARTICIPANTS AND METHODS

Study design

The Food4Me Study [14] was a 6-month, 4-arm, internet-based RCT conducted in seven European countries, designed to compare the effects of personalised dietary and physical activity advice with generalized advice in changing dietary and lifestyle behaviours. [7; 12; 15; 16; 17] Recruitment included newspapers, radio advertisements and flyers and participants could

participate in the study by registering their details on the Food4Me website. [14] Participants and were asked via email to complete online questionnaires and to provide biological samples at baseline and after 3 and 6 months intervention. Participants could interact via email with the dietitians, nutritionists and researchers at each center during the 6-month intervention. Participants were randomized to one of four intervention arms and received either non-personalised, generalized dietary advice (Control; Level 0), or one of three levels of PN based on dietary, physical activity (PA), phenotypic and genotypic data (see below). Behaviour change techniques were included in the study protocol. [12; 18] Participants were asked to complete an online food frequency questionnaire (FFQ), the Baecke PA questionnaire, [19] to wear accelerometers and to provide self-measured anthropometric information, buccal swabs and dry blood spot cards.

Ethics approval and participant consent

Participants (n=1607) were recruited between August 2012 and August 2013. The Research Ethics Committees at each university or research centre delivering the intervention granted ethics approval for the study. The Food4Me trial was registered as a RCT (NCT01530139) at Clinicaltrials.gov. Participants signed online consent forms. [12]

Eligibility criteria

Participants aged ≥18 years were included in the study. The following exclusion criteria were applied: (i) pregnant or lactating; (ii) no or limited access to the Internet; (iii) following a prescribed diet for any reason, including weight loss, in the last 3 months; (iv) diabetes, coeliac disease, Crohn's disease, or any metabolic disease or condition altering nutritional requirements.

Randomization and masking

An urn randomization scheme was used to allocate individuals to each treatment arm. Participants randomized to Level 1 (L1) received personalized dietary advice based on current diet and physical activity (PA) alone, Level 2 (L2) received personalized dietary advice based on dietary, PA and phenotypic data and Level 3 (L3) received personalized dietary advice based on dietary, PA, phenotypic and genotypic data. Personalized dietary feedback was based on how intakes of specific nutrients compared with recommended

intakes, which was then translated into advice on changing intakes of food groups (fruits and vegetables, whole grain products, fish, dairy products and meat). Personalized phenotypic feedback utilized anthropometric measurements and nutrient- and metabolic-related biomarkers to derive personalized feedback and specific variants in five nutrient-responsive genes were used to provide personalized genotypic feedback. Personalized advice on PA was based on responses to the Baecke Questionnaire and accelerometer data.

Participants randomized to the control group (L0) received dietary advice based on population-level healthy eating guidelines. This non-personalized dietary advice was derived from national dietary recommendations in each of the seven European countries and included generalized advice on the food groups listed above. In addition, these recommendations included a generic PA recommendation. Further details of the Food4Me PoP study are provided elsewhere [12].

Personalised feedback report

Participants randomized to L1, L2 and L3 received personalised feedback reports via email at baseline and at months 3 and 6 of the intervention. For those randomized to L1, L2 and L3, algorithms were used to provide participants with three specific top priority food-based dietary goals according to the individual's intakes of foods and nutrients. [20] For participants randomized to L2 and L3, the dietary advice was also based on phenotypic data (L2) and phenotypic plus genotypic data (L3). [12]

Dietary and anthropometric measures

Participants completed an online FFQ to estimate usual dietary intake at baseline and at months 3 and 6 of the intervention. This FFQ was developed and validated for the Food4Me Study [21; 22] and included 157 food items consumed frequently in each of the seven recruitment countries. Intakes of foods and nutrients were computed in real time using a food composition database. [23]

The Healthy Eating Index (HEI) 2010 was used to assess diet quality according to the 2010 Dietary Guidelines for Americans. [24] The HEI included 12 food groups, 9 of which assessed adequacy of the diet: 1) total fruit; 2) whole fruit; 3) total vegetables; 4) greens and beans; 5) whole grains; 6) dairy; 7) total protein foods; 8) seafood and plant proteins; and 9) fatty acids. The remaining 3 groups, refined grains, sodium, and "empty calories" (i.e. energy from solid

fats, alcohol, and added sugars), included dietary components that should be consumed in moderation. Less beneficial food groups were scored such that lower intakes receive higher scores. For all components, higher scores reflected better diet quality. The scores of the 12 components were summed to yield a total score with a maximum value of 100. [24] For use in sensitivity analyses, adherence to the Mediterranean diet (MD) was estimated based on a 14-point criteria. Participants scored 1 point for each of the 14 criteria they met and 0 for each they did not meet; points were summed to create an overall MD score, ranging from 0-14. More details are provided elsewhere. [25; 26]

Body weight (kg), height (m) and waist circumference (WC; cm) were self-measured and self-reported. Body mass index (BMI; kg/m^2) was estimated from body weight and height. Self-reported measurements were validated in a sub-sample of the participants (n=140) and showed a high degree of reliability. [27]

Study measures

Participants self-reported smoking habits and occupations. Country of residence was treated as dummy variables, such that the odds of benefiting for participants from one country were compared to all other countries. PA level (PAL), the percentage of individuals meeting PA recommendations (>150 min moderate PA or >75 min vigorous PA or an equivalent combination of moderate and vigorous PA per week [28]) and sedentary time were estimated from triaxial accelerometers (TracmorD, Philips Consumer Lifestyle, The Netherlands) and the Baecke PA questionnaire. An online screening questionnaire collected information on meal habits, healthy eating perceptions, self-efficacy for sticking to healthy foods and motivation for participation in the study (Supplemental Table 1).

Participants collected buccal cell samples at baseline using Isohelix SK-1 DNA buccal swabs and Isohelix dried-capsules. LGC Genomics (Hertfordshire, United Kingdom) extracted DNA and genotyped specific loci using TaqMan genotyping assays to provide bi-allelic scoring of single nucleotide polymorphisms: *FTO* (rs9939609), *MTHFR* (rs1801133), *TCF7L2* (rs7903146), *APOE(e4)* (rs429358 and rs7412) and *FADS1* (rs174546). Dried blood spots were collected for measurements of total cholesterol, carotenoids, n-3 fatty acid index, 32 individual fatty acids and vitamin D (25-OH D2 and 25-OH D3). [29; 30; 31]

Statistical analysis

All statistical analyses were performed using Stata (version 15; StataCorp, College Station, TX, USA). Data were analyzed based on intention-to-treat (ITT) of all individuals randomized into the intervention. Multiple imputation by chained equations and fully conditional specification methods, including augmentation, were used to address missing data for all outcomes. A total of 20 imputed datasets were used based on recent literature and the percent of missing data. Given that adjustment for multiple comparisons may increase the risk of type 2 error,[32] no adjustment for multiple comparisons was included.

The sample size was estimated a priori using Minitab® (version 16.1.0) based on data for n-3 fatty acids and glucose concentrations in European adults. To address the primary aim of the Food4Me intervention, a sample size of n=326 was planned for each of the four intervention arms. This would enable detection of 0.22 SD differences in the main outcomes with 80 % power and alpha=0.05. Assuming that the population standard deviation for n-3 fatty acid index was 1.5 units and for glucose was 1.05 mmol l−1, a total sample of n=1,280 was estimated as sufficient to detect a difference of 0.33 units for n-3 PUFA and 0.23 mmol/L glucose post-intervention. Allowing for a potential 20% drop out, recruitment was targeted at 1,540 participants (220 participants per centre).[7]

For our primary objective, participants randomized to L1, L2 or L3 of the intervention were identified as benefiting from the intervention if their HEI at month 6 was ≥5% better than at baseline. For our secondary outcomes, details for each definition of benefit are summarised in Supplemental Table 2. Briefly, benefit was defined as: i) ≥5% reduction in body weight and/or WC, ii) ≥5% increase in omega-3 index, iii) ≥5% increase in carotenoids, iv) ≥5% reduction in cholesterol, v) ≥5% reduction in sedentary time and vi) ≥5% increase in PA at month 6. Cut points of 5% were based on recent literature, where a change of ≥5% in body weight was identified as clinically significant. [16; 33] Logistic regression analyses, using multiple imputation estimation commands, were employed to examine associations between benefiting from the intervention (independent variable) and participant characteristics (dependent variables). Logistic regression analyses were also used to examine associations between benefiting from the intervention (independent variable) and participant characteristics (dependent variable) among participants randomized to L0 of the intervention only. An interaction effect between the characteristic and study arm (Control vs PN) was included in the model to determine whether characteristics of benefit differed between the Control and intervention groups. Analyses were adjusted for baseline age (continuous), sex, country (categorical), intervention arm (categorical) and baseline values of the outcome (i.e.

HEI, WC and body weight). PA outcomes were further adjusted for accelerometer wear time at baseline (continuous) and season (categorical). Correlations between behavioural characteristics were explored used Pearson's correlation coefficients.

As a sensitivity analysis, any impact of regression towards the mean in our estimate of change in HEI was evaluated by including a correction factor in our models according to the following equation $x_{adj}=\bar{x}+p(x-\bar{x})$. [34] Benefit from the intervention (i.e. change in HEI and body weight/WC at month 6) was also treated as a continuous variable. To determine whether findings were robust for different measures of diet quality, benefit was defined according to change in MD score (continuous). To account for multiple comparisons, results were deemed significant at a conservative $P<0.02$.

RESULTS

A total of 1607 participants were randomized into the intervention and 1270 of these completed the intervention **(**Figure 1). For the purposes of this analysis, only individuals who were randomized into L1 (n=414), L2 (n=404) and L3 (n=402) were included in the main analyses (n=1220). Data were imputed for individuals who dropped out between baseline and month 6 (Supplemental Table 3 and Supplemental Table 4).

The distributions of change in HEI, body weight and WC are shown in Figure 2, with the proportion of participants benefiting from the intervention by country shown in Table 1. The country with the highest proportion of participants benefiting based on the primary outcome (HEI) was Spain, whereas Greece and the Netherlands had the greatest proportion of participants with improvements in secondary outcomes (body weight and WC; Table 1).

(Table 1 here)

Baseline socio-demographic, anthropometric, health behaviour and biological characteristics of participants according to whether they benefited more from the PN intervention are shown in Table 2. The odds of benefiting were higher in women than in men. Older participants and participants with lower baseline HEI scores had higher odds of benefiting. The characteristics

of individuals benefiting did not differ by other health-related, anthropometric or genotypic characteristics (Table 2).

(Table 2 here)

Behavioural characteristics of participants benefiting from the PN intervention are shown in Table 3. The odds of a participant benefiting more from the intervention at month 6 were higher among those who reported greater self-efficacy for "sticking to healthful foods" and who "felt weird if [they] didn't eat healthily" (HEI only), which were correlated (r 0.25, P<0.0001). Participants had a higher odds of benefiting if they were interested in improving their health and improving their wellbeing (HEI only), which were highly correlated (r 0.40, P<0.0001). The characteristics of individuals who benefited more from the intervention did not differ by other healthy eating habits or perceptions (Table 3). Baseline socio-demographic, anthropometric, health-related and behavioural characteristics of participants randomized to L1, L2 and L3 of the intervention associated with benefiting from the PN intervention at month 6 according to each definition of benefit (HEI, weight loss/WC reduction, physical activity, sedentary time, cholesterol, carotenoids, omega-3 index) are shown Supplemental Table 5 and Table 6. Few participant characteristics were comparable across definitions.

When stratified by PN intervention arm, odds of benefitting were higher with higher age in L2 (OR 1.05, CI: 1.01-1.08) and L3 (1.02, 1.00-1.06), with being female in L2 (3.75, 1.57-8.96), with being a participant in the Netherland in L3 (3.19, 1.41-7.22). Odds were higher in participants who reported with being able to stick to healthy foods even if they had to re-think their way of nutrition (4.96, 1.55-15.81) in L1 and even if they had to try several times until it worked in L1 (22.69, 1.64-313.2) and L2 (4.96, 1.55-15.81). Odds of benefiting were also higher in participants who wanted to know what foods are best for them in L2 (5.46, 1.88-15.90) and in those who reported frequently eating healthily (3.04, 1.30-7.11) in L3. Odds of benefitting were lower in participants in Germany (0.32, 0.12-0.88) in L3. No other significant differences by PN arm were observed.

When the analyses were restricted to participants randomized to generalized (non-personalised) dietary advice (L0), the odds of benefiting from the intervention were lower in *APOE* (rs429358) risk carriers (OR 0.53 [0.32, 0.91], P=0.020) but higher among individuals

reporting being in control of their own health (OR 1.71 [1.01, 2.91], P=0.047) and wanting to gain weight (OR 0.17 [0.03, 0.99], P=0.049). All other characteristics were consistent with those of participants randomized to PN. There was no interaction between participant characteristic and study arm (Control vs PN) on extent of benefit (change in HEI), with the exception of the *MTHFR* risk allele and participants who wanted to improve their health. HEI improved in participants randomised to PN advice who were carriers of the MTHFR risk allele (coeff 0.08, SE 0.39, P=0.043) and who wanted to improve their health (coeff 0.08, SE 0.38, P=0.038) compared to those in the control arm who were not carriers of the MTHFR risk allele and did not want to improve their health, respectively.

(Table 3 here)

Sensitivity analyses

The pattern of results was similar when change in HEI and body weight/WC at month 6 was treated as a continuous outcome (data not shown). The characteristics of participants benefiting most from the PN intervention were similar when benefit was defined using MD (data not shown) and when results for benefit (defined by HEI) were adjusted for regression towards the mean (data not shown). Comparison of benefit from the PN intervention as defined based on HEI, adiposity, omega-3 index, carotenoids, cholesterol, sedentary time and physical activity are summarised in Table 4 and Table 5.

(Table 4 here)

(Table 5 here)

DISCUSSION

This study aimed to characterize the participants benefiting most from a 6-month, internet-based PN intervention. Our main findings are that older participants, women and those with less healthy diets at baseline benefited most from PN advice. The odds of benefiting did not differ by weight status, genetic risk or socio-economic position. These findings confirm the need to enhance the effectiveness of PN interventions in certain groups e.g. young men and those with unhealthier eating perceptions/motivations. These individuals may require

additional tailoring of PN advice using individual characteristics that were not investigated in this study. Nonetheless, since many participant characteristics did not affect the extent of benefit, our findings suggest that most population groups would benefit from PN advice.

To the best of our knowledge, no previous studies have investigated the characteristics of individuals benefiting most from an internet-based PN intervention. Studies have shown that women, older individuals, and generally healthier individuals are more likely to participate in nutrition interventions, [35] including internet-based interventions. [36] This may be due to a greater desire to lose weight among women and older adults being more time-rich than younger adults. In addition, individuals with greater motivation to be healthy and to participate in nutrition interventions may be more knowledgeable about the benefits of healthy eating. [37] Similarly, of the 5662 individuals who expressed an interest in participating in the Food4Me Study, 65% were women. [38] Nonetheless, these individuals were broadly representative of the wider European population in terms of need to improve dietary and PA behaviours, [38] and were not skewed towards individuals who were already healthy (i.e. the worried well). In addition, in the Food4Me Study, individuals who met fewer recommendations at baseline [39] and who had lower self-perception of healthy eating habits [40] showed greatest improvement in diet following the intervention. In the present analysis, despite the odds of benefiting being higher in participants with better self-reported healthy eating perceptions and motivations, the odds of benefitting from PN advice were lower in those with higher HEI at baseline. The proportion of participants benefiting most appeared to differ by country, which suggests that there may be opportunities to tailor PN advice to different cultural norms.

To a large extent, the characteristics of participants benefiting from the Control intervention were similar to those of participants benefiting most from the PN intervention. If this is a true effect, it implies that participants who benefit from PN advice are comparable to those who received general dietary advice. Moreover, it suggests that benefit extends beyond those receiving the intervention. This confirms our observed effect of the intervention on improvements in diet, where participants in the control group showed modest improvements in their diet as a result of participating in the intervention.[7] Where there were differences between treatment arms, reduced power in the Control arm could have influenced these findings.

The effects of the intervention on adiposity markers (benefit from the intervention was defined as ≥5% weight loss or WC reduction), showed a somewhat different range of

participant characteristics compared with those benefiting more in respect of HEI. This may be that those who needed to lose weight were different from the general population. Moreover, the study has shown large individual variation in changes in health behaviours following a PN intervention. Such inter-individual variation is common in (dietary) intervention studies. For example, in the DIETFITS weight loss intervention study, individual body mass changes ranged over approximately 40 kg within each treatment group with some participants losing 30 kg over 12 months and others gaining 10 kg body weight.[41] Such inter-individual variation is one of the major challenges that personalised nutrition approaches aim to address. With better understanding of the participant characteristics that lead to no (or adverse) responses to interventions, there is scope to refine the personalization process and to develop intervention features that improve the target behaviours.

This study had a number of strengths. The Food4Me study is the largest RCT on the effectiveness of PN advice in European adults to date, it used a rigorous design and it investigated change in health-related outcomes sustained to 6 months. We applied multiple imputation to our analyses, thus limiting bias associated with missing data and the robustness of our findings was confirmed through extensive sensitivity analyses. The pattern of results remained consistent regardless of whether benefit was defined as binary or continuous change in HEI or any of the secondary definitions and following adjustment for regression towards the mean in HEI.

A limitation of our study is that data were self-measured and self-reported via the internet. Nonetheless, the accuracy of internet-based, self-reported anthropometric data have been confirmed in the Food4Me Study. [27] Dietary intakes may be subject to misreporting error, which was minimized by validation of the FFQ against a 4-day weighed food record. [22] Since 97% of our study participants were Caucasians, research in wider ethnicity groups is required to generalize our findings to other populations. Our sample is a self-selected group of individuals who may be more health-conscious than the general population. However, participants interested in joining the study were similar to the wider population of European adults, who would benefit from improved diet and PA. [42] In addition, although the cut-off points for defining benefit were based on previous research, [33] the clinical relevance of a 5% in outcome measures warrants further investigation. The present analyses requires replication in a larger study, which would provide more statistical power, particularly for testing subgroup differences in benefit. Moreover, while analyses were adjusted for appropriate confounders, we cannot discount the possibility of residual confounding. Given that analyses

were not adjusted for multiple testing, the risk of type 1 error is higher and so results should be interpreted with this in mind. Finally, although we included outcomes for 7 different health-related biomarkers, future PN interventions may wish to consider the impact of PN on the gut microbiota and on other markers of health. [43]

These findings have implications for the design of more effective future PN intervention studies and tailored nutritional advice in the public health or clinical settings. Future studies should consider ways of tailoring PN advice to improve efficacy in certain population groups such as young men. Nonetheless, with many characteristics, such as weight status and occupation, being unrelated to extent of benefit in the Food4Me Study, our findings suggest that most population groups will benefit from PN advice. Further improvements in the design, delivery and efficacy of PN interventions will support integration of PN strategies into public health policies.

In conclusion, older individuals, women and those with less healthy diets at baseline were likely to benefit most (i.e. improve their diet and achieve weight loss, where appropriate) from PN advice. Our findings confirm the need to enhance the effectiveness of PN interventions in certain groups e.g. young men. The odds of benefiting did not differ by weight status, genotype or socio-economic position. Since few characteristics affected the degree of benefit from the PN intervention, our findings suggest that PN approaches may be widely applicable.

Acknowledgments

The authors acknowledge Silvia Kolossa and Miroslaw Jarosz for their contribution to the design of the study and collection of the data.

Conflict of interest

TEG is the CEO of Vitas Ltd. TEG and CAD have shares in Vitas Ltd, and CAD is a board member and consultant in Vitas Ltd; no other conflict of interests. KML is a consultant for HeadUpLabs. WHMS 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. MG reports that he is a non-remunerated member of the Google Food Innovation Lab Community of Practice on

Personalized Nutrition. JCM 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. JAL has received research funding outside of the submitted work from Medical Research Council, Biotechnology and Biological Sciences Research Council and European Union with in kind provision of foods from Arla, AAK and Unilever and research funding from the Dairy Council, UK. She was a member of the UK Governments Scientific Advisor Committee for Nutrition (SACN) and a member of SACNs Carbohydrate Working Group and Saturated Fats Working Group during and after the study.

Author contributions

CCM, KML and JCM 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: KML, CCM and JCM. Acquisition, analysis or interpretation of data: YM, IT, MJ, TEG, CAD, ERG, LB, JAL, JAM, WHS, HD, MG and JCM. Drafting of the manuscript: CCM, KML and JCM. Statistical analysis: KML, CCM, and JCM. Critical revision and final approval of the manuscript: All authors contributed to a critical review of the manuscript during the writing process. All authors approved the final version to be published.

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Table 1. Proportion of participants (%) randomized to a PN intervention arm (L1, L2 or L3) benefiting from the intervention by country[1]

	Total (n=493)	**Germany (n=63)**	**Greece (n=47)**	**Ireland (n=64)**	**NL (n=121)**	**Poland (n=62)**	**Spain (n=69)**	**UK (n=67)**
HEI	56·8	57·1	48·9	57·8	61·2	58·1	60·9	47·8
BW and/or WC	27·0	20·6	36·1	21·9	31·4	19·4	30·4	26·9
Physical activity	21·5	19·1	19·2	20·3	22·3	17·7	30·4	19·4
Sedentary time	38·5	42·9	34·0	32·8	40·5	45·2	43·5	28·4
Cholesterol	46·7	50·8	29·8	46·9	52·1	35·5	34·8	67·2
Carotenoids	42·2	30·2	34·0	39·1	52·9	53·2	31·9	43·3
Omega-3 index	51·9	42·9	53·2	59·4	63·6	41·9	47·8	44·8

NL, The Netherlands; BW, Body weight (kg); WC, waist circumference (cm). 1, Benefit was defined as a ≥5% improvement in the outcomes from baseline to month 6.

Table 2. Baseline socio-demographic, anthropometric, health-related and genotypic characteristics of participants randomized to L1, L2 and L3 of the intervention, and multivariable adjusted odds ratio (95% CI) of benefiting from the PN intervention at month 6 as defined by extent of improvement in HEI (n=493)[1]

	Total	No Benefit	Benefit	Odds of benefiting[2] OR, 95% CI	P value
HEI score	50·0 (9·54)	54.6 (8.07)	46.5 (9.11)	0·89 (0·86, 0·91)	<0·001
Demographics					
Age, years	43·9 (13·0)	43.0 (13.3)	44.6 (12.7)	1·03 (1·01, 1·04)	<0·002
Female, %	55·6	54.5	56.4	1·64 (1·07, 2·50)	0·023
Occupation, %					
Professional and managerial	43·6	42.3	42.9	1·09 (0·73, 1·64)	0·67
Intermediate occupations	25·2	23.5	26.4	1·06 (0·66, 1·69)	0·82
Routine and manual	8·32	7.98	8.57	1·04 (0·50, 2·16)	0·91
Country, %					
Germany	12·8	12.7	12.9	0·67 (0·37, 1·21)	0·19
Greece	9·53	11.3	8.21	0·72 (0·36, 1·42)	0·33
Ireland	13·0	12.7	13.2	1·08 (0·59, 1·97)	0·80
Netherlands	24·5	22.1	**26.4**	1·62 (1·01, 2·60)	0·044
Poland	12·6	12.2	12.9	0·59 (0·30, 1·15)	0·12
Spain	14·0	12.7	15.0	1·39 (0·78, 2·48)	0·26
UK	13.6	16.4	11.4	0·85 (0·48, 1·53)	0·60
Anthropometrics					
Body weight, kg	75·0 (14·8)	74.6 (14.3)	75.3 (15.1)	1·00 (0·98, 1·01)	0·81
BMI, kg/m^2	25·5 (4·45)	25.1 (3.89)	25.8 (4.83)	1·02 (0·97, 1·07)	0·16
Waist circumference, cm	86·4 (12·8)	85.6 (12.4)	87.0 (13.0)	1·00 (0·98, 1·02)	0·66
Health behaviours					
PAL	1·75 (0·18)	1.75 (0.17)	1.76 (0.18)	1·60 (0·48, 5·35)	0·45
MVPA	45·8 (30·5)	47.1 (31.4)	44.8 (29.8)	1·00 (0·99, 1·01)	0·99
Sedentary behaviour, min/d	758 (70·6)	756.6 (71.7)	758.8 (69.9)	1·00 (0·99, 1·01)	0·95
Current smoker, %	8·11	7.04	8.93	1·03 (0·46, 2·31)	0·84
Medication use, %	33·5	31.9	34.6	0·96 (0·62, 1·47)	0·84
Genotype[3]					
FTO (rs9939609)	70·4	72.3	68.9	0·91 (0·59, 1·41)	0·67
FADS1 (rs174546)	42·8	42.3	43.2	0·91 (0·60, 1·36)	0·63
TCF7L2 (rs7903146)	48·9	49.8	48.2	0·96 (0·64, 1·44)	0·85
APOE (rs429358)	27·4	30.1	25.4	0·95 (0·61, 1·48)	0·81
APOE (rs7412)	12·6	13.6	11.8	0·72 (0·39, 1·32)	0·29
MTHFR (rs1801133)	55·6	57.3	54.3	1·01 (0·67, 1·52)	0·96

Values represent means (SD) or percentages, L=Level; L1, Participants received personalised nutrition advice based on their current diet; L2, Participants received personalised nutrition advice based on their current diet and phenotype; L3, Participants received personalised nutrition advice based on their current diet, phenotype and genotype; MVPA, Moderate to vigorous physical activity

1, Multiple logistic regression was used to test for differences in characteristics between individuals who benefited most and the remaining participants, respectively. Analyses were adjusted for age, sex, country, intervention arm (except when used as the dependent variable) and baseline values of the outcome (i.e. HEI). PAL, MVPA and sedentary behaviour were additionally adjusted for time wearing the accelerometer and season.

2, More benefit: ≥5% increase in HEI from baseline to month 6; Less benefit: <5% increase in HEI from baseline to month 6.

3, probability carrier of minor allele

Table 3. Baseline behavioural characteristics of participants randomized to L1, L2 and L3 of the intervention and multivariable adjusted odds ratio (95% CI) of benefiting from the PN intervention at month 6 as defined by improvement in HEI (n=493)[1]

	Total	No Benefit	Benefit	Odds ratio of benefiting[2] (OR, 95% CI)	P value
Meal habits					
Often eat main meal away from home	34·3	32.9	35.4	1·08 (0·69, 1·66)	0·55
Often skip meals and replace them with snacks	6.09	4.69	7.14	0·78 (0·33, 1·93)	0·62
Often prepare a meal "from scratch"	30·8	28.2	32.9	0·93 (0·59, 1·45)	0·74
Often eat hot or cooked meals	28·4	29.6	27.5	1·12 (0·71, 1·75)	0·63
Spend a lot of time preparing a main meal	43·8	45.5	42.5	1·08 (0·72, 1·62)	0·72
Heathy eating perceptions					
Believe I am in control of my health	71·6	70.9	72.1	1.16 (0·74, 1·82)	0·51
Can stay healthy by taking care of myself	86·6	85.5	87.5	1·17 (0·65, 2·10)	0·61
Efforts to improve health are a waste of time	2·43	2.35	2.50	0·71 (0·18, 2·83)	0·63
Bored by attention paid to health and disease	1·42	0.94	1.79	1·29 (0·19, 8·87)	0·79
There's no use of being concerned about health	5·27	3.29	6.79	1·45 (0·53, 3·83)	0·46
Frequently eating healthily	76·3	77.9	75.0	1·74 (1·05, 2·89)	0·033
Eat healthily without thinking about it	44·6	47.0	42.9	1·01 (0·67, 1·51)	0·97
Feel weird if don't eat healthily	47·7	47.4	47.9	1·67 (1·10, 2·55)	0·017
Self-efficacy for sticking to healthful foods					
Even if I need time to develop the routines	93·1	92.0	93.9	2·35 (1·33, 4·14)	0·006
Even if I have to try several times until it works	96·4	94.4	97.9	2·45 (1·25, 4·78)	0·009
Even if I have to rethink my way of nutrition	85·8	83.6	87.5	1·74 (1·14, 2·46)	0·010
Even if I do not receive support from others	87·2	87.8	86.8	1·22 (0·80, 1·87)	0·36
Even if I have to make a detailed plan	88·4	86.9	89.6	1·30 (0·83, 2·04)	0·27
Motivation for participating in the study					
Interested in personalised nutrition	75·7	78.4	73.6	1·19 (0·74, 1·92)	0·47
Want to know what foods are best for him/her	79·3	76.5	81.4	1·83 (1·11, 3·02)	0·018
Want to lose weight	43·4	39.0	46.8	1·38 (0·91, 2·10)	0·13
Want to improve my family's health	27·6	25.8	28.9	0·98 (0·63, 1·54)	0·93
Want to improve my health	55·8	50.7	59.6	1·52 (1·06, 2·28)	0·047
Want to improve my wellbeing	54·8	52.6	56.4	1·31 (1·87, 1·97)	0·19
Want to improve my sports performance	35·7	36.2	35.4	1·40 (0·90, 2·16)	0·14
Want to prevent a future illness	60·0	56.8	62.5	1·37 (0·91, 2·07)	0·13
Have a family history of diet-related illness	8·92	7.98	9.64	1·35 (0·67, 2·75)	0·41
Think it is important to help academic studies	69·6	68.1	70.7	1·36 (0·88, 2·12)	0·17
Curious to find out what happens in PN studies	47·1	45.1	48.6	1·24 (0·83, 1·86)	0·30

Values represent percentages. L=Level; L1, Participants received personalised nutrition advice based on their current diet; L2, Participants received personalised nutrition advice based on their current diet and phenotype; L3, Participants received personalised nutrition advice based on their current diet, phenotype and genotype;

1, Multiple logistic regression was used to test for differences in characteristics between individuals who benefited most and the remaining participants, respectively. Analyses were adjusted for age, sex, country, intervention arm (except when used as the dependent variable) and baseline values of the outcome (i.e. HEI). PAL, MVPA and sedentary behaviour were additionally adjusted for time wearing the accelerometer and season. For the purposes of this table, phrasing of characteristics has been paraphrased from the original questionnaire (see Supplemental Table 1)

2, Benefit: ≥5% increase in HEI from baseline to month 6; No benefit: <5% increase in HEI from baseline to month 6.

Figure 1. Consort diagram of participants included in the Food4Me study

Figure 2. Distribution of change among Food4Me participants in a) Healthy Eating Index (HEI); b) waist circumference (WC); and c) body weight (BW). Participants achieving a greater than 5% improvement in HEI and BW/WC at month 6 are in light grey.

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

Supplemental Table 2. Definitions for benefit from the intervention for secondary outcomes

Supplemental Table 3. Summary of missing data for variables at baseline

Supplemental Table 4. Baseline socio-demographic, anthropometric, health behaviour-related and genotypic characteristics of all participants randomized to L1, L2 and L3 of the intervention in imputed dataset and complete case analysis

Supplemental Table 5. Baseline socio-demographic, anthropometric, health-related and genotypic characteristics of participants randomized to L1, L2 and L3 of the intervention associated with benefiting from the PN intervention at month 6 according to each definition of benefit 1 ✓=significant benefit, X=significant non-benefit

Supplemental Table 6. Baseline behavioural characteristics of participants randomized to L1, L2 and L3 of the intervention benefiting from the PN intervention at month 6 according to each definition of benefit 1 ✓=significant benefit, X=significant non-benefit

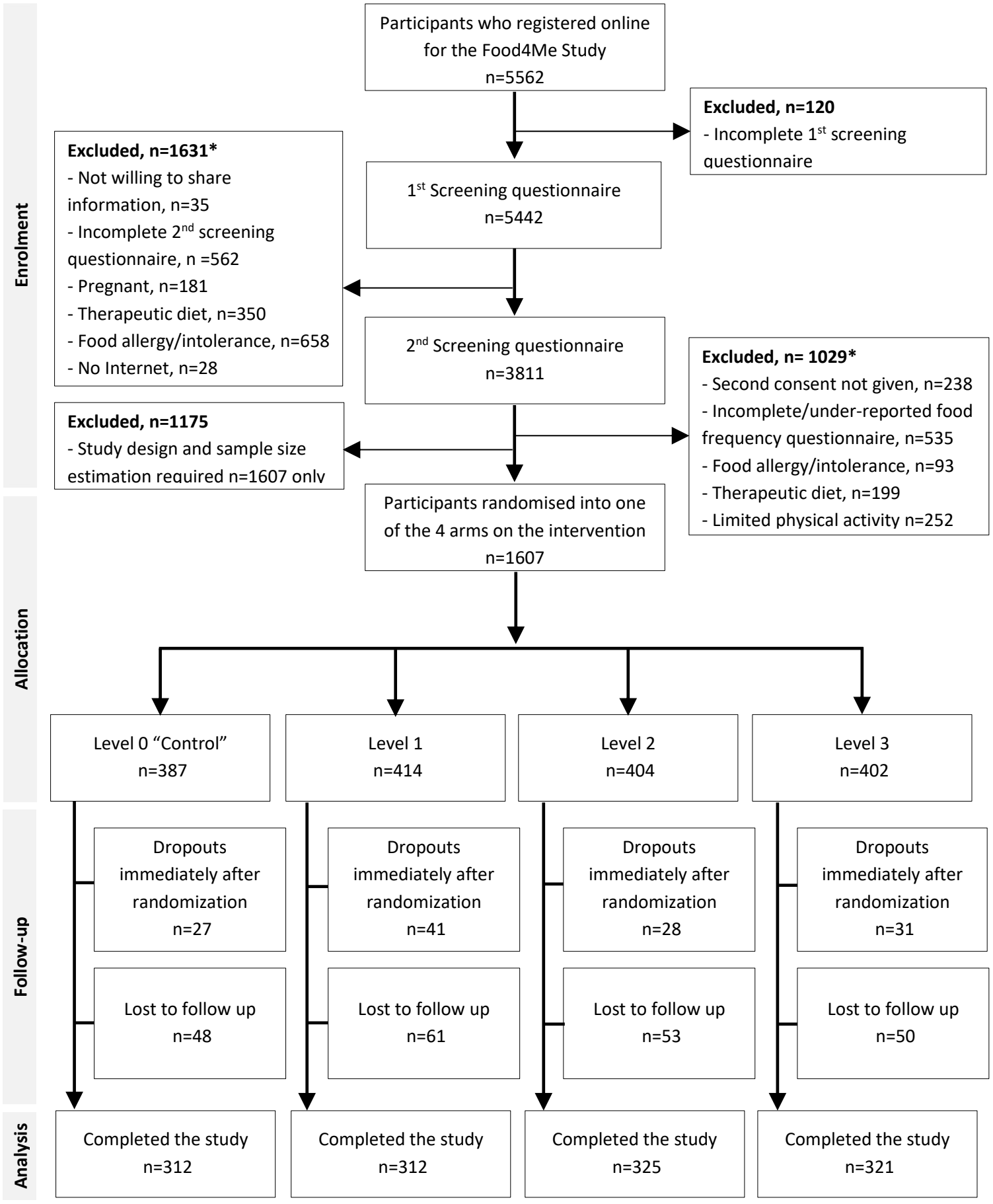
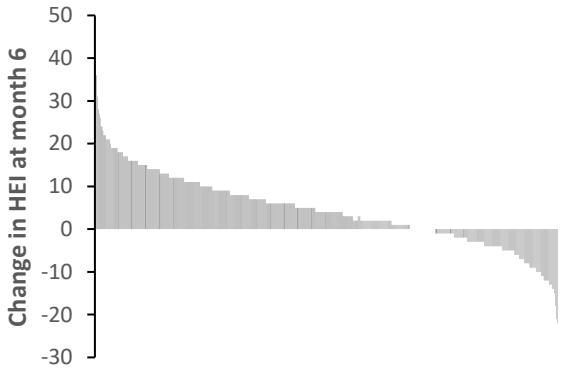
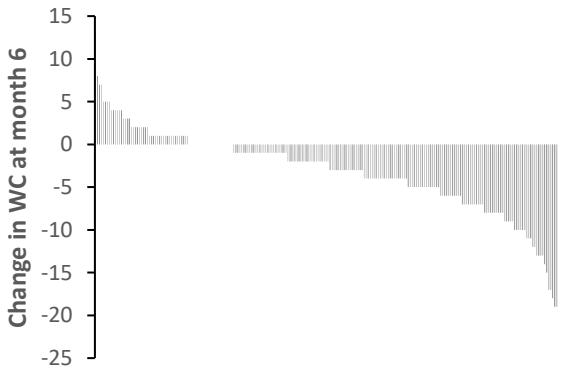

Enrolment
Allocation
Follow-up
Analysis
Participants who registered online for the Food4Me Study n=5562
Excluded, n=120
- Incomplete 1st screening questionnaire
1st Screening questionnaire n=5442
Excluded, n=1631*
- Not willing to share information, n=35
- Incomplete 2nd screening questionnaire, n =562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

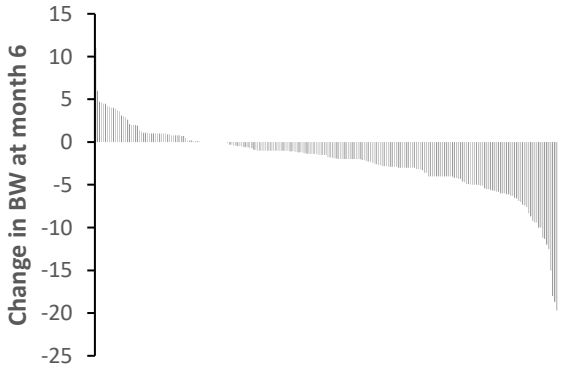
Figure 1


Change in HEI at month 6
50
40
30
20
10
0
-10
-20
-30

A


Change in WC at month 6
15
10
5
0
-5
-10
-15
-20
-25

B


Change in BW at month 6
15
10
5
0
-5
-10
-15
-20
-25

C

Figure 2

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

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	Often Rarely
Do you skip meals and replace them with snacks?	(Almost) never	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 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 Eating healthily is something he/she does without having to think about doing	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'm interested in personalised nutrition 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	No Yes	No Yes
I can manage to stick to healthful foods: even if I need a long time to develop the necessary routines 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	Very uncertain Rather uncertain Rather certain Very certain	Not certain Certain

Supplemental Table 2. Definitions for benefit from the intervention for secondary outcomes

Outcome	Definition
Body weight and/or WC	≥5% reduction in body weight and/or WC among individuals were advised to lose weight (i.e. if they had a BMI >25 kg/m^2 or a WC >88cm in women and >102 in men)
Omega-3 index	≥5% increase in omega-3 index among individuals who were advised to increase their omega-3 intake (i.e. who had a blood cholesterol concentration <4% and/or dietary intake <0.2% of total energy and for whom omega-3 was a top 3 priority target)
Carotenoids	≥5% increase in carotenoids among individuals who were advised to increase their carotenoid intake (i.e. who had a blood carotenoid concentration <1.3uM and for whom carotenoids was a top 3 priority target)
Cholesterol	≥5% reduction in cholesterol among individuals who were advised to improve their cholesterol concentrations (i.e. who had a blood cholesterol concentration >8mmol/L and for whom cholesterol was a top 3 priority target)
Sedentary time	≥5% reduction in sedentary time among individuals who were advised to increase their PA (i.e. who had a PAL <1.5 or a total activity index <5.5)
Physical Activity (PA)	≥5% increase in PA among individuals who were advised to increase their PA (i.e. who had a PAL <1.5 or a total activity index <5.5)

Supplemental Table 3. Summary of missing data for variables at baseline[1]

Variable	Number of participants imputed	Percentage of imputed relative to baseline
Delta HEI at month 6	337	21·0
Delta MD at month 6	337	21·0
HEI	127	7·90
MD	127	7·90
PAL	320	19·9
Sedentary time	320	19·9
Moderate to vigorous physical activity	320	19·9
Wear time of accelerometer	320	19·9
Season accelerometer worn	23	1·43
Professional occupation	129	8·03
Intermediate occupation	129	8·03
Manual occupation	129	8·03
Body weight	127	7·90
Waist circumference	131	8·15
BMI	127	7·90
FTO (rs9939609)	125	7·78
FADS1 (rs174546)	125	7·78
TCF7L2 (rs7903146)	128	7·97
APOE (rs429358)	125	7·78
APOE (rs7412)	131	8·15
MTHFR (rs1801133)	125	7·78
Self-efficacy for sticking to healthful foods:		
Even if I need time to develop the routines	44	2·74
Even if I have to try several times until it works	44	2·74
Even if I have to rethink my entire way of nutrition	44	2·74
Even if I do not receive support from others	44	2·74
Even if I have to make a detailed plan	44	2·74

BMI, Body Mass Index, HEI, Healthy Eating Index, MD, Mediterranean Diet score, PAL, Physical Activity Level

1, All data refer to baseline with the exception of "Delta HEI at month 6" and "Delta MD at month 6"

Supplemental Table 4. Baseline socio-demographic, anthropometric, health behaviour-related and genotypic characteristics of all participants randomized to L1, L2 and L3 of the intervention in imputed dataset and complete case analysis

	Imputed dataset[1] (n=1220)	**Complete case[2] (n=930)**
HEI score	49·1 (0·30)	49·3 (9·77)
Demographics		
Age, years	39·7 (0·37)	41·1 (12·9)
Female, %	59·3 (1·41)	56·7
Occupation, probability		
Professional and managerial	39·3 (1·46)	40·3
Intermediate occupations	26·6 (1·33)	27·0
Routine and manual	9·89 (0·89)	9·25
Country, %		
Germany	13·8 (0·99)	14·3
Greece	14·5 (1·01)	14·6
Ireland	13·8 (1·00)	12·6
Netherlands	13·8 (1·00)	17·4
Poland	13·8 (1·00)	13·1
Spain	13·9 (1·00)	14·7
The UK	14·6 (1·01)	13·2
Anthropometrics		
Body weight, kg	74·6 (0·48)	75·0 (15·8)
BMI, kg/m^2	25·5 (0·15)	25·5 (4·84)
Waist circumference, cm	85·5 (0·40)	86·1 (13·7)
Health behaviours		
PAL	1·74 (0·57)	1·74 (0·17)
MVPA	46·2 (0·99)	45·5 (29·7)
Sedentary behaviour, min/d	744 (2·47)	747 (74·6)
Current smoker, %	11·6 (0·92)	11·1
Medication use, %	29·5 (1·31)	30·3
Genotype, % carrier of minor allele		
FTO (rs9939609)	67·7 (1·41)	68·0
FADS1 (rs174546)	42·9 (1·48)	43·9
TCF7L2 (rs7903146)	47·5 (1·49)	47·4
APOE (rs429358)	25·6 (1·29)	26·3
APOE (rs7412)	12·6 (0·99)	12·4
MTHFR (rs1801133)	54·4 (1·47)	55·3

L=Level; L1, Participants received personalised nutrition advice based on their current diet; L2, Participants received personalised nutrition advice based on their current diet and phenotype; L3, Participants received personalised nutrition advice based on their current diet, phenotype and genotype; MVPA, Moderate to vigorous physical activity

1, Values have been imputed using multiple imputation. Values represent means (SE) or probabilities (SE)

2, Values represent means (SD) or percentage

Supplemental Table 5. Baseline socio-demographic, anthropometric, health-related and genotypic characteristics of participants randomized to L1, L2 and L3 of the intervention associated with benefiting from the PN intervention at month 6 according to each definition of benefit [1] ✓=significant benefit, X=significant non-benefit

	HEI (n=493)	Weight loss/ WC reduction (n=231)	Physical activity (n=333)	Sedentary time (n=333)	Cholesterol (n=36)	Carotenoids (n=140)	Omega-3 index (n=88)
HEI score			X				
Demographics							
Age, years	✓						
Female, probability	✓			✓			
Occupation, probability							
Professional and managerial				X			
Intermediate occupations			✓				
Routine and manual							
Country, probability							
Germany							
Greece						X	
Ireland							
Netherlands	✓						
Poland							
Spain			✓				
UK							
Anthropometrics							
Body weight, kg							
BMI, kg/m^2							
Waist circumference, cm		✓			X		
Health behaviours							
PAL							✓
MVPA							✓
Sedentary behaviour, min/d							X
Current smoker, probability							
Medication use, probability							
Genotype, probability carrier of minor allele							
FTO (rs9939609)							
FADS1 (rs174546)							
TCF7L2 (rs7903146)							
APOE (rs429358)							✓
APOE (rs7412)		✓				X	
MTHFR (rs1801133)							

Supplemental Table 6. Baseline behavioural characteristics of participants randomized to L1, L2 and L3 of the intervention benefiting from the PN intervention at month 6 according to each definition of benefit [1] ✓=significant benefit, X=significant non-benefit[1]

	HEI (n=493)	Physical activity (n=333)	Sedentary time (n=333)	Carotenoids (n=140)	Omega-3 index (n=88)
Meal habits					
Often eat main meal away from home					
Often skip meals and replace them with snacks			X		X
Often prepare a meal "from scratch"		✓			
Often eat hot or cooked meals		✓			
Spend a lot of time preparing a main meal					
Heathy eating perceptions					
Believe I am in control of my health					
Can stay healthy by taking care of myself		✓	✓		
Efforts to improve health are a waste of time					
Bored by attention paid to health and disease					
There's no use of being concerned about health					
Frequently eating healthily	✓				
Eat healthily without thinking about it					X
Feel weird if don't eat healthily	✓				
Self-efficacy for sticking to healthful foods					
Even if I need time to develop the routines	✓				
Even if I have to try several times until it works	✓				
Even if I have to rethink my way of nutrition	✓				
Even if I do not receive support from others					
Even if I have to make a detailed plan					
Motivation for participating in the study					
Interested in personalised nutrition					
Want to know what foods are best for him/her	✓				
Want to lose weight					X
Want to improve my family's health					
Want to improve my health	✓				
Want to improve my wellbeing					
Want to improve my sports performance					
Want to prevent a future illness					
Have a family history of diet-related illness					
Think it is important to help academic studies				✓	

Curious to find out what happens in PN studies

1, Columns for Weight loss/ WC reduction (n=231) and Cholesterol (n=36) were removed due to a lack of significant result

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	4-5
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	6
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	8
	4b	Settings and locations where the data were collected	7-8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8-10
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	11-12
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	NA
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA

Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	NA
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	NA
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11-12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	11-12
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7-8
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	23-24
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	12

Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	25-27
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	14
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	16-17
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	17
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	14-16
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	3
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	18

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.