Effect of personalized nutrition on health-related behaviour change: evidence from the Food4me European randomized controlled trial

Article

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EFFECT OF PERSONALIZED NUTRITION ON HEALTH-RELATED BEHAVIOUR CHANGE

EVIDENCE FROM THE FOOD4ME EUROPEAN RANDOMIZED CONTROLLED TRIAL

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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 7 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 (5 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 BMI was 25·5 $kg.m^{-2}$. From the enrolled participants, 1269 completed the study. Following a six-month intervention, participants randomized to PN consumed less red meat (-5.48g, [95%CI:-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 behavior than a conventional approach.

TRIAL REGISTRATION - NCT01530139 (http://clinicaltrials.gov/show/NCT01530139)

KEY WORDS – Personalized nutrition, internet-based, randomized controlled trial, genotype, phenotype, obesity, diet, metabolic health.

KEY MESSAGES

1. This study demonstrates clearly the value of personalisation in improving key lifestyle factors relevant to a wide range of health outcomes.

2. Personalised interventions can be delivered successfully to individuals across several countries using the internet.

3. 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.(1, 2) 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.(3) 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'.(4) However, the global burden of NCD continues to rise, underlining the need for more effective prevention.(5) 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.(6, 7) However, the effectiveness of genetic-based information in facilitating behavior 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 behavioral changes.(8)

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, analyze 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,(9) it is important that interventions reach all social groups. Use of the internet is rising rapidly in Europe.(5, 10)

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.(5, 10) 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 behavior than standard "one size fits all" population advice.

METHODS

Study design

The Food4Me 'Proof of Principle' study was a six-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.(11)

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; "Control group"): 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 six 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, United Kingdom, Poland and Germany) as described elsewhere.(11) We aimed to recruit a total of 1540 study participants aged ≥18 years.(11). Participants were randomized to the intervention groups (L0- L3), stratified by country, sex and age (<45 or ≥45 years) using an automated server designed for the study using an urn randomization scheme(12).

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: 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 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. Prior to participation, potential volunteers completed an informed consent form online before submitting personal data (Supplementary Methods).

Personalized feedback report

Participants randomized to L1, L2 and L3 received personalized feedback. Personalised 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 dieticians 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 to the local language. At baseline, three months and six months, dietary intakes were assessed using a validated online Food Frequency Questionnaire (FFQ) (13, 14) 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.(11, 13, 14) 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 the Supplementary Methods (Figure S1 and S3), and elsewhere.(11)

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.(11) Time points for each measurement are summarized in Table S1.

Participants provided socio-demographic, health and anthropometric data online at screening, and detailed information on dietary intake and food preferences.(11) 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(13, 14), and evaluated using the updated (2010) Healthy Eating Index (HEI).(15) Physical activity (PA) patterns were determined using a PA monitor (TracmorD) and self-reported Baecke PA questionnaire.(16) 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_2 and 25-OH D_3). 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 (11) and in Supplementary Methods.

Statistical analysis

Data were analyzed 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. Firstly, 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. Secondly, 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 sub-set 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.(17) The first 1607 volunteers meeting the inclusion criteria were recruited to the RCT and randomized to one of the four intervention arms (Figure 1).(11) Baseline characteristics of the participants by intervention arm are shown in Table 1 and in supplementary material (Table S3 and Table S4). 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% 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.(11) After six months, 21% of participants randomized to the intervention were lost to follow-up with 8% dropping out immediately after randomization (Figure 1).

(Table 1 here)

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 six-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). Similar results were found at month 3 (Table S5). Changes in dietary outcomes did not differ between Levels 1, 2 and 3 of PN (Tables 2, Table S5, and Table S6). No evidence of differences was

observed for other food groups (Table 2, Table S5 and Table S6). Similar results were found when dietary mis-reporters were excluded (data not shown).

(Table 2 here)

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 (Table 3). Outcomes were analyzed for those who received PN targeting these nutrients compared with the sub-set 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 six 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 three, there were improvements for salt, saturated fat, blood carotenoids, body weight and BMI by participants receiving PN (Table S7). Changes in these outcomes at both three and six months were similar for all three types of PN advice (comparisons between Levels 1 – 3 are presented in Tables S7 and Table S8). Similar results were found when dietary mis-reporters were excluded (data not shown).

(Table 3 here)

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.(5, 18) Internet-based personalized interventions were more effective in reducing body weight (-1.00 kg, $P<0.001$)(18) and in increasing fruit and vegetable consumption (0.35 servings.day^{-1}, $P < 0.001$)(5), 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.(7, 19) Despite suggestions that genotype-based interventions would have greater efficacy, few studies have tested this hypothesis.(20, 21) 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 behavior are not supported by the evidence'.(8) Disclosing the outcomes of genomic testing in 2240 participants was not associated with changes in behavioral outcomes (fat intake or exercise) after 3 or 12 months.(22) 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 $mg.day^{-1}$ vs. -129 $mg.day^{-1}$) among participants who carried the risk version of the *ACE* gene compared with the control group.(23) No effects of personalized genotype-based dietary advice were found for 3 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(24)) to weight control advice enhanced readiness to control weight but had no effect on actual behaviour change.(25) Moreover, an intervention conducted in 107 participants using information on *APOE* genotype as a tool for promoting lifestyle changes, found that provision of personalised genetic information, based on *APOE* genotype, may improve dietary fat quality in the short-term. (21)

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(26) and web-based(22) or face-to-face(25) genetic-based interventions. A recent study of direct-to-consumer genomic testing by Bloss et al. reported 44% and 63% dropouts at months 3 and 12, respectively.(22, 27) Moreover, the profile of those interested in participating in the Food4Me intervention study was similar to that of European adults,(11, 17) 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 "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 "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).(28) 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.(5)

CONCLUSION

After six 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.

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AUTHOR CONTRIBUTION

Dr Celis-Morales, Dr Livingstone and Professor Mathers 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.

Study concept and design: JC Mathers, Mike Gibney, H Daniel, JA Martinez, JA Lovegrove, ER Gibney, L Brennan, WHM Saris, Y Manios and CA Drevon.

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Management of the trial: MC Walsh, JC Mathers and M Gibney,

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CONFLICT OF INTEREST DISCLOSURES

K Grimaldi, reports personal fees from Eurogenetica Limited, outside the submitted work; CA Drevon, 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; WHM Saris, 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 advisor for the International Life Science Institute, ILSI Europe; JNS Matthews, reports grants from European Union, during the conduct of the study; M Gibney reports that he is a non-remunerated member of the Google Food Innovation Lab Community of Practice on Personalized Nutrition; JC Mathers 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

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Figure 1. CONSORT diagram for the Food4Me Study.

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 Health Eating Index was calculated as described by Guenther et al.(15).