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Frequent Nutritional Feedback, Personalized Advice, and Behavioral Changes: Findings From the European Food4Me Internet-Based RCT

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Introduction: This study tested the hypothesis that providing personalized nutritional advice and feedback more frequently would promote larger, more appropriate, and sustained changes in dietary behavior as well as greater reduction in adiposity.

Study design: A 6-month RCT (Food4Me) was conducted in seven European countries between 2012 and 2013.

Setting/participants: A total of 1,125 participants were randomized to Lower- (*n*=562) or Higher- (*n*=563) Frequency Feedback groups. Participants in the Lower-Frequency group received personalized nutritional advice at baseline and at Months 3 and 6 of the intervention, whereas the Higher-Frequency group received personalized nutritional advice at baseline and at Months 1, 2, 3 and 6.

Main outcome measures: The primary outcomes were change in dietary intake (at food and nutrient levels) and obesity-related traits (body weight, BMI, and waist circumference). Participants completed an online food frequency questionnaire to estimate usual dietary intake at baseline and at Months 3 and 6 of the intervention. Overall diet quality was evaluated using the 2010 Healthy Eating Index. Obesity-related traits were self-measured and reported by participant via the Internet. Statistical analyses were performed during the first quarter of 2018.

Results: At 3 months, participants in the Lower- and Higher-Frequency Feedback groups showed improvements in Healthy Eating Index score; this improvement was larger in the Higher-Frequency group than the Lower-Frequency group (Δ=1.84, 95% CI=0.79, 2.89, *p*=0.0001). Similarly, there were greater improvements for the Higher- versus Lower-Frequency group for body weight (Δ= –0.73 kg, 95% CI= –1.07, –0.38, *p*<0.0001), BMI (Δ= –0.24 kg, 95% CI= –0.36, –0.13, *p*<0.0001), and waist circumference (Δ= –1.20 cm, 95% CI= –2.36, –0.04, *p*=0.039). However, only body weight and BMI remained significant at 6 months.

Conclusions: At 3 months, higher-frequency feedback produced larger improvements in overall diet quality as well as in body weight and waist circumference compared with lower-frequency feedback. However, only body weight and BMI remained significant at 6 months.

Trial registration: Clinicaltrials.gov, NCT01530139.

INTRODUCTION

Poor diet and lack of physical activity are major risk factors for non-communicable diseases, including type 2 diabetes, cardiovascular diseases, and many cancers.[1,2] Up to 80% of these diseases could be prevented by eliminating shared risk factors, including unhealthy diet, physical inactivity, and excess alcohol consumption.[3] This emphasizes the importance of changing lifestyle to improve public health.

Most population strategies to reduce non-communicable disease burden have used "one-size-fits-all" public health recommendations such as "eat at least five portions of fruit and vegetables daily."[4] However, the prevalence of obesity and the global burden of non-communicable diseases continue to rise, underlining the need for more effective intervention strategies.[5] Personalized dietary interventions, designed according to key characteristics of the individual participants,[5,6] have been shown to be effective in improving lifestyle-related behaviors.[7–10] Recent evidence from the Food4Me study, a European RCT, suggests that the Internet is a feasible and acceptable platform for delivering effective and large-scale lifestyle-based interventions.[7] However, the intervention designs that are associated with larger and more sustainable behavioral changes are unknown. As providing feedback is a behavior change technique associated with increased efficacy of dietary interventions,[11] within the Food4Me Study, the authors investigated whether higher-frequency feedback led to larger and more appropriate changes in health-related behaviors (diet and adiposity) than lower-frequency feedback and whether any advantage was sustained in the medium term.

METHODS

Study Population

The Food4Me "Proof of Principle" study was a 6-month RCT, conducted across seven European countries to compare the effects of three levels of personalized nutrition (PN) advice with standard population dietary recommendations (Control group) on health-related outcomes. Participants were randomized to one of four intervention arms (Level 0 [L0]: Control group; L1, L2, and L3: PN groups). Full details of the study protocol have been summarized in the Appendix and elsewhere.[12] The current study aimed to determine whether the provision of more frequent feedback and advice was more efficacious in assisting and motivating study participants to make, and to sustain, appropriate health-promoting behavior changes, than less frequent feedback. To answer this question, those participants randomized to L1, L2, and L3 only were further randomized into Lower- and Higher-Frequency Feedback groups (more details on the personalized feedback provided for L1, L2, and L3 participants are provided in the Appendix). For that reason, participants randomized to the L0 Control group were not included in this analysis. The following feedback was provided to Lower- and Higher-Frequency Feedback groups:

1. Lower-Frequency Feedback: personalized dietary advice based on individual dietary intake (at food and nutrient levels), phenotypic data, genotypic data, or all of these. Personalized feedback and advice was delivered at baseline, 3 months, and 6 months.
2. Higher-Frequency Feedback: personalized dietary advice based on individual dietary intake (at food and nutrient levels), phenotypic data, genotypic data or all of these. Personalized feedback and advice was delivered at baseline and at 1, 2, 3, and 6 months.

The primary outcomes were change in dietary intake of food items or target nutrients and obesity-related traits (body weight, BMI, and waist circumference [WC]) between Higher- and Lower-Frequency Feedback groups, at Months 3 and 6.

Participants were recruited in seven European countries (Ireland, The Netherlands, Spain, Greece, United Kingdom, Poland, and Germany). Participants were screened online between August 2012 and August 2013 as described elsewhere.[12] The authors aimed to recruit a total of 1,540 study participants aged ≥18 years.[12] Participants were randomized using an automated server designed for the study according to an urn randomization scheme stratified by country, sex, and age (<45 or ≥45 years).[13]

Participants aged ≥18 years were included in the study with no restrictions on BMI levels. The following minimal sets of exclusion criteria were applied: (1) pregnant or lactating; (2) no or limited access to the Internet; (3) following a prescribed diet for any reason, including weight loss, in the last 3 months; and (4) diabetes, celiac disease, Crohn disease, or any metabolic disease or condition altering nutritional requirements, food allergies, or intolerances.

The Research Ethics Committees at each University or Research Center delivering the intervention granted approval for the study. Prior to participation, potential volunteers completed an informed consent form online before submitting personal data.

Participants randomized to PN groups (L1, L2, and L3) received personalized feedback and advice that was derived manually using decision trees, developed specifically for the Food4Me study (Appendix Tables 1 and 2).[14] For individuals randomized to the Lower-Frequency Feedback group, dietary intake (at food and nutrient levels), physical activity and anthropometric measures were assessed and feedback provided within 1 week at baseline, Month 3 and Month 6 only, whereas measurements in those randomized to the Higher-

Frequency Feedback group were performed and feedback provided within 1 week additionally at Months 1 and 2 (Appendix 1). For body weight, BMI, and WC participants were provided PN advice to reduce these phenotypic markers for both groups if their BMI was ≥25.0 $kg \cdot m^{-2}$ or WC was >88 cm and >102 cm for women and men, respectively. Dietary intakes were assessed using a validated online Food Frequency Questionnaire[14–17] and intakes of food groups and nutrients categorized as too high or too low were identified and ranked (Appendix Figure 1). Contributing foods were identified and specific messages were developed, according to standardized algorithms, to advise change in intake of those foods and targeted nutrients.[12,14–17] To maximize potential for translation into improved dietary behavior, this advice was operationalized as three individual food-based dietary goals. For participants randomized to L2 and L3, the feedback also included, and referred to, phenotypic measures (including blood glucose, cholesterol, carotenoids, fatty acids, and obesity-related markers; [L2]) and phenotypic plus genotypic data (L3). Details of these feedback reports are described in the Appendix Table 2, Appendix Figures 1 and 2, and elsewhere.[12]

Measures

Participants consented to self-report their measures via the Internet and to send biological samples (buccal swabs for DNA extraction and dried blood spots) by post (detail are provided in Appendix 1). A summary of all measurements made at each time point is provided in Appendix Table 1.

Participants provided sociodemographic (age, sex, and ethnicity), smoking behavior, medically diagnosed diseases, and anthropometric data online at screening, and detailed information on dietary intake and food preferences.[12] Occupations were grouped according to

the European classifications (professional and managerial, intermediate, routine and manual, service and sales workers, elementary occupations, students and retired).[18]

Body weight, height, and WC were self-measured and self-reported by participants via the Internet. Participants were instructed to measure body weight after an overnight fast, without shoes and wearing light clothing using a home or commercial scale, and to measure height, barefoot, using a standardized measuring tape provided by the researchers. WC was measured at the midpoint between the lower rib and the iliac crest using the provided tape.[19] Central obesity was defined as WC >88 cm for women and >102 cm for men. BMI ($kg \cdot m^{-2}$) was calculated from body weight and height. Adiposity status was defined using WHO criteria for BMI (underweight, <18.5 $kg \cdot m^{-2}$; normal weight, ≥18.5 $kg \cdot m^{-2}$ to ≤24.9 $kg \cdot m^{-2}$; overweight, ≥25.0 $kg \cdot m^{-2}$ to ≤29.9 $kg \cdot m^{-2}$; obese, ≥30.0 $kg \cdot m^{-2}$). At least 5% and 10% body weight reduction at Months 3 and 6 was used as a clinically meaningful degree of weight loss, as reported previously.[9,20] Self-reported measurements were validated in a subsample of the participants (n=140) across seven European countries and showed a high degree of reliability (Appendix 1).[19]

Participants completed an online Food Frequency Questionnaire to estimate usual dietary intake at baseline and at Months 3 and 6 of the intervention. This Food Frequency Questionnaire, which was developed and validated for the Food4Me Study,[21,22] included 157 food items consumed frequently in each of the seven recruitment countries.[21] Overall diet quality was evaluated using the 2010-Healthy Eating Index (HEI-2010).[23] Further details on dietary intake measures are provided in Appendix 1.

Physical activity levels (i.e., total energy expenditure/calculated basal metabolic rate) and time spent in sedentary behaviors (minutes/day) were measured objectively using triaxial accelerometers (TracmorD, Philips Consumer Lifestyle, The Netherlands). Physically active individuals were defined as those achieving ≥150 minutes of moderate-equivalent physical activity per week.[24] Further details on physical activity measures are described in detail in Appendix 1.

Statistical Analysis

To answer the research question of whether higher frequency of feedback is more effective in assisting and motivating study participants to make, and to sustain, appropriate health-promoting changes than lower frequency of feedback, intervention effects on overall diet quality and targeted personalized nutrients were assessed. Participants randomized to L1–3 only were included in this analysis because only they were randomized by feedback frequency.

Twenty multiple imputations were performed following current guidelines for epidemiologic and clinical research[25] by fully conditional specification methods,[26] which are powerful and statistically valid methods for creating imputations in large data sets that include both categorical and continuous variables. It specifies the multivariate imputation model on a variable-by-variable basis and offers a principled yet flexible method of addressing missing data, which is particularly useful for large data sets with complex data structures (level of missing data is summarized in Appendix Table 4).

Results from descriptive analyses are presented as means and SDs or 95% CIs for continuous variables or as percentages for categorical variables. To answer the primary research

question, the authors used a linear mixed model with fixed effects and random intercept for participants with time point fitted into the model as a linear term (baseline, Month 3, and Month 6), baseline age, sex, occupation, country, and intervention arm as covariates (models for body weight, BMI, and WC were additionally adjusted for total physical activity levels). Contrast analyses were used to determine changes in outcomes (diet quality, target nutrients, body weight, BMI, and WC) from baseline to Month 3 and from baseline to Month 6 by feedback frequency group (Lower and Higher). These results were reported as Δ [Month 3 – Month 0] and 95% CIs. Similar estimations were performed for change at Month 6. The differences between Δ for Lower- and Higher-Frequency Feedback groups at Month 3 and at Month 6 were tested using a linear mixed model and reported as Δ [Higher – Lower] and 95% CIs. The effect size for the Δ between Feedback groups at Months 3 and 6 were estimated as the ratio of the observed Δ to the baseline SD of each measure. This gives a value similar to a Cohen's d; therefore, effects sizes <0.2 would be considered small. These analyses were performed under two main scenarios. Scenario 1 included all participants randomized to the Lower- or Higher-Frequency Feedback groups with the overall HEI score as the outcome measure. Scenario 2 was conducted using a restricted sample, which included only those participants who were advised to reduce, or increase, the intake of specific nutrients (salt, saturated fat, dietary fiber, folate, polyunsaturated fat, and total energy intake) or received advice to change obesity-related traits (body weight, BMI, and WC).

Binomial regression with a log link to directly estimate risk ratios (RRs) were performed to investigate whether participants allocated to the Higher-Frequency Feedback group were more likely to achieve ≥5% and ≥10% weight loss in comparison with those in the Lower-Frequency group and findings are reported as RRs and 95% CIs. Similarly, to investigate differences in drop out from the study at Months 3 and 6 between frequency groups, binomial

regression analyses were performed and RRs were estimated (Lower-Frequency Feedback group was used as the ref) (Appendix Table 5).

All statistical analyses were performed using Stata, version 14 during the first quarter of 2019, and significance was set at $p<0.05$.

RESULTS

A total of 5,562 participants were screened online between August 2012 and August 2013; the characteristics of these individuals have been reported elsewhere.[27] The first 1,607 volunteers meeting the inclusion criteria were recruited to the RCT (Figure 1); however, for the purpose of this study, only those randomized to Lower-Frequency (n=562) and Higher-Frequency (n=558) Feedback groups were included in this analysis. Of these, 498 and 460 participants completed the study for the Lower- and Higher-Frequency groups, respectively (i.e., 85.2% of all participants) (Figure 1). However, the analysis revealed that, compared with the Lower-Frequency group, individuals in the Higher-Frequency group were more likely to have dropped out of the study by Months 3 and 6 (RRs=1.78, 95% CI=1.1.21, 2.62, p=0.003 and RRs=1.58, 95% CI=1.16, 2.16, p=0.004, respectively) independent of age, intervention arm, sex, country, occupation, and BMI (Appendix Table 6). Baseline characteristics of the participants by feedback frequency are shown in Appendix Table 5. No major differences in dietary intakes at baseline were observed between frequency groups (Table 1 and Appendix Table 7).

Participants in the Food4Me study who were randomized to PN improved their overall diet quality over the 3-month intervention period (Table 1 and Figure 1). However, the improvement was significantly greater in the Higher-Frequency group compared with the

Lower-Frequency group (Δ=1.84 points, 95% CI=0.79, 2.89, *p*=0.0001). The analysis by HEI subcomponent showed that, at Month 3, both groups achieved improvements in all HEI subcomponents except for dairy, seafood, and plant proteins and empty calories for both Frequency groups (Appendix Table 7). However, compared with the Lower-Frequency group, participants in the Higher-Frequency group achieved significantly larger health-promoting changes in fatty acid ratio (Δ=0.07, 95% CI=0.03, 0.11, *p*=0.001), refined grains (Δ= –6.96, 95% CI= –13.6, –0.29, *p*=0.041), and salt intake (Δ= –0.08, 95% CI= –0.14, –0.01, *p*=0.019) (Appendix Table 7). There were no differences between frequency groups for fruit, vegetables, greens and beans, whole grains, dairy, total protein, refined grains, and empty calories (Appendix Table 7).

At Month 6, there were improvements in the overall HEI score and for HEI subcomponents, except for dairy, seafood, and plant proteins and empty calories, in both Lower- and Higher-Frequency groups compared with baseline. However, the magnitudes of these changes between Frequency groups were no longer significant (Appendix Table 7).

To determine effects on feedback frequency on specific nutrients targeted by the PN intervention, the authors assessed changes in the five most common targets for personalized advice (salt, saturated fat, dietary fiber, folate, and polyunsaturated fats). In addition, changes in total energy intake, body weight, BMI, and WC were assessed for those participants who were advised to reduce these variables.

At Month 3, there were improvements from baseline for all target outcomes in both the Lower- and Higher-Frequency groups, except folate, which was not improved at 3 months in the Lower-Frequency Feedback group (Table 1). The magnitude of these changes was

significantly greater for participants in the Higher-Frequency group compared with the Lower-Frequency group for salt and saturated fat intake as well as body weight, BMI, and WC (Table 1). At Month 6, all target outcomes showed improvements compared with baseline for both Lower- and Higher-Frequency groups except for dietary fiber in the High Feedback group. Differences between Frequency groups were no longer significant except for body weight and BMI (Table 1 and Figure 2).

Figure 3 shows the percentage of participants who achieved at least 5% or 10% weight loss at Months 3 and 6 by frequency group. Individuals randomized to the Higher-Frequency group were more likely to achieve ≥5% and ≥10% reduction in body weight compared with the Lower-frequency group at Month 3 (RRs=1.72, 95% CI=1.24, 2.37, p=0.001 and RRs=1.81, 95% CI=1.29, 2.54, p=0.001, respectively). At Month 6, although participants in the Higher-Frequency group were more likely to achieve a ≥5% weight loss compared to the Lower-Frequency group (RRs=1.54, 95% CI=1.12, 2.10, p=0.008), no differences were found for participants achieving a 10% weight loss between intensity groups (RRs=1.14, 95% CI=0.54, 2.35, p=0.703).

DISCUSSION

The main finding of this study is that using either lower- or higher-frequency feedback in an Internet-based PN intervention is efficacious in improving health-related behaviors, including overall diet quality. In the short term (at 3-month follow-up), higher-frequency feedback produced significant benefits in overall diet quality, although the effect sizes were relatively small. These included reducing salt and saturated fat intake as well as reducing body weight, BMI, and WC in individuals who were overweight or obese at baseline. The public health implications of these findings are important because 10.8% and 14.9% of men and women

are obese worldwide.[28] Thus, implementing higher-frequency feedback interventions (feedback provided once a month) could lead to significant improvement in diet and greater weight reductions than using lower-frequency feedback (feedback provided once every 3 months). However, in this study, most of these advantages in the Higher-Frequency Feedback group were not sustained at 6 months. The exception was in the percentage of participants achieving ≥5% weight loss, where the RR of achieving weight loss was significantly greater for the Higher-Frequency Feedback group at 6 months as well as at 3 months (Figure 1). Achieving ≥5% weight loss is often used as a cut off for clinically significant weight loss, although smaller weight losses are also associated with improvements in markers of cardiovascular disease risk.[9,20,29] Similarly, improving the diet quality has important implication for health. For example, reduced salt intake is associated with lower risk of developing hypertension, a major risk factor for cardiovascular diseases,[30] and improving the overall quality of the diet is associated with reduced all-cause and cause-specific mortality.[31,32]

The definition of feedback frequency for lifestyle interventions reported in the literature varies considerably,[10,33,34] incorporating frequency and total number of contacts, total contact time, and duration of the intervention. A recent meta-analysis of 12 randomized controlled weight loss interventions delivered via mobile phones reported that duration and interaction frequency improved efficacy of weight loss interventions.[10] Although this meta-analysis confirms that more feedback may lead to larger behavioral changes, the nature of the intervention (delivered via mobile phones) and the frequency of contact (once or more per day) differed from the current protocol. O'Brien et al.[35] reported outcomes from a trial in which overweight/obese Australian adults were randomized to a standard online weight loss program or to an enhanced version of this program that provided additional personalized

feedback and reminders. The intervention targeted self-efficacy, goal setting, and self-monitoring of weight, dietary intake, and physical activity levels. Participants who were randomized to the enhanced group (personalized feedback and weekly contact) had larger weight reductions compared with those who were randomized to the basic intervention group (weekly contact) after 12 weeks. By contrast, change in diet quality, measured using an Australian diet quality score, was not significantly different between the enhanced and basic interventions.[35] In this case, the nature of the additional contacts differed between treatment groups so it is uncertain whether more feedback/contacts per se would be equally effective. Similarly, a meta-analysis of face-to-face trials reported that "higher-intensity" interventions (i.e., those with more frequent face-to-face contacts) were associated with larger changes in dietary intake and that this difference was significant for total dietary fat intake and for daily servings of fruits and vegetables.[36] The present findings corroborate the larger difference in total fat intake, but a significant difference between frequency groups for fruit and vegetable intake was not observed.

Importantly, the current results show that participants randomized to the Higher-Frequency Feedback group resulted in slightly, but significantly, fewer participants completing the 3-month study, 92.2% compared with 98.5% for those randomized to the Lower-Frequency group (Appendix Table 6). However, between Month 3 and Month 6 when both Higher- and Lower-Frequency groups had the same number of feedbacks, the number of dropouts was the same (n=20) for both groups. Compared with the Lower Feedback group, the participants randomized to the Higher-Frequency group were more likely to have dropped out of the study by Months 3 and 6 (RRs=1.78 vs 1.58).

Although the two groups compared in this analysis differed in frequency of feedback (five times versus three times), all of the additional feedback occurred within the first 3 months of the study so that there was no difference in feedback frequency between the groups for the second half of the study (i.e., from 3 months to 6 months). Although there was good evidence that the Higher-Frequency Feedback group performed better at 3 months, almost all of those advantages had disappeared by 6 months. This suggests that the benefits of higher-frequency feedback do not endure when the extra feedback events are stopped; therefore, from a longer-term perspective, there may be no advantage in devoting resources to provide additional feedback beyond that offered to those in the Lower-Frequency Feedback group. In addition, randomization to the Higher-Frequency Feedback group resulted in slightly fewer participants completing the 6-month study. Although the impact of the intervention on the diet of those dropouts is not known, it would be reasonable to assume that they will not have benefitted as much in terms of dietary change as those who remained in the study. Therefore, these findings question the overall benefit for public health in those randomized to the Higher-Frequency Feedback group.

The Food4Me study is the largest Internet-based PN intervention study to date and provides robust evidence for the beneficial impact of personalized lower- and higher-frequency feedback on dietary intake and obesity-related outcomes. An Internet-based platform to deliver the intervention was effective in retaining participants: 85.2% completed the follow-up after 6 months of intervention, which is high compared with a previous web-based survey.[37]

Limitations

Compared with conventional face-to-face interventions, the Internet-based design of the present study limited the number of collected measures. Furthermore, all data collected during the study were self-reported or derived from biological samples collected remotely. Thus, there is the potential for non-differential information bias.[19]

CONCLUSIONS

Both lower- and higher-frequency feedback interventions were efficacious in promoting health-related behavior changes. Higher-frequency interventions produced significant (but relatively small) improvements in overall diet quality and weight loss than lower-frequency interventions at the 3-month follow-up. However, most of these advantages were not sustained at the 6-month follow-up, except for body weight and BMI, when the frequency of delivery of PN advice and feedback over Months 3 to 6 was identical between the two groups. In addition, attrition was significantly higher in participants in the Higher-Frequency group in the first 3 months. These results suggest that higher-frequency feedback may not be advantageous in improving public health using such Internet-delivered PN interventions.

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Month 6). Analyses were adjusted for age, sex, personalized nutrition intervention arm, country, occupation, total physical activity, and baseline body weight.

Table 1. Changes in Dietary Intake Anthropometric Characteristics at Month 3 and Month 6 Between Frequency Feedback Groups

Measure/month	Lower-Frequency Feedback group (95% CI)	Higher-Frequency Feedback group (95% CI)	Δ [Higher – Lower][c] value (95% CI)	Δ *p*-value	Effect size
HEI score					
M0 (mean)[a]	49.6 (48.8, 5,04)	48.6 (47.8, 49.4)	–1.11 (–2.26, 0.03)	0.058	
M3 (Δ [M3 – M0])[b]	**2.60 (1.94, 3.25)****	**4.44 (3.61, 5.27)****	1.84 (0.79, 2.89)	**0.0001**	0.19
M6 (Δ [M6 – M0))[b]	**3.38 (2.70, 4.07)****	**4.03 (3.20, 4.87)****	0.65 (–0.43, 1.71)	0.240	0.07
Salt (g·day^{-1})					
M0 (mean)[a]	7.43 (7.13, 7.73)	7.36 (7.07, 7.66)	–0.07 (–0.48, 0.35)	0.752	
M3 (Δ [M3 – M0])[b]	**–1.12 (–1.40, –0.84)****	**–1.59 (–1.89, –1.29)****	–0.47 (–0.87, –0.05)	**0.026**	0.17
M6 (Δ [M6 – M0))[b]	**–1.29 (–1.56, –1.02)****	**–1.29 (–1.56, –1.01)****	0.003 (–0.38, 0.39)	0.984	0.01
Saturated fat (% TE)					
M0 (mean)[a]	14.1 (13.8, 14.4)	14.1 (13.9, 14.4)	–0.01 (–0.37, 0.35)	0.956	
M3 (Δ [M3 – M0])[b]	**–0.84 (–1.08, –0.61)****	**–1.25 (–1.51, –0.98)****	–0.40 (–0.75, –0.048)	**0.026**	0.14
M6 (Δ [M6 – M0))[b]	**–1.12 (–1.37, –0.87)****	**–1.18 (–1.45, –0.91)****	–0.06 (–0.42, 0.31)	0.760	0.02
Dietary fiber (g·day^{-1})					
M0 (mean)[a]	30.1 (28.9, 30.5)	29.1 (27.9, 30.4)	–0.96 (–2.62, 0.71)	0.261	
M3 (Δ [M3 – M0])[b]	**–1.34 (–2.39, –0.29)***	**–1.92 (–3.12, –0.72)****	–0.59 (–2.17, 0.98)	0.460	0.04
M6 (Δ [M6 – M0])[b]	**–1.19 (–2.24, –0.13)***	–0.90 (–2.07, 0.27)	0.29 (–1.30, 1.83)	0.739	0.02
Folate (µg·day^{-1})					
M0 (mean)[a]	429.6 (412.8, 446.4)	405.7 (388.9, 422.6)	–23.8 (–47.6, –0.08)	0.049	
M3 (Δ [M3 – M0])[b]	–25.9 (–52.2, 0.25)	**–38.5 (–64.7, –12.3)****	–12.9 (–50.1, 24.1)	0.493	0.05
M6 (Δ [M6 – M0])[b]	**–47.7 (–64.5, –31.0)****	**–44.3 (–60.9, –27.7)****	3.11 (–20.4, 26.7)	0.796	0.02
Polyunsaturated fat (% TE)					
M0 (mean)[a]	5.67 (5.55, 5.78)	5.78 (5.66, 5.90)	0.12 (–0.05, 0.28)	0.166	
M3 (Δ [M3 – M0])[b]	**0.17 (0.06, 0.28)****	**0.31 (0.18, 0.44)****	0.14 (–0.02, 0.31)	0.099	0.10
M6 (Δ [M6 – M0])[b]	**0.20 (0.07, 0.33)****	0.11 (–0.03, 0.21)	–0.11 (–0.29, 0.07)	0.243	0.08
Energy intake (Kj·day^{-1})					
M0 (mean)[a]	10,845 (10,481, 11,210)	10,693 (10,327, 11,059)	–152.7 (–669.3, 363.9)	0.563	
M3 (Δ [M3 – M0])[b]	**–1,366 (–1,699, –1,034)****	**–1,825 (–2,457, –1,193)****	–459.6 (–956.8, 37.5)	0.070	0.14

M6 (Δ [M6 – M0])[b]	**–1,549 (–1,894, –1,203)****	**–1,538 (–1,891, –1,193)****	11.2 (–479.7, 502.1)	0.964	0.003
Body weight (kg)					
M0 (mean)[a]	73.9 (72.7, 75.1)	75.5 (74.3, 76.7)	1.64 (–0.04, 3.28)	0.065	
M3 (Δ [M3 – M0])[b]	**–0.38 (–0.61, –0.14)****	**–1.11 (–1.37, –0.84)****	–0.73(–1.07, –0.38)	**<0.0001**	0.05
M6 (Δ [M6 – M0])[b]	**–0.64 (–0.93, –0.35)****	**–1.36 (–1.70, –1.02)****	–0.71 (–1.15, –0.27)	**0.002**	0.05
BMI ($kg \cdot m^{-2}$)					
M0 (mean)[a]	25.1 (24.8, 25.5)	25.7 (25.3, 26.1)	0.58 (–0.03, 1.17)	0.054	
M3 (Δ [M3 – M0])[b]	–0.13 (–0.21, –0.05)	–0.37 (–0.46, –0.28)	–0.24 (–0.36, –0.13)	**<0.00001**	0.05
M6 (Δ [M6 – M0])[b]	–0.22 (–0.3, –0.12)	–0.46 (–0.57, –0.34)	–0.23 (–0.38, –0.79)	**0.003**	0.05
WC (cm)					
M0 (mean)[a]	1.02.7 (101.3, 104.2)	102.1 (100.7, 103.4)	–0.69 (–2.68, 1.29)	0.494	
M3 (Δ [M3 – M0])[b]	**–1.25 (–2.30, –0.19)***	**–2.65 (–3.40, –1.89)****	–1.20 (–2.36, –0.04)	**0.039**	0.12
M6 (Δ [M6 – M0])[b]	**–2.43 (–3.38, –1.48)****	**–3.82 (–4.7, –2.93)****	–1.21 (–2.59, 0.16)	0.083	0.12

Notes: Boldface indicates statistical significance (*p<0.05; **p<0.01). Data are presented as adjusted mean or Δ with the corresponding 95% CI. Analysis is restricted to participants randomized to Levels 1–3 who received personalized advice targeting the specified dietary and anthropometric outcomes, except for HEI, which include all participants randomized to Levels 1–3. Analyses were adjusted for baseline age, sex, personalized nutrition intervention arm, occupation, and country. Body weight, BMI, and WC were additionally adjusted for total physical activity levels. The effect sizes for the Δs between Lower- and Higher-Frequency Feedback groups at Month 3 and Month 6 were estimated as the ratio of the observed Δ to the baseline SD of each measure. This gives a value like a Cohen's d; therefore, effects sizes <0.2 would be consider small. Significant differences between baseline and Month 3 or Month 6 were derived from the Linear Mixed Effect Models and post-hoc contrast analyses and denoted as *p<0.05 and **p<0.01.

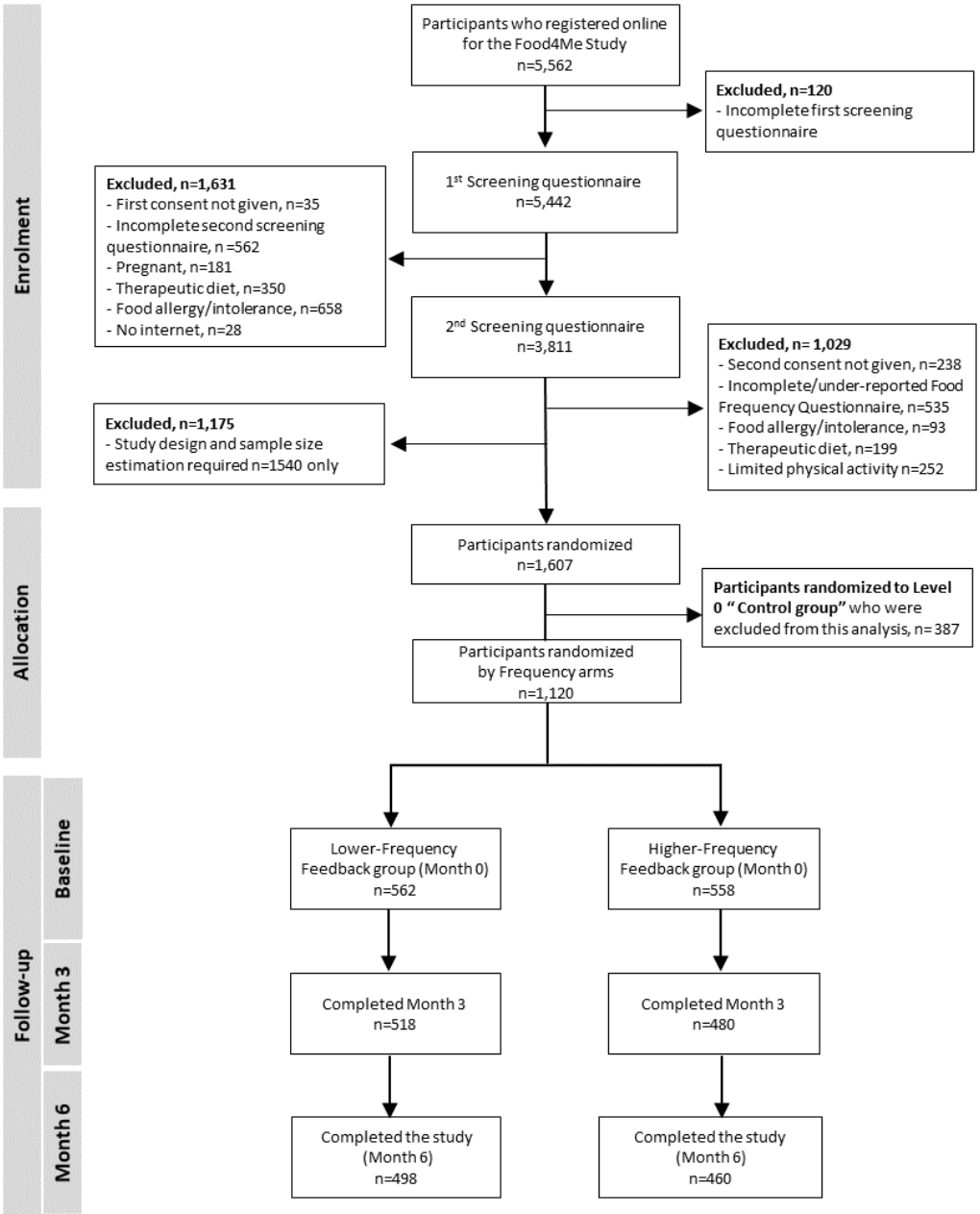
[a]Adjusted mean at baseline.

[b]Δ between Month 3 and baseline or Month 6 and baseline.

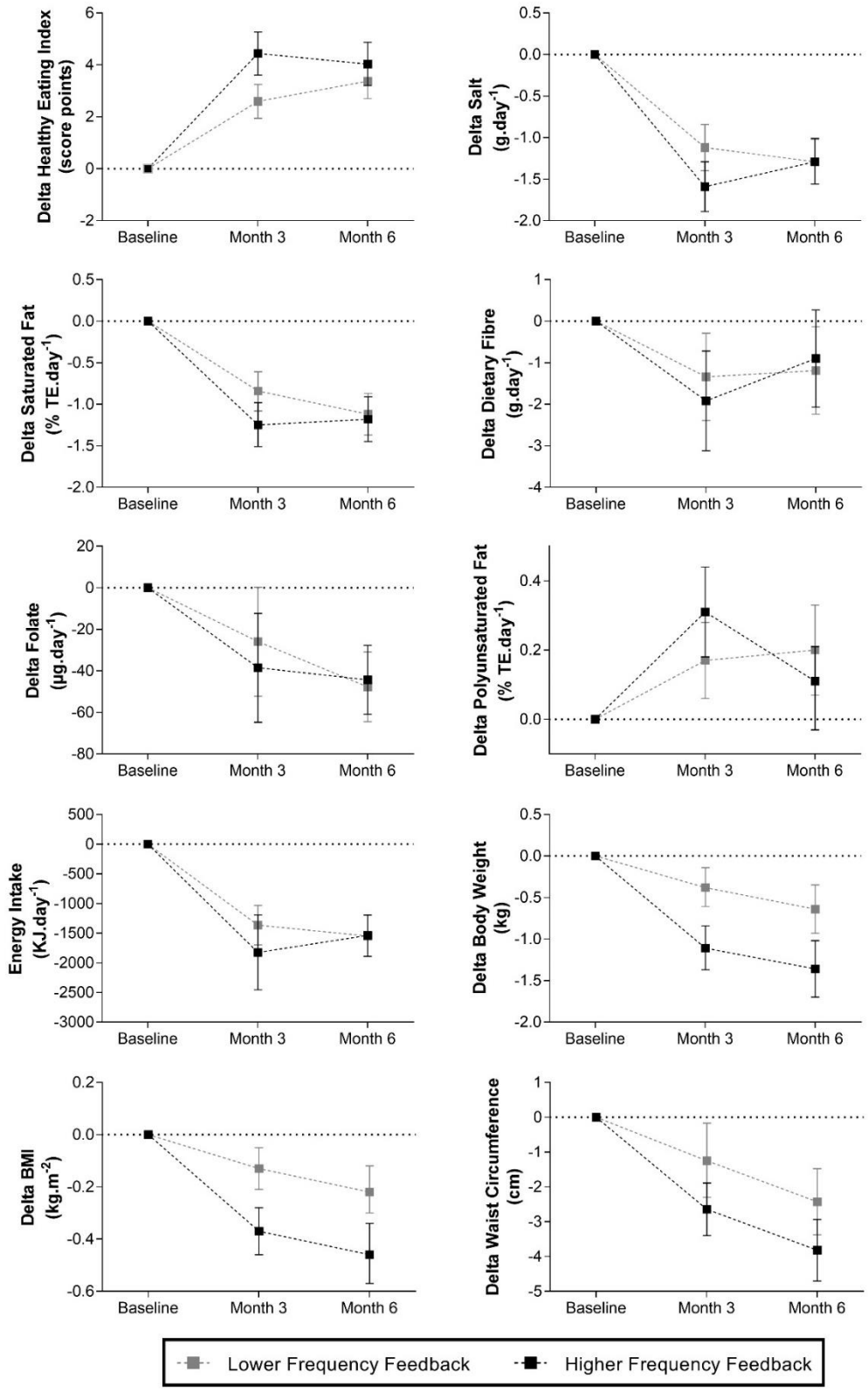
[c]Δ estimated from differences between Higher- and Lower-Frequency Feedback groups.

Kj, kilojoules; HEI, Healthy Eating Index score; M0, baseline; M3, Month 3; M6, Month 6; g, grams; TE, total energy; WC, waist circumference.

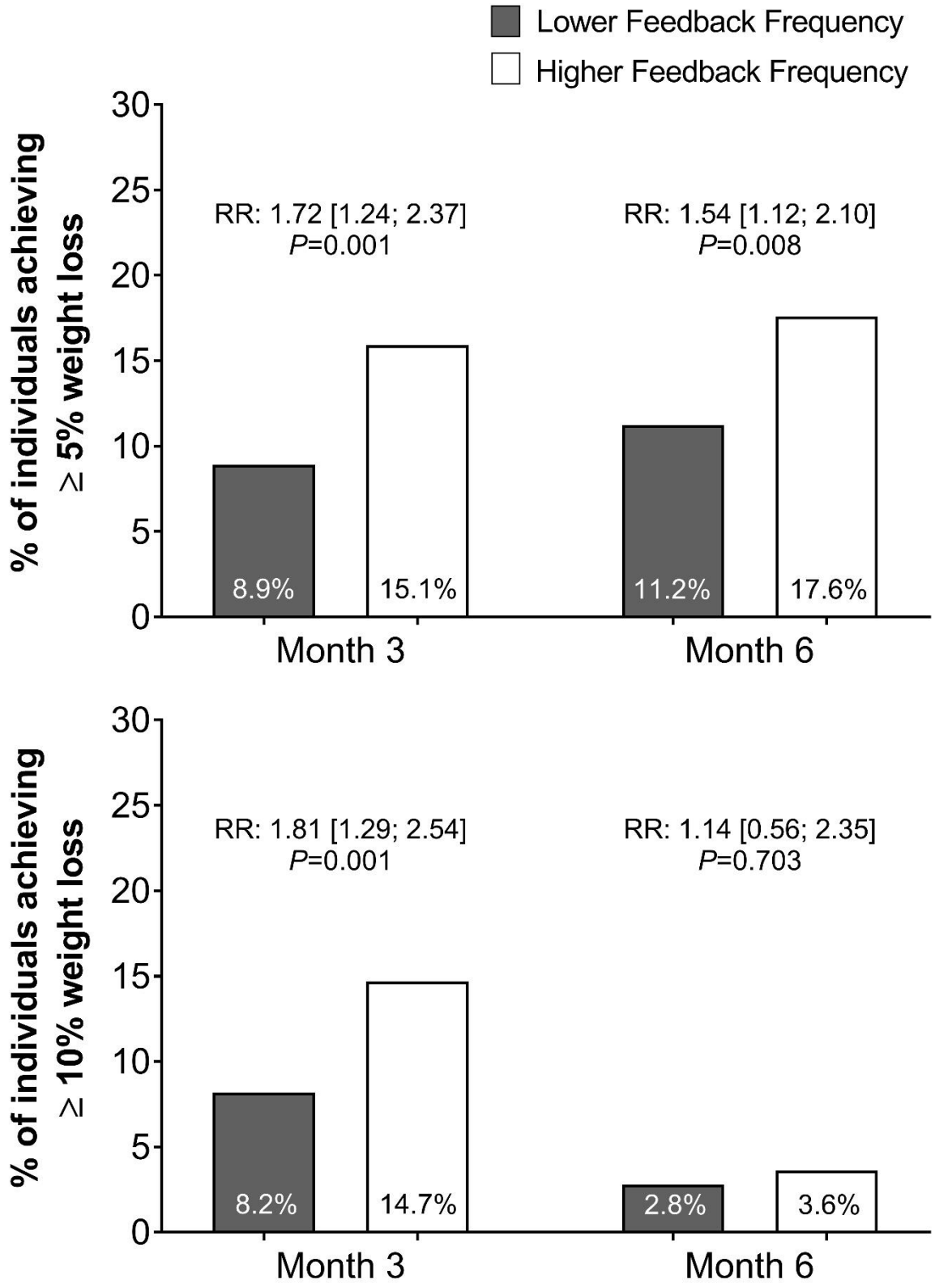
1


Enrolment
Allocation
Follow-up
Baseline
Month 3
Month 6
Participants who registered online for the Food4Me Study n=5,562
Excluded, n=120 - Incomplete first screening questionnaire
1st Screening questionnaire n=5,442
Excluded, n=1,631 - First consent not given, n=35 - Incomplete second screening questionnaire, n =562 - Pregnant, n=181 - Therapeutic diet, n=350 - Food allergy/intolerance, n=658 - No internet, n=28
2nd Screening questionnaire n=3,811
Excluded, n= 1,029 - 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=1,175 - Study design and sample size estimation required n=1540 only
Participants randomized n=1,607
Participants randomized to Level 0 "Control group" who were excluded from this analysis, n= 387
Participants randomized by Frequency arms n=1,120
Lower-Frequency Feedback group (Month 0) n=562
Higher-Frequency Feedback group (Month 0) n=558
Completed Month 3 n=518
Completed Month 3 n=480
Completed the study (Month 6) n=498
Completed the study (Month 6) n=460

2


Delta Healthy Eating Index (score points)
Delta Salt (g.day-1)
Delta Saturated Fat (% TE.day-1)
Delta Dietary Fibre (g.day-1)
Delta Folate (µg.day-1)
Delta Polyunsaturated Fat (% TE.day-1)
Energy Intake (KJ.day-1)
Delta Body Weight (kg)
Delta BMI (kg.m-2)
Delta Waist Circumference (cm)
Baseline
Month 3
Month 6
Lower Frequency Feedback
Higher Frequency Feedback

3


Lower Feedback Frequency
Higher Feedback Frequency
% of individuals achieving ≥ 5% weight loss
RR: 1.72 [1.24; 2.37]
P=0.001
RR: 1.54 [1.12; 2.10]
P=0.008
8.9%
15.1%
11.2%
17.6%
Month 3
Month 6
% of individuals achieving ≥ 10% weight loss
RR: 1.81 [1.29; 2.54]
P=0.001
RR: 1.14 [0.56; 2.35]
P=0.703
8.2%
14.7%
2.8%
3.6%
Month 3
Month 6

APPENDICES

APPENDIX 1. METHODS AND STUDY DESIGN

Ethics Approval and Participant Consent

Prior to participation, an information sheet was provided online 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 countersigned and archived. A second online informed consent form was completed before randomization to the intervention study only for those participants who met the inclusion criteria. A two-step consenting process was applied to permit collection of sociodemographic and dietary information for those interested in participating in personalized nutrition (PN) even if they were ineligible for enrolment, for example, because of prescribed diets or food allergies. All ethics 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 by mail to the respective recruitment center. The research ethics committees at each university or research center 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. (Details will be reported elsewhere.)[1].

A list of the ethics review boards is available at http://clinicaltrials.gov/show/NCT01530139).

Intervention Design of the Proof of Principle Study

Participants allocated to one of the four intervention arms of the study were asked to complete the data and sample collection summarized in Appendix Table 1. At the end of the study (Month 6), all participants received a personalized report including dietary, phenotypic, and genotypic information, which summarized changes in their individual dietary intake and phenotypic measures between baseline and Month 6 of the intervention.[1]

Data Collection

Participants consented to self-report their measures via the Internet and to send biological samples (buccal swabs for DNA extraction and dried blood spots) by post, using pre-paid, stamped and addressed envelopes. To ensure that procedures were similar in all recruiting centers, standardized operating procedures were prepared for all measurements, and researchers underwent centralized training. Moreover, to enable participants to collect and report the required information and to collect, process, and dispatch the biologic samples correctly, participants were given detailed instructions, and video demonstrations were available on the Food4Me website (www.food4me.org), in their own language.[2] A summary of all measurements made at each time point is provided in Appendix Table 1.

Appendix Table 1. Summary of Data and Biological Samples Collected During the Intervention

Data collection	Time point						
	First screening	**Second screening**	**Month 0 (baseline)**	**Month 1[b]**	**Month 2[b]**	**Month 3**	**Month 6**
Sociodemographics (name, age, sex)	x	x					
Eligibility criteria (pregnancy, therapeutic diet, food allergy or intolerance, internet access)	x	x					
First online consent	x						
Second sociodemographic data (age, sex, address, ethnicity)		x					
Health-related questionnaire (weight, height, medical health status, smoking, sun exposure)		x					
Food choice and eating habits		x					
Health perception		x					
Second online consent		x					
Online Food Frequency Questionnaire (FFQ)		x	x	x	x	x	x
Anthropometrics (weight; height; waist, hip and upper leg circumference)		x[a]	x	x	x	x	x
Buccal cells for genetic analysis			x				
Dried blood spot, metabolic analysis			x			x	x
Physical activity measurement			x	x	x	x	x
Validation study questionnaire							x
Consumer aptitude questionnaire							x

[a]Only weight and height were collected at second screening questionnaire.

[b]Data collected at Month 1 and Month 2 were only for the Higher Frequency Feedback Group.

First Screening Questionnaire

Participants consenting to take part in the study completed an online screening questionnaire that included basic sociodemographic and health statistics and information about Internet access, pregnancy and lactation, prescribed diets, food intolerance, and allergies (used as exclusion criteria).[1] Persons who were deemed unsuitable for the study, for example because of inadequate internet access, pregnancy, or use of a therapeutic diet, received a formal e-mail notification that they did not match the inclusion criteria and were thanked for their time.

Second Screening Questionnaire

Eligible participants for inclusion in the RCT completed a second online questionnaire and provided more detailed sociodemographic, health, and anthropometric data, as well as detailed information on food choices and dietary habits using a Food Frequency Questionnaire developed and validated specifically for this study.[3,4] Following assessment of this information, participants considered suitable for inclusion in the RCT 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 noncompliance in completion of the screening Food Frequency Questionnaire, received a formal notification that they did not match the inclusion criteria and were thanked for their time.

Comorbidities

Participants provided information on medically diagnosed diseases. Disease history included cancer, high blood pressure, heart disease, liver disease, kidney disease, arthritis, osteoporosis, ulcers, fibromyalgia, diabetes, lung disease, allergies, epilepsy, thyroid disease, anemia, blood disorders, alcohol abuse, drug addiction, and depression at the second screening questionnaire.

Anthropometry

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

Validation of Self-Reported Anthropometric Measures

In e-health intervention studies, there are concerns about the reliability of internet-based, self-reported data and about the potential for identity fraud. Therefore, we have conducted a validation study to validate anthropometric and demographic data via measurements performed face-to-face. Participants (n=140) from seven European countries, participating in the Food4Me intervention study were invited to take part in the validation study. Participants visited a research center in each country within 2 weeks of providing self-reported data via the Internet. Participants received detailed instructions on how to perform each measurement. The validation results show strong intra-class correlation coefficients between self-reported and validation study for anthropometric data (height 0.990, weight 0.994, and BMI 0.983). However, internet-based self-reported weight was underreported (Δ –0.70 kg [95% CI –3.6, 2.1], p<0.0001) and,

therefore, BMI was lower for self-reported data (Δ –0.29 $kg.m^{-2}$) [95% CI –1.5, 1.0], $p<0.0001$). BMI classification was correct in 93% of cases.[5]

Food Frequency Questionnaire

Intakes of foods and nutrients were computed in real time using a food composition database based on McCance and Widdowson's "The composition of foods."[6] Intakes were assessed using a standardized set of recommendations[7] for foods and food groups that were integrated and harmonized across eight European countries (UK, Ireland, Germany, The Netherlands, Spain, Greece, Poland and Norway).[8–11]

Habitual dietary intake was quantified using an online Food Frequency Questionnaire developed for this study including food items consumed frequently in each of the seven countries. The Food4Me online Food Frequency Questionnaire has been validated against a 4-day weighed food record, and the correlation between methods varied, from 0.23 (vitamin D) to 0.65 (protein, % total energy) for nutrient intakes and 0.11 (soups, sauces, and miscellaneous foods) to 0.73 (yogurts) for food group intake.[3,4] Intakes of foods and nutrients were computed in real time using a food composition database based on McCance and Widdowson's "The composition of foods."[12]

The HEI-2010 includes 12 food groups, nine of which assess adequacy of the diet, including (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 three, refined grains, sodium, and empty calories (i.e., energy from solid fats, alcohol, and added sugars), assess dietary components that should be consumed in moderation. For all components,

higher scores reflect better diet quality because the less beneficial food groups are scored such that lower intakes receive higher scores. The scores for each of the 12 components are summed to yield a total score with a maximum value of 100. The food groups of the HEI-2010 and their respective standards are described in detail in Appendix Table 3 and elsewhere.[13]

Metabolic Markers

Feedback on metabolic markers were only provided to participants randomized to Levels 2 and 3. Finger-prick blood samples were collected by participants using a collection pack provided by Vitas Ltd., Oslo, Norway. To optimize blood collection, participants had access to an online video demonstration with instructions and frequently asked questions. Each participant was asked to fill two filter cards (equivalent to five drops of blood or 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 hours, but not longer than 4 hours, before samples were put in an air-tight aluminum-lined envelope with drying sachet and returned by post to the corresponding recruiting center. The centers shipped the samples to Vitas Ltd., Norway, and 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) (Appendix Table 2). More details of biomarker analyses have been published elsewhere.[1]

Genotypic Analyses

Genetic-based feedback was only provided to participants randomized to Level 3. 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 center for shipment to LCG

Genomics (Hertfordshire, UK) for DNA extraction and genotyping of the five loci used for derived personalized advice (Appendix Figure 2). These loci were analyzed using KASP genotyping assays to provide bi-allelic scoring of single nucleotide polymorphisms (SNPs) and insertions and deletions at specific loci. Validation and more detailed description of the technique have been published elsewhere.[14]

Physical Activity Monitoring

PA was objectively assessed using the TracmorD tri-axial accelerometer (Philips Consumer Lifestyle, The Netherlands; www.directlife.philips.com).[15] The device is small (3.2 × 3.2 × 0.5 cm), light (12.5 g), waterproof to a depth of 30 m, and has a battery life of 3 weeks and an internal memory that can store data for up to 22 weeks. The accelerometer registers accelerations in the mediolateral (x-axis), longitudinal (y-axis) and anterioposterior (z-axis) axes as the number of activity counts per minute.[15]

In the present study, participants received a TracmorD accelerometer by post and activated it by creating an account online, installing an application on their computer and connecting the device to the computer using the USB-adapter provided. Upon activation, men could choose between three wearing positions (pocket, belt, or necklace) and women between four wearing positions (pocket, belt, necklace, or bra). Participants were instructed to wear the accelerometer every day during waking hours, except when taking a shower. Participants uploaded data by connecting their monitor to their computer. The data transferred were stored on a secured server as described elsewhere.[16]

Physical Activity Data Processing

Data were recorded with a time sampling interval of 1 minute (i.e., 1-minute epochs). Sufficient PA data to be included in the analyses was defined as having at least 3 valid weekdays and 2 valid weekend days of accelerometer wear, since PA patterns may vary between week and weekend.[16] A day was considered valid if the participant had worn the TracmorD between 10–18 hours. Wear time was defined as 24 hours minus non-wear time. To define non-wear time, we adapted the recommendations of Choi et al.[17] to the TracmorD. Physical activity level (PAL) per minute and per day was estimated from activity counts.[15] Non-wear time was then defined by an interval of at least 90 consecutive minutes of PAL per minute values below 1.3889, allowing for 2-minute intervals of values above the threshold with the upstream or downstream 30-minute window of consecutive values below the threshold for detection of artifactual movements. The R software version 3.1.2 was used for all data handling.

Physical Activity Variables

PA is presented in several ways: (1) daily PAL, (2) estimates of time spent in different PA intensities according to METs, and (3) estimates of adherence to the latest WHO physical activity recommendation[18] (150 minutes·week^{-1}) of moderate-to-vigorous PA.

PAL per day calculations are based upon that described by Bonomi et al.[15] Mean PAL was calculated using all valid week and weekend days, as follows: mean=(mean for weekdays × 5 + mean for weekend days × 2) / 7.

Times spent in sedentary behavior, light PA, moderate PA, and vigorous PA were based on the application of thresholds for activity energy expenditure (AEE) corresponding to 1.5, 3, and 6 METs. A MET represents the ratio of energy expended divided by resting energy expenditure

and was estimated as 1 kcal·kg·h^{-1}. 1.5, 3 and 6 METs were therefore assumed to equal 1.5, 3, and 6 kcal·kg^{-1}·h^{-1} respectively or 0.025, 0.05, and 0.1 kcal·kg^{-1}·min^{-1}.[19] AEE per minute data were calculated as: (0.9 × PAL per minute– 1) × BMR / 1440, where PAL per minute was derived from accelerometer activity counts per minute, and BMR is the daily basal metabolic rate estimated using the Oxford equations developed by Henry, based on the participants' sex, age, and weight at baseline.[20] Sedentary time and light, moderate, and vigorous PA were then determined by summing minutes in a day where AEE per minute met the criterion for the appropriate intensity, and mean data were calculated using all valid week and weekend days as follows: mean=(mean for weekdays × 5 + mean for weekend days × 2) / 7.

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. 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 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 center).[1,21]

Appendix Table 2. Description of the Feedback Given to Participants Randomized to Different Levels of Personalized Nutrition

Level 1 (L1) "dietary group"

- ✓ Participant feedback and advice *was delivered at* month 0, 1, 2, 3 and 6.

Advice for this group was based on:

- ✓ Feedback on how food group intakes compare with guidelines (to optimize the consumption of fruits and vegetables, whole-grain products, fish, dairy products, and meat)
- ✓ Participant anthropometric profile (weight, BMI)
- ✓ Participant PA Profile (Baecke Questionnaire and Accelerometry)[a]
- ✓ Participant nutritional profile based on the online-FFQ (protein, carbohydrates, total fat, monounsaturated fat, polyunsaturated fat, saturated fat, salt, omega-3, fiber, calcium, iron, vitamin A, folate, thiamine, riboflavin, vitamin B12, vitamin C)

Personalized advice was provided for weight, PA and dietary intake.

Level 2 (L2) "dietary + phenotypic group"

- ✓ Participant feedback and advice *was delivered at* month 0, 1, 2, 3 and 6.

Advice for this group was based on:

- ✓ Feedback on how food group intakes compare with guidelines (to optimise the consumption of fruits and vegetables, whole-grain products, fish, dairy products, and meat)
- ✓ Participant anthropometric profile (weight, BMI, WC)
- ✓ Participant PA profile (Baecke Questionnaire and Accelerometry)[a]
- ✓ Participant nutritional profile based on the online-FFQ (protein, carbohydrates, total fat, monounsaturated fat, polyunsaturated fat, saturated fat, salt, omega-3, fiber, calcium, iron, vitamin A, folate, thiamine, riboflavin, vitamin B12, vitamin C)
- ✓ Participant blood profile related to nutrition (glucose, total cholesterol, carotenoids, n-3 index)

Personalized advice was provided for weight, WC, PA, dietary intake and blood markers

Level 3 (L3) "Dietary + phenotypic + genomic group"

- ✓ Participant feedback and advice *was delivered at* month 0, 1, 2, 3 and 6.

Advice for this group was based on:

- ✓ Feedback on how food group intakes compare with guidelines (to optimise the consumption of fruits and vegetables, whole-grain products, fish, dairy products, and meat)
- ✓ Participant anthropometric profile (weight, BMI, WC)
- ✓ Participant PA profile (Baecke Questionnaire and Accelerometry)[a]
- ✓ Participant nutritional profile based on the online-FFQ (protein, carbohydrates, total fat, monounsaturated fat, polyunsaturated fat, saturated fat, salt, omega-3, fiber, calcium, iron, vitamin A, folate, thiamine, riboflavin, vitamin B12, vitamin C)
- ✓ Participant blood profile related to nutrition (glucose, total cholesterol, carotenes, n-3 index)
- ✓ Participant genetic profile related to nutrition (MTHFR, FTO, TCF7L2, APOE ε4 and FADS1 genes)

Personalized advice was provided for weight, WC, PA, dietary intake, and blood and genomic markers

Note: Feedback provided at Month 1 and Month 2 for L1, L2, and L3 was for those participants in the "Higher-Frequency Feedback" group only.

[a]Feedback on participants PA profile for the "Lower-Frequency Feedback" group was derived from accelerometer. The Baecke Questionnaire[22] was used only when insufficient data were available from the accelerometer. For participants in the "Higher-Frequency Feedback" group, both accelerometry and the Baecke questionnaire were used.
[b]Feedback on blood profile related to nutrition was only available for Month 0, Month 3, and Month 6 for both "Lower- and Higher-Frequency Feedback" groups.

FFQ, Food Frequency Questionnaire; WC, waist circumference; PA, physical activity.

Description of the Intervention Groups

Following receipt of baseline measures, participants received either standard nutrition advice (control group) or PN advice based on three levels of information. Participants randomized to PN groups (L1, L2, and L3) received personalized feedback and advice, which was derived manually using decision trees developed specifically for the Food4Me study (Appendix Tables 1 and 2).[23] These decision trees were implemented by trained nutritionists and dieticians in the research centers leading the intervention in each of the seven recruitment countries.[23] To ensure uniformity in delivery of the intervention across countries, the same decision trees were used in each country and the resulting PN messages were translated to the local language.[24] The information provided to each group is described below.

Level 1 ("Diet Group")

Participants randomized 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 guidelines. In addition, personalized dietary advice was given based on their reported intake of nutrients (proteins, carbohydrates, total fat, saturated fat, monounsaturated fat, polyunsaturated

fat, salt, omega-3, fiber, calcium, iron, vitamin A, folate, thiamine, riboflavin, vitamin B 12, vitamin C), at baseline and month 3 (Appendix Table 2). They also received personalized feedback on BMI and PA.

Level 2 ("Diet + Phenotype Group")

Participants randomized to L2 received personalized 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 (BMI and waist circumference) and blood nutrient- and metabolic-related biomarkers (omega-3 index, carotenoids, glucose, and cholesterol). They also received personalized feedback on PA (Appendix Table 2).

Level 3 ("Diet + Phenotype + Genotype Group")

Participants randomized to L3 received personalized dietary advice based on their dietary intake plus phenotypic and genotypic data collected at baseline (including PA). The genotypic feedback was based on specific variants in five nutrient-responsive genes selected specifically for the Food4Me Study. A description of these five genes and the related dietary factors is given in Appendix Table 2.

Development of a Personalized Feedback Report

Participants randomized to L1, L2, and L3 received personalized feedback 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 categorized 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

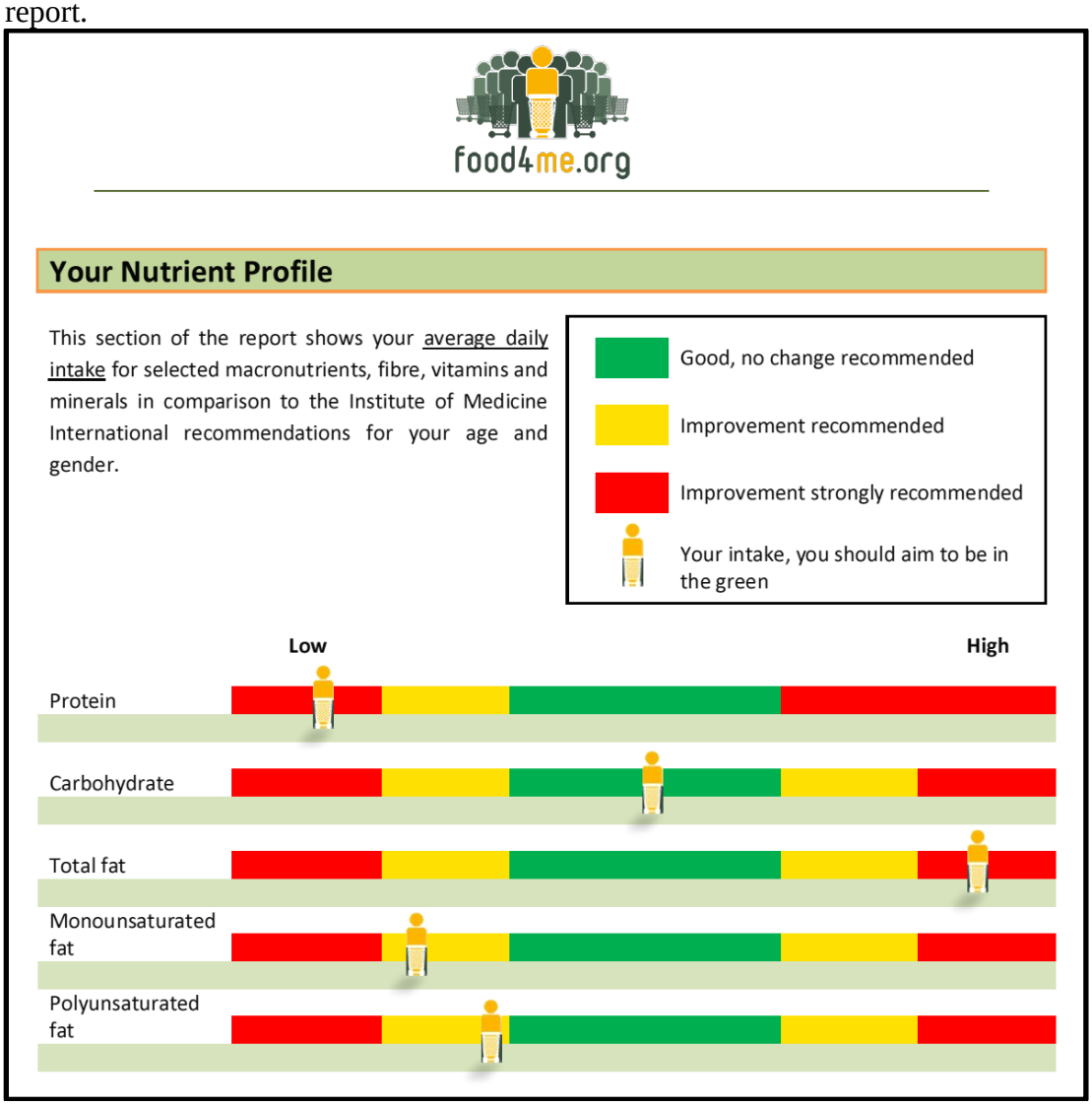
trees will be published elsewhere. Protocols for the decision trees were standardized across the seven research centers and translated into the respective mother tongues. Nutritionists and dietitians implementing the decision trees were trained to ensure consistency in the PN advice given throughout the study across all seven countries; these professionals participated in frequent teleconferences (every other week) to resolve issues and to share best practices.

The participants' reports included information on how their health-related characteristics compared with recommendations. The following sections were given in the report:

- A message from your nutritionist (available for Levels 1, 2, and 3)
- Section 1. How your diet compares to recommendations (available for Levels 1, 2, and 3)
- Section 2. Your physical characteristics (available for Levels 1, 2, and 3)
- Section 3a. Your nutrient profile (available for Levels 1, 2, and 3)
- Section 3b. Your blood profile relating to nutrition (available for Levels 2 and 3)
- Section 3c. Your genetic profile relating to nutrition (available for Level 3)
- Section 4. Your Personalised Nutrition Advice (available for Levels 1, 2, and 3)

Evaluations of healthy behaviors were explained using a three-color sliding scale: green representing "good, no change recommended," amber representing "improvement recommended," and red representing "improvement strongly recommended." An example of the feedback is provided in Appendix Figure 1a. An example of the template used to provide a personalized feedback based on food groups and nutrients is illustrated in Appendix Figures 1a, 1b and 1c.

Appendix Figure 1a. Example of a three-color sliding scale used in the personalized nutrition report.



Appendix Figure 1b. Example of personalized nutrition report including list of target nutrients and food groups.

A message from your nutritionist

[Add note]

Outlined below are your main goals to focus on:

- [Weight and physical activity recommendation]
- [1st Target nutrient]
- [2nd Target nutrient]
- [3rd Target nutrient]

We have provided you with tips to help you to achieve these goals in section 4 of your report.

To go straight to your personalised nutrition advice (section 4), click here

Section 1: How your diet compares to recommendations

Food Group	Your average number of portions	Guideline amount
Fruit and vegetables 	[add values] a day	At least 5 a day
Wholegrains 	[add values] a day	At least 50g a day
Dairy products 	[add values] a day	3 a day
Oily Fish 	[add values] a week	At least 1 a week
Red meat 	[add values] a week	No more than 3 a week

For more information on the food guidelines and general portion sizes click here or visit your personal login page on the Food4me website.

To return to the start of your report, click here

Appendix Figure 1c. Example of personalized nutrition report including the format of the feedback provided for targets nutrients.

Section 4: Your Personalised Nutrition Advice

Your Weight and Physical Activity Recommendations

Add message from body weight tree
For more information on body weight, click here

Your dietary goals

As it is very difficult to try to improve all of your nutrient profile at once, we have selected your top 3 nutritional targets to focus on until your next assessment:

Target	Sources	Goals and Tips
Add	Name foods Your main contributing food groups (and foods): **1st (only add if it is something to reduce)** 2nd	•**Message from decision tree**
Add	Name foods Your main contributing food groups (and foods): **1st (only add if it is something to reduce)** 2nd	**Message from decision tree**
Add	Name foods Your main contributing food groups (and foods): **1st (only add if it is something to reduce)** 2nd	**Message from decision tree**

For more information on each nutrient, food sources, recommended portion sizes and recipe ideas check the nutrients and Recipies4me sections on your personal login page on the Food4me website.

For genotype 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 as specified in Appendix Figure 2. Finally, each report included a personalized message from the dietitian/nutritionist. This message provided tailored advice for body weight and PA and specific nutrition-related goals derived from dietary, phenotypic, and/or genotypic markers (according to the participant's intervention group). Based on person-centered counseling models for facilitating dietary change,[25] 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 cutoff points for each of the nutritional and phenotypic variables were used to derive personalized goals and advices.[1]

Appendix Figure 2. Genotype-based information delivered to Level 3, "Diet + phenotype + genotype"

food4me.org

Your Genetic Profile

Genes	Nutritional influences associated with some variations of this gene	Do you have the genetic variation that can be modified by dietary change?
MTHFR	People with a specific variation of this gene can benefit by increasing their intake of the vitamin folate. Increasing folate intake (found in green leafy vegetables) has been associated with an improvement in factors relating to cardiovascular health in these individuals.	Add info yes/no
FTO	A specific variation of this gene is associated with a greater need to maintain a healthy body weight and engage in physical activity. A healthy weight combined with exercise may provide added health benefits for these individuals.	
TCF7L2	A specific variation of this gene is associated with improved weight loss when following a low fat diet compared to other weight loss diets. Reducing dietary fat may enhance weight loss in these individuals.	
ApoE(e4)	A specific variation of this gene is associated with a greater need to maintain healthy cholesterol levels. Decreasing saturated fat intake has been associated with an improvement in cholesterol and factors relating to cardiovascular health in these individuals.	
FADS1	People with a specific variation of this gene can benefit by increasing their intake of the healthy omega-3 fat found in oily fish. Increasing omega-3 intake has been associated with an improvement in factors relating to cardiovascular health in these individuals.	

APPENDIX 2. SUPPLEMENTARY RESULTS

Appendix Table 3. Healthy Eating Index-2010 Components and Standards for Scoring

HEI-2010[a] – component	Maximum points	Standard for maximum score	Standard for minimum score of zero
Adequacy			
Total fruit[b]	5	≥0.8 cup equivalent per 1,000 kcal	No fruit
Whole fruit[c]	5	≥0.4 cup equivalent per 1,000 kcal	No whole fruit
Total vegetable[d]	5	≥1.1 cup equivalent per 1,000 kcal	No vegetables
Greens and beans[d]	5	≥0.2 cup equivalent per 1,000 kcal	No dark green vegetables or beans and peas
Whole grains	10	≥1.5 oz equivalent per 1,000 kcal	No whole grains
Dairy[e]	10	≥1.3 cup equivalent per 1,000 kcal	No dairy
Total protein foods[f]	5	≥2.5 oz equivalent per 1,000 kcal	No protein foods
Seafood and plant proteins[f,g]	5	≥0.8 oz equivalent per 1,000 kcal	No seafood or plant proteins
Fatty acids[h]	10	(PUFAs+ MUFAs)/SFAs ≥2.5	(PUFAs+ MUFAs)/SFAs ≤1.2
Moderation			
Refined grains	10	≤1.8 oz equivalent per 1,000 kcal	≥4.3 oz equivalent per 1,000 kcal
Sodium	10	≤1.1 grams per 1,000 kcal	≥2.0 grams per 1,000 kcal
Empty calories[i]	20	≤19% of energy	≥50% of energy

[a]Intakes between the minimum and maximum standards are scored proportionately.
[b]Includes fruit juice.
[c]Includes all forms except juice.
[d]Includes any beans and peas not counted as Total Protein Foods.
[e]Includes all milk products, such as fluid milk, yogurt, and cheese, and fortified soy beverages.
[f]Beans and peas are included here (and not with vegetables) when the Total Protein Foods standard is otherwise not met.
[g]Includes seafood, nuts, seeds, soy products (other than beverages) as well as beans and peas counted as Total Protein Foods.
[h]Ratio of poly- and monounsaturated fatty acids to saturated fatty acids.
[i]Calories from solid fats, alcohol, and added sugars; threshold for counting alcohol is >13 grams/1000 kcal.

HEI, X; PUFA, X; MUFA, X; SFA, X.

Appendix Table 4. Number of Participants Imputed for Targeted Outcomes at Months 3 and 6 of the Intervention.

Target outcome	Month 3	Month 6
Salt ($g \cdot day^{-1}$)[a]	66	87
Saturated fat (% TE)	55	76
Dietary fiber ($g \cdot day^{-1}$)	41	54
Folate ($\mu g \cdot day^{-1}$)	30	40
Polyunsaturated fat (% TE)	16	22
Energy intake ($Mj \cdot day^{-1}$)	61	75
Weight (kg)	61	75
Waist circumference (cm)	36	41

TE, X; Mj, X.

Appendix Table 5. Baseline Characteristics by Lower- and Higher-Frequency Feedback Group

Variables	Lower-Frequency Feedback group	Higher-Frequency Feedback group
Total, n	562	563
Sex – women, n (%)	328 (58.4)	328 (58.3)
Age, years	39.7 (12.6)	40.3 (13.3)
Age categories, n (%)		
<30 years	165 (29.4)	160 (28.4)
30–49 years	252 (44.8)	241 (42.8)
50–70 years	144 (25.6)	157 (27.9)
>70 years	1 (0.2)	5 (1.0)
Ethnicity, n (%)		
White	544 (96.8)	545 (97.3)
Other ethnic groups	18 (3.2)	12 (2.7)
Occupation, n (%)		
Professional	224 (39.9)	218 (39.0)
Intermediate	151 (26.9)	147 (26.4)
Manual	57 (10.1)	51 (9.2)
Student	70 (12.5)	84 (15.1)
Retired/unemployed	60 (10.7)	58 (10.4)
Anthropometrics		
Height (cm)	171 (9.6)	171 (9.3)
Weight (kg)	74.0 (15.9)	75.6 (16.1)
BMI ($kg \cdot m^{-2}$)	25.2 (5.0)	25.8 (4.8)
BMI categories, n (%)		
Underweight (<18.5 $kg \cdot m^{-2}$)	14 (2.5)	17 (3.1)
Normal weight (18.5–24.9 $kg \cdot m^{-2}$)	317 (56.4)	261 (46.8)
Overweight ≥25.0–29.9 $kg \cdot m^{-2}$)	146 (26.0)	183 (32.8)
Obese (≥30.0 $kg \cdot m^{-2}$)	85 (15.1)	97 (17.4)
Waist circumference (cm)	84.9 (13.8)	86.5 (13.7)
Central obesity, n (%)	123 (21.9)	153 (27.5)

Smoking behavior, n (%)		
Current smokers	52 (9.3)	74 (13.1)
Ex-smokers	137 (24.4)	154 (27.5)
Non-smokers	373 (66.4)	332 (59.3)
Physical activity		
Physical activity level (PAL)	1.74 (0.2)	1.71 (0.2)
Sedentary behavior (minutes/day^{-1})	742 (77.4)	746 (76.2)
Moderate equivalent PA	58.5 (43.5)	57.6 (47.6)
Physically active individuals, n (%)	387 (78.8)	385 (78.3)
Medical history, n (%)		
Disease history[a]	234 (41.6)	249 (44.2)
Medication[b]	164 (29.2)	167 (30.0)

Notes: Data presented as means (SD) or as percentages for categorical variables. Physically active individuals were those who accumulated >600 MET·min·week^{-1}. Central obesity was defined as a WC >88 cm for women and >102 cm for men.

[a]Disease history included cancer, high blood pressure, heart disease, liver disease, kidney disease, arthritis, osteoporosis, ulcers, fibromyalgia, diabetes, lung disease, allergies, epilepsy, thyroid disease, anemia, blood disorders, alcohol abuse, drug addiction, and depression.
[b]X

PAL, physical activity levels; min, minutes.

Appendix Table 6. RRR for Dropping Out at Month 3 and Month 6 of the Study in the Higher- Compared with Lower- Frequency Feedback Groups

	Month 3			Month 6		
	Lower-Frequency Feedback group	Higher-Frequency Feedback group		Lower-Frequency Feedback group	Higher-Frequency Feedback group	
Models	**RRR**	**RRR (95% CI)**	***p*-value**	**RRR**	**RRR (95% CI)**	***p*-value**
Model 0	1.00 (ref)	1.99 (1.36, 2.92)	<0.0001	1.00 (ref)	1.72 (1.26, 2.35)	<0.0001
Model 1	1.00 (ref)	2.02 (1.38, 2.94)	<0.0001	1.00 (ref)	1.72 (1.27, 2.34)	<0.0001
Model 2	1.00 (ref)	2.00 (1.37, 2.92)	<0.0001	1.00 (ref)	1.71 (1.26, 2.33)	<0.0001
Model 3	1.00 (ref)	2.00 (1.37, 2.92)	<0.0001	1.00 (ref)	1.72 (1.26, 2.33)	<0.0001
Model 4	1.00 (ref)	1.85 (1.26, 2.71)	0.002	1.00 (ref)	1.62 (1.19, 2.22)	0.002
Model 5	1.00 (ref)	1.84 (1.25, 2.70)	0.002	1.00 (ref)	1.62 (1.18, 2.21)	0.002
Model 6	1.00 (ref)	1.78 (1.21, 2.62)	0.003	1.00 (ref)	1.58 (1.16, 2.16)	0.004

Data presented as RRR and its 95% CI. Lower-Frequency Feedback group was used as reference group in the analysis. RRR were estimated using binomial regression with a log link function.

Model 0 was unadjusted.
Model 1 was adjusted for age.
Model 2 was adjusted for age and sex.
Model 3 was adjusted for age, sex, and country.
Model 4 was adjusted for age sex, country, and occupation.
Model 5 was adjusted for age, sex, country, occupation, and intervention arm.
Model 6 was adjusted for age, sex, country, occupation, intervention arm, and BMI.

Appendix Table 7. Changes in Healthy Eating Index Subcomponents at Month 3 and Month 6 Between Lower and Higher Frequency Feedback Groups

Food/nutrient group and month	Lower-Frequency Feedback group	Higher-Frequency Feedback group	Δ [Higher – Lower][2]	Δ *p*-value	Effect size
Total fruit (g equivalent per 1,000 kcal·day^{-1})					
M0 (mean)[a]	159.9 (150.1, 169.6)	158.1 (148.2, 167.8)	–1.83 (–15.6, 11.9)	0.794	
M3 (Δ [M3 – M0])[b]	29.8 (19.1, 40.4)*	37.8 (26.3, 49.4)**	8.02 (–7.62, 23.6)	0.315	0.06
M6 (Δ [M6 – M0])[b]	36.3 (25.4, 47.2)**	38.4 (27.6, 49.1)**	2.34 (–12.9, 17.6)	0.764	0.02
Whole fruit (g equivalent per 1,000 kcal·day^{-1})					
M0 (mean)[a]	111.3 (103.4, 119.3)	114.2 (106.2, 122.2)	2.88 (–8.41, 14.1)	0.617	
M3 (Δ [M3 – M0])[b]	22.3 (14.7, 29.9)**	28.3 (18.5, 38.1)**	5.84 (–6.45, 18.1)	0.352	0.06
M6 (Δ [M6 – M0])[b]	30.4 (22.6, 38.2)**	36.9 (27.7, 46.1)**	6.43 (–5.53, 18.4)	0.291	0.05
Total vegetables (g equivalent per 1,000 kcal·day^{-1})					
M0 (mean)[a]	94.7 (89.4, 100.0)	93.1 (87.8, 98.4)	–1.57 (–9.06, 5.92)	0.681	
M3 (Δ [M3 – M0])[b]	20.1 (14.4, 25.6)**	23.8 (18.1, 29.6)**	3.79 (–4.25, 11.8)	0.356	0.05
M6 (Δ [M6 – M0])[b]	18.0 (13.0, 23.0)**	20.7 (14.8, 26.6)**	2.60 (–5.09, 10.3)	0.507	0.04
Greens and beans (g equivalent per 1,000 kcal·day^{-1})					
M0 (mean)[a]	45.7 (42.8, 48.6)	42.9 (40., 45.8)	–2.80 (–6.88, 10.27)	0.178	
M3 (Δ [M3 – M0])[b]	5.01 (1.83, 8.17)**	8.93 (5.77, 12.0)**	3.89 (–0.57, 8.37)	0.088	0.10
M6 (Δ [M6 – M0])[b]	6.53 (3.70, 9.35)**	10.0 (6.88, 13.2)**	3.45 (–0.76, 7.67)	0.108	0.09
Whole grains (g equivalent per 1,000 kcal·day^{-1})					
M0 (mean)[a]	68.0 (63.4, 72.5)**	62.4 (57.8, 66.9)**	–5.60 (–12.1, 0.85)	0.089	
M3 (Δ [M3 – M0])[b]	3.21 (0.76, 7.01)*	5.51 (1.11, 9.92)*	2.11 (–3.80, 8.03)	0.485	0.04
M6 (Δ [M6 – M0])[b]	7.28 (2.51, 12.4)**	9.76 (5.50, 14.02)**	2.25 (–4.17, 8.68)	0.492	0.04
Dairy (g equivalent per 1,000 kcal·day^{-1})					
M0 (mean)[a]	131.1 (123.1, 139.1)	126.9 (118.9, 134.9)	–4.18 (–15.4, –7.07)	0.466	
M3 (Δ [M3 – M0])[b]	6.42 (–1.74, 14.6)	6.36 (–1.13, 13.8)	–0.5 (–11.1, 11.1)	0.993	0.005

M6 (Δ [M6 – M0])[b]	6.71 (–1.72, 15.1)	2.18 (–5.66, 10.0)	–4.55 (–16.1, 7.00)	0.440	0.05
Total protein (g equivalent per 1,000 kcal·day^{-1})					
M0 (mean)[a]	42.9 (42.1, 43.6)	42.2 (41.5, 42.9)	–0.67 (–1.76, 0.41)	0.224	
M3 (Δ [M3 – M0])[b]	0.67 (0.04, 1.31)*	1.35 (0.56, 2.15)**	0.69 (–0.31, 1.70)	0.176	0.08
M6 (Δ [M6 – M0])[b]	1.02 (0.37, 1.67)**	1.26 (0.50, 2.02)**	0.25 (–0.74, 1.25)	0.616	0.02
Seafood and plant proteins (g equivalent per 1,000 kcal·day^{-1})					
M0 (mean)[a]	100.0 (94.1, 105.9)	93.3 (87.5, 99.2)	–6.6 (–14.9, 1.66)	0.117	
M3 (Δ [M3 – M0])[b]	–3.89 (–9.7, 1.96)	0.84 (–4.48, 6.18)	4.81 (–3.12, 12.7)	0.235	0.07
M6 (Δ [M6 – M0])[b]	–2.17 (–8.03, 3.68)	4.61 (–1.52, 10.7)	6.86 (–1.59, 15.3)	0.112	0.10
Fatty acids ratio (PUFAs+MUFAs)/SFATs					
M0 (mean)[a]	1.41 (1.38, 1.44)	1.44 (1.41, 1.47)	0.03 (–0.01, 0.06)	0.203	
M3 (Δ [M3 – M0])[b]	0.09 (0.06, 0.12)**	0.16 (0.13, 0.19)**	0.07 (0.30, 0.11)	**0.001**	0.18
M6 (Δ [M6 – M0])[b]	0.12 (0.08, 0.14)**	0.13 (0.09, 0.15)**	0.01 (–0.03, 0.05)	0.644	0.03
Refined grains (oz equivalent per 1,000 kcal·day^{-1})					
M0 (mean)[a]	89.8 (84.8, 94.7)	95.1 (90.1, 100.1)	5.31 (–1.73, 12.3)	0.139	
M3 (Δ [M3 – M0])[b]	–5.80 (–9.75, –1.86)**	–12.7 (–18.2, –7.3)**	–6.96 (–13.6, –0.29)	**0.041**	0.14
M6 (Δ [M6 – M0])[b]	–4.98 (–9.1, –0.83)*	–9.4 (–14.6, –4.28)**	–4.55 (–11.1, 2.03)	0.176	0.09
Sodium (g equivalent per 1,000 kcal·day^{-1})					
M0 (mean)[a]	2.85 (2.80, 2.90)	2.87 (0.82, 2.90)	0.02 (–0.05, 0.08)	0.600	
M3 (Δ [M3 – M0])[b]	–0.07 (–0.12, –0.02)**	–1.55 (–0.20, –0.10)**	–0.8 (–0.14, –0.01)	**0.019**	1.45
M6 (Δ [M6 – M0])[b]	–0.09 (–0.13, –0.04)**	–0.11 (–0.16, –0.06)**	–0.02 (–0.08, 0.04)	0.499	0.03
Empty calories (% of total energy)					
M0 (mean)[a]	36.6 (36.1, 37.2)	36.8 (36.2, 37.3)	0.15 (–0.62, 0.92)	0.697	
M3 (Δ [M3 – M0])[b]	0.36 (–0.16, 0.88)	0.16 (–0.47, 0.81)	–0.19 (–1.02, 0.63)	0.642	0.02
M6 (Δ [M6 – M0])[b]	–0.13 (–0.70, 0.43)	–0.01 (–0.59, 0.57)	0.13 (–0.68, 0.95)	0.751	0.02

Notes: Boldface indicates statistical significance (*p<0.05 and **p<0.01). Data are presented as adjusted mean or Δ with the corresponding 95% CI.

[a]Adjusted mean at baseline.
[b]Δ between Month 3 and baseline or Month 6 and baseline.
[c]The Δs have been estimated from differences between Higher- and Lower-Frequency Feedback groups. Analysis included all participants randomized to Levels 1–3. Analyses were adjusted for baseline age, sex, personalized nutrition intervention arm, occupation, and country. Body weight and waist circumference were additionally adjusted for total physical activity levels. The effect size for the Δ between Lower- and Higher-Frequency Feedback groups at Month 3 and Month 6 were estimated as the ratio of the observed Δ to the baseline SD of each measure. This gives a value like a Cohen's d; therefore, effects sizes <0.2 would be considered small. Significant differences between baseline and Month 3 or Month 6 were derived from the Linear Mixed Effect Models and post-hoc contrast analyses and denoted as *p<0.05 and **p<0.01.

Kj, kilojoules; M0, baseline; M3, Month 3; M6, Month 6; kcal, kilocalories; PUFA, polyunsaturated fatty acids; MUFA, monounsaturated fatty acids; SFATs, saturated fatty acids; g, grams; oz, ounce.

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