AJCN. First published ahead of print April 5, 2017 as doi: 10.3945/ajcn.116.145680.

Can genetic-based advice help you lose weight? Findings from the Food4Me European randomized controlled trial[1–3]

*Carlos Celis-Morales,[4,5,16,18] Cyril FM Marsaux,[6,16,18] Katherine M Livingstone,[4,16,18] Santiago Navas-Carretero,[7] Rodrigo San-Cristobal,[7] Rosalind Fallaize,[8] Anna L Macready,[8] Clare O'Donovan,[9] Clara Woolhead,[9] Hannah Forster,[9] Silvia Kolossa,[10] Hannelore Daniel,[10] George Moschonis,[11] Christina Mavrogianni,[11] Yannis Manios,[11] Agnieszka Surwillo,[12] Iwona Traczyk,[12] Christian A Drevon,[13] Keith Grimaldi,[14] Jildau Bouwman,[15] Mike J Gibney,[9] Marianne C Walsh,[9] Eileen R Gibney,[9] Lorraine Brennan,[9] Julie A Lovegrove,[8] J Alfredo Martinez,[7] Wim HM Saris,[6,17,18] and John C Mathers[4,17,18]**

[4]Human Nutrition Research Center, Institute of Cellular Medicine, Newcastle University, Newcastle Upon Tyne, United Kingdom; [5]Glasgow Cardiovascular Research Center, Institute of Cardiovascular and Medical Science, University of Glasgow, Glasgow, United Kingdom; [6]Department of Human Biology, School of Nutrition and Translational Research in Metabolism (NUTRIM), Maastricht University Medical Center, Maastricht, Netherlands; [7]Department of Nutrition, Food Science and Physiology, Center for Nutrition Research, University of Navarra, Pamplona, Spain; [8]Hugh Sinclair Unit of Human Nutrition and Institute for Cardiovascular and Metabolic Research, University of Reading, Reading, United Kingdom; [9]University College Dublin (UCD) Institute of Food and Health, UCD, Dublin, Ireland; [10]Research Center of Nutrition and Food Sciences (ZIEL), Biochemistry Unit, Technical University of Munich, Munich, Germany; [11]Department of Nutrition and Dietetics, Harokopio University, Athens, Greece; [12]National Food and Nutrition Institute, Warsaw, Poland; [13]Department of Nutrition, Institute of Basic Medical Sciences, Faculty of Medicine, University of Oslo, Oslo, Norway; [14]Eurogenetica Ltd, Burnham-on-Sea, United Kingdom; and [15]Netherlands Organization for Applied Scientific Research (TNO), Microbiology and Systems Biology Group, Zeist, Netherlands

ABSTRACT

Background: There has been limited evidence about whether genotype-tailored advice provides extra benefits in reducing obesity-related traits compared with the benefits of conventional one-size-fits-all advice.

Objective: We determined whether the disclosure of information on fat-mass and obesity-associated (*FTO*) genotype risk had a greater effect on a reduction of obesity-related traits in risk carriers than in nonrisk carriers across different levels of personalized nutrition.

Design: A total of 683 participants (women: 51%; age range: 18–73 y) from the Food4Me randomized controlled trial were included in this analysis. Participants were randomly assigned to 4 intervention arms as follows: level 0, control group; level 1, dietary group; level 2, phenotype group; and level 3, genetic group. *FTO* (single nucleotide polymorphism rs9939609) was genotyped at baseline in all participants, but only subjects who were randomly assigned to level 3 were informed about their genotypes. Level 3 participants were stratified into risk carriers (AA/AT) and nonrisk carriers (TT) of the *FTO* gene for analyses. Height, weight, and waist circumference (WC) were self-measured and reported at baseline and months 3 and 6.

Results: Changes in adiposity markers were greater in participants who were informed that they carried the *FTO* risk allele (level 3 AT/AA carriers) than in the nonpersonalized group (level 0) but not in the other personalized groups (level 1 and 2). Mean reductions in weight and WC at month 6 were greater for *FTO* risk carriers than for noncarriers in the level 3 group [−2.28 kg (95% CI: −3.06, −1.48 kg) compared with −1.99 kg (−2.19, −0.19 kg), respectively ($P = 0.037$); and −4.34 cm (−5.63, −3.08 cm) compared with −1.99 cm (−4.04, −0.05 cm), respectively, ($P = 0.048$)].

Conclusions: There are greater body weight and WC reductions in risk carriers than in nonrisk carriers of the *FTO* gene. This trial was registered at clinicaltrials.gov as NCT01530139. *Am J Clin Nutr* doi: 10.3945/ajcn.116.145680.

Keywords: *FTO*, genotype, personalized nutrition, randomized controlled trial, weight

INTRODUCTION

Over the past 30 y, the prevalence of obesity has increased markedly with 17% of European adults (1) and 9% of adults globally now being obese (2). Obesity is a major risk factor for noncommunicable diseases including type 2 diabetes, cardiovascular diseases, and many cancers (3, 4), which emphasizes the importance of initiatives that are aimed at changing lifestyles to prevent and to reduce excess body

[1] Supported by the European Commission under the Food, Agriculture, Fisheries and Biotechnology Theme of the 7th Framework Programme for Research and Technological Development (project 265494).

[2] The sponsor had no role in the study design or conduct; the data collection, management, analysis, or interpretation; or the manuscript preparation, review, or approval.

[3] Supplemental Figures 1–3, Supplemental Methods, and Supplemental Tables 1–3 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

[16] These authors are joint first authors.

[17] These authors are joint senior authors.

[18] These authors contributed equally to this work.

*To whom correspondence should be addressed. E-mail: john.mathers@ncl.ac.uk.

Received September 16, 2016. Accepted for publication March 3, 2017. doi: 10.3945/ajcn.116.145680.

weight (5). Although previous intervention strategies have mainly focused on one-size-fits-all approaches to change dietary and physical activity (PA)[19] behaviors, some studies have used personalized approaches (e.g., tailored web-based interventions) (6–10). There has been mixed evidence about the effect of personalized interventions compared with that of conventional interventions in achieving behavioral changes, but results for weight loss seem promising (11–14).

Reductions in the cost and time that are needed for genome sequencing and an enhanced ability to extract relevant information (e.g., disease risk) have fueled interest in the use of personal genetics to tailor interventions (15, 16). However, the effectiveness of genetic-based information in facilitating a behavioral change is unclear. A systematic review called for more and larger randomized controlled trials (RCTs) to determine whether DNA-based advice motivates people to make appropriate behavioral changes (17).

Variants in the first intron of the fat-mass and obesity-associated (*FTO*) gene have been shown to be strongly associated with the development of obesity (10, 18–20). Individuals who were homozygous for the *FTO* risk allele AA (rs9939609) weighed, on average, 3 kg more and had 1.7-fold increased odds of being obese than did subjects who were homozygous for the lower-risk allele TT (21). Although there is increasing evidence that the *FTO* genetic susceptibility to obesity can be modulated by lifestyle factors such as PA (10, 22, 23), there has been a lack of evidence about whether the disclosure of information on the *FTO* genotype would motivate individuals to adopt healthier lifestyles to reduce weight (24). A recent study showed that feedback on *FTO* risk increased the readiness to control weight in young and healthy adults, but no evidence of an actual behavior change was shown (25). The current study was part of the Food4Me intervention trial, which was designed to investigate the effectiveness of different levels of personalized nutrition, including dietary, phenotypic-, and genotype-based advice, on improving diet and health-related outcomes (14). The genotype-based advice in the Food4Me trial used 5 different genetic variants, each of which were associated with a specific nutrient or phenotypic marker. However, the current study focused on the effect of disclosing information about the *FTO* genotype, which was the only variant for which personalized advice for weight loss was provided. Thus, the aims of the current study were to assess the impact of disclosing personalized *FTO*-based information on changes in obesity-related markers and to investigate whether changes in obesity markers were different from those that were observed in other interventions groups who received non–genotype-based personalized nutrition advice.

METHODS

Study design

Subjects were participants in the Food4Me proof-of-principle study, which was a 6-mo web-based RCT on personalized nutrition that was conducted across 7 European countries (Germany, Greece, Ireland, the Netherlands, Poland, Spain, and the United Kingdom) (clinicaltrials.gov; NCT01530139). As outlined elsewhere (26), 1607 adults aged ≥18 y were included in the study. Exclusion criteria included no or limited access to the Internet, consumption of a prescribed diet, or having altered nutritional requirements because of medical conditions. Participants were screened online between August 2012 and August 2013; characteristics of these individuals have been reported elsewhere (27).

Intervention arms

Full details of the study design have been published elsewhere (26). Briefly, participants were randomly allocated to one of 4 groups as follows: level 0, standard, nonpersonalized dietary and PA guidelines; level 1, personalized advice on the basis of current weight, diet, and PA; level 2, personalized advice on the basis of current weight, diet, PA, and phenotype [e.g., waist circumference (WC) and blood cholesterol]; and level 3, personalized advice on the basis of current weight, diet, PA, phenotype, and genotype information for 5 genetic variants [*FTO*, fatty acid desaturase 1 (*FADS1*), transcription factor 7 like 2 (*TCF7L2*), apolipoprotein (*Apo*) E (e4), and 5,10-methylenetetrahydrofolate reductase (*MTHFR*)]. All data were collected remotely (i.e., at home) at baseline and at months 3 and 6 according to standardized operating procedures (26).

After the analysis of data that were collected at baseline and 3 mo, participants received personalized feedback on their weights, diets, and PAs (levels 1–3) or nonpersonalized guidelines (level 0) depending on their randomly assigned group at both time points. The personalized feedback was based on predefined algorithms that incorporated anthropometric, dietary, and PA data (levels 1–3) as well as phenotypic data (levels 2 and 3) and genotypic data (level 3 only). Results in the personalized feedback reports were indicated for each anthropometric, dietary, and PA items (levels 1–3) as well as phenotypic items (levels 2 and 3) on 3-color–graded lines (green: good; amber: improvement recommended; and red: improvement strongly recommended). In addition, all level 3 participants received information on whether they carried the risk variant for 5 nutrition- and lifestyle-related genes (**Table 1**). The feedback provided for each of these 5 genetic variants is described in Table 1 (26). Target nutrients or phenotypic markers that were related to these genotypic variants and for which participants received personalized advice were body weight for the *FTO* gene, ω-3 fatty acid intake for the *FADS1* gene, fat intake for the *TCF7L2* gene, saturated fat intake for the *ApoE(e4)* gene, and folate for the *MTHFR* gene. However, for the purposes of this study, we included only participants who received genotype-based advice for the *FTO* gene and who were advised to reduce their body weights (Table 1, **Supplemental Figures 1** and **2**).

For *FTO*, the following message was included in reports that were delivered to level 3 participants: "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." Level 3 participants were informed about their *FTO* rs9939609 status (i.e., whether they carried the risk allele or not; yes or no, respectively). However, this feedback did not include any numerical information about how much

[19] Abbreviations used: *FTO*, fat mass and obesity associated; PA, physical activity; RCT, randomized controlled trial; SNP, single nucleotide polymorphism; WC, waist circumference.

TABLE 1
Genetic feedback that was delivered to participants who were randomly assigned to level 3[1]

Genes	Targeted recommendation	Nutritional influences associated with some variations of the gene	Do you have the genetic variation that can be modified by dietary change?
FTO	Reduce body weight	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.	Yes/no
FADS1	Increase ω-3 intake	People with a specific variation of this gene can benefit by increasing their intake of the healthy ω-3 fat in oily fish. Increasing ω-3 intake has been associated with an improvement in factors relating to cardiovascular health in these individuals.	Yes/no
TCF7L2	Reduce fat intake	A specific variation of this gene is associated with improved weight loss when consuming a low-fat diet compared with the effect of other weight-loss diets. Reducing dietary fat may enhance weight loss in these individuals.	Yes/no
ApoE(e4)	Reduce saturated fat intake	A specific variation of this gene is associated with a greater need to maintain healthy cholesterol concentrations. Decreasing saturated fat intake has been associated with an improvement in cholesterol and factors relating to cardiovascular health in these individuals.	Yes/no
MTHFR	Increase folate intake	People with a specific variation of this gene can benefit by increasing their intake of the vitamin folate. Increasing folate intake (present in green leafy vegetables) has been associated with an improvement in factors related to cardiovascular health in these individuals.	Yes/no

[1] Genetic information was provided to participants who were randomly assigned to level 3 and who received personalized advice on the basis of diet, phenotypic markers, and the genetic markers shown. *ApoE(e4)*, apolipoprotein E (e4); *FADS1*, fatty acid desaturase 1; *FTO*, fat mass and obesity associated; *MTHFR*, 5,10-methylenetetrahydrofolate reductase; *TCF7L2*, transcription factor 7 like 2.

extra weight an individual with a risk-conferring variant of *FTO* would be expected to carry (Supplemental Figures 1 and 2). Each personalized report (levels 1–3) contained a specific message that was related to body weight, which, for level 3 participants only, referred to *FTO*. For example, an AA/AT level 3 participant with increased BMI and WC would read "We recommend reducing your body weight and waist circumference to a healthy normal range because you have a genetic variation that can benefit by reducing these 2 obesity-related markers."

Data collection

Participants consented to self-report their measures via the Internet and to send biological samples (buccal swabs for DNA extraction) by postal service with the use of prepaid 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 a centralized training. Moreover, to enable participants to collect and report the required information and to collect, process, and dispatch the biological samples correctly, participants were given detailed instructions, and video demonstrations were available on the Food4Me website (www.food4me.org) in their own languages (26).

Ethical approval and participant consent

A total of 1607 participants were randomly assigned to the study and were recruited between August 2012 and August 2013 from the following centers: University College Dublin (Ireland), Maastricht University (Netherlands), University of Navarra (Spain), Harokopio University (Greece), University of Reading (United Kingdom), National Food and Nutrition Institute (Poland), and Technical University of Munich (Germany). The research ethics committee at each university or research center that delivered the intervention granted ethical approval for the study. All participants who expressed an interest in the study were asked to sign online consent forms at 2 stages in the screening process. The consent forms were automatically directed to the local study investigators to be countersigned and archived (26).

Anthropometric and lifestyle measures

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 wearing shoes and while wearing light clothing with the use of a home or commercial scale and to measure height (barefoot) with the use of a standardized measuring tape that was provided by the researchers. WC was measured at the midpoint between the lower rib and the iliac crest with the use of the provided tape (26). Central obesity was defined as WC >88 cm for women and >102 cm for men. BMI (in kg/m^2) was calculated from body weight and height. Adiposity status was defined with the use of WHO criteria for BMI (underweight: <18.5; normal weight: ≥ 18.5 to ≤ 24.9; overweight: ≥ 25.0 to ≤ 29.9; and obesity ≥ 30.0). Self-reported measurements were validated

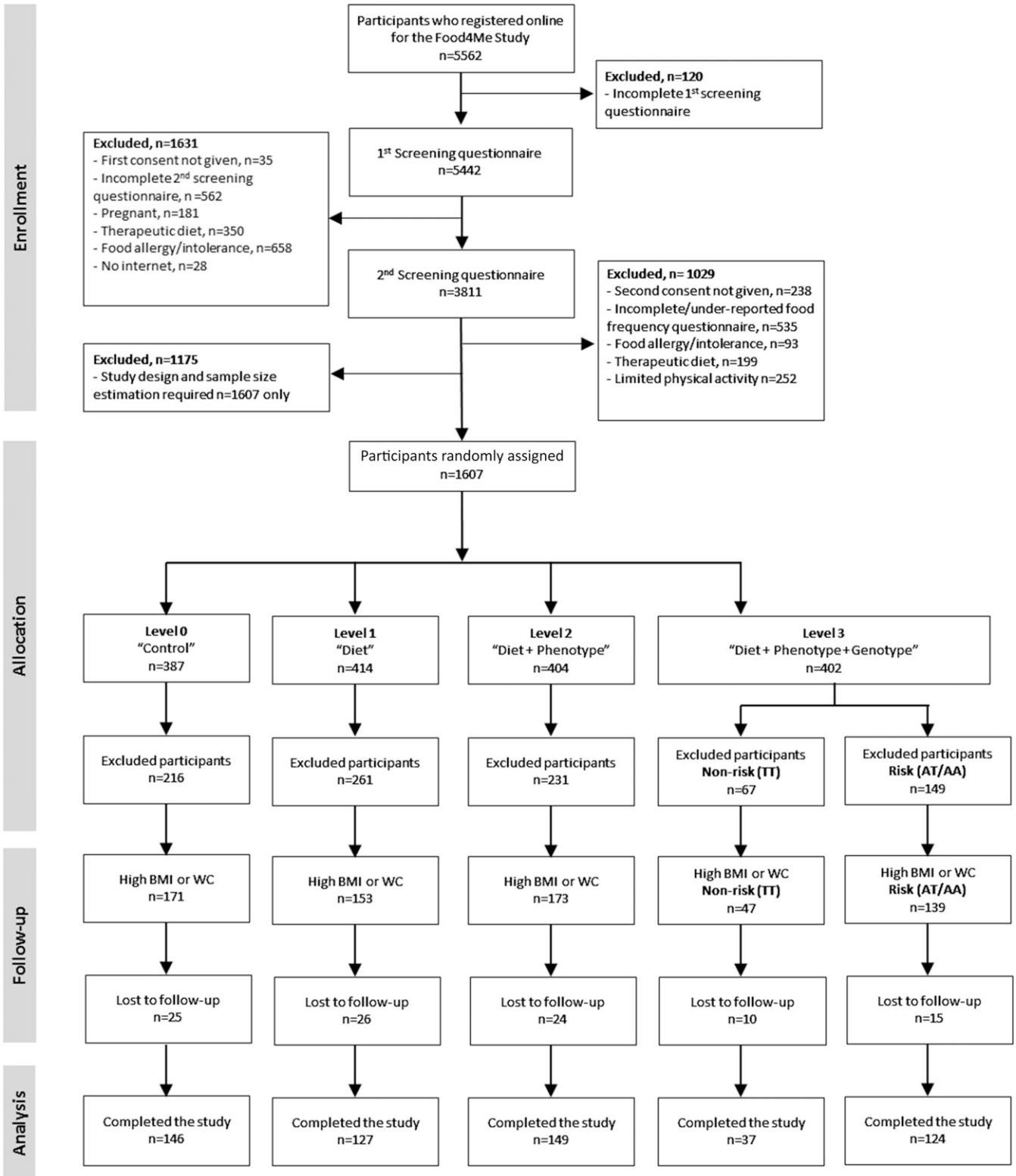

FIGURE 1 Consolidated Standards of Reporting Trials diagram. During the intervention, participants in level 0 received nonpersonalized advice, whereas participants in levels 1–3 received personalized advice. Participants in levels 1–3 with high BMI ($\geq$25 kg/m^2) or WC (>88 or 102 cm for women or men, respectively) at baseline were advised to reduce their body weight. For analyses, level 3 was stratified on the basis of the fat-mass and obesity-associated genotype (TT: nonrisk; and AT/AA: risk). WC, waist circumference.

in a subsample of the participants across 7 European countries and showed a high degree of reliability (26). The PA level, which was defined as the ratio between total energy expenditure and the predicted basal metabolic rate (28) and time spent sedentary (minutes per day) were estimated from triaxial accelerometers (TracmorD; Philips Consumer Lifestyle).

TABLE 2
Baseline characteristics of the Food4Me participants with high BMI or WC by intervention arm[1]

	Level				
	1 (control)	1 (diet)	2 (diet + phenotype)	3 [*FTO* nonrisk (TT)]	3 [*FTO* risk (AT/AA)]
BMI ≥25.0, total *n*	171	153	173	47	139
WC,[2] total *n*	84	82	96	27	71
Sex, F, (%)	53.8	49.0	47.4	48.9	54.6
Age, y	42.9 ± 12.2[3]	44.2 ± 11.4	43.9 ± 12.1	42.2 ± 13.3	43.7 ± 11.9
Anthropometric measures					
Weight, kg	85.1 ± 12.6	87.5 ± 15.0	87.3 ± 12.8	83.9 ± 12.4	86.1 ± 12.9
BMI, kg/m^2	29.0 ± 3.8	29.7 ± 4.5	29.8 ± 3.9	28.7 ± 3.1	29.4 ± 4.3
WC, cm	95.7 ± 11.1	96.0 ± 0.12	96.9 ± 11.6	94.2 ± 10.8	96.1 ± 11.0
Physical activity					
PAL[4]	1.69 ± 0.13	1.72 ± 0.16	1.70 ± 0.16	1.71 ± 0.13	1.69 ± 0.13
Sedentary time, min/d	761.9 ± 77.5	761.9 ± 73.9	761.0 ± 84.2	756.5 ± 74.7	767.7 ± 79.4

[1] Participants in level 0 received nonpersonalized advice. Participants in levels 1–3 received personalized advice on the basis of diet, diet + phenotype, or diet + phenotype + genotype, respectively. Baseline characteristics for all interventions arms include only participants with BMI (in kg/m^2) ≥25.0 or WC >88 and >102 cm for women and men, respectively. *FTO*, fat mass and obesity associated; PAL, physical activity level; WC, waist circumference.
[2] Defined as >88 or >102 cm for women and men, respectively.
[3] Mean ± SD (all such values).
[4] Ratio between total energy expenditure and the basal metabolic rate.

Genotyping

Participants collected buccal cell samples at baseline with the use of SK-1 DNA buccal swabs (Isohelix) and dried capsules (Isohelix) and posted samples to each recruiting center for shipment to LGC Genomics. LGC Genomics extracted the DNA and genotyped specific loci with the use of KASP genotyping assays (LGC limited) to provide biallelic scoring of *FTO* single nucleotide polymorphisms (SNPs) rs9939609 and rs1121980. These 2 SNPs showed a high linkage disequilibrium ($r^2 = 0.96$), and therefore, results for rs1121980 are not reported. No significant deviation from the Hardy-Weinberg equilibrium was observed for rs9939609 ($\chi^2 = 0.51$; $P = 0.48$).

Statistical analyses

In this analysis, we included participants with BMI ≥25.0 or with high WC (>88 or >102 cm for women or men, respectively) at baseline and for whom *FTO* genotype data were

TABLE 3
Changes in obesity-related markers at month 6 in risk and nonrisk carriers of the *FTO* genotype[1]

	FTO nonrisk (TT)	*FTO* risk (AT/AA)	*P*-difference in change between groups
Analysis of participants in levels 0–3[2]			
Weight, kg			
n	192	491	—
δ (95% CI)	−1.19 (−1.79, −0.59)	−2.10 (−2.49, −1.70)	0.023
WC, cm			
n	107	252	—
δ (95% CI)	−2.46 (−3.40, −1.51)	−3.85 (−4.49, −3.21)	0.016
Analysis restricted to participants in level 3[3]			
Weight, kg			
n	47	139	—
δ (95% CI)	−1.19 (−2.19, −0.19)	−2.28 (−3.06, −1.48)	0.037
WC, cm			
n	27	71	—
δ (95% CI)	−1.99 (−4.04, −0.05)	−4.34 (−5.63, −3.08)	0.048

[1] Models were adjusted for country, age, sex, and baseline outcome measures. The intervention arm was included as an additional covariate in the analysis. δ Values were calculated as month 6 minus baseline values. All δ (95% CI) changes between baseline and month 6 were significant at $P < 0.001$. *FTO*, fat mass and obesity associated; WC, waist circumference.
[2] Analyses pooled participants from all interventions groups (control and levels 1–3) who were advised to lose body weight or to reduce their WC irrespective of whether they were informed of their genetic risk.
[3] Analyses were restricted to participants who were randomly assigned to level 3, were informed of their *FTO* genotype (risk or nonrisk), and were advised to lose body weight or reduce their WC. Significant changes in the outcomes from baseline were tested with the use of multiple regression analysis. Differences in the outcome δ between risk and nonrisk carriers were tested with the use of a regression analysis.

available as well as were anthropometric measures at month 3 or 6. These individuals were advised to reduce their weights or WCs at baseline (levels 1–3) or would have been advised to do so (level 0) if they had not been in the control group.

Results from descriptive analyses are presented as means ± SDs for continuous variables or as percentages for categorical variables. All models were adjusted for baseline outcome values age, sex, and country. Multiple regression analyses were used to determine significant changes ($P < 0.05$) from baseline to month 3 and from baseline to month 6 for *FTO* risk (AA/AT) as well as for nonrisk carriers (TT). To answer our first research question (i.e., Does knowledge of the *FTO* genotype influence changes in body weight and WC in carriers and noncarriers of the *FTO* risk allele?), we compared level 3 risk and nonrisk carriers, for whom the *FTO* genotype was disclosed with the use of multiple regression analysis. Our secondary research question (i.e., Is *FTO*-based personalized advice more effective at reducing body weight and WC than are nonpersonalized guidelines or personalized advice on the basis of diet or diet and phenotype alone?), was tested with the use of multiple regression via a comparison of level 3 risk carriers (reference group) with changes observed in levels 0–2.

Multiple imputations according to conditional specification methods (29) were used to address missing data for body weight and WC. All statistical analyses were performed with the use of Stata software (version 14; StataCorp LP), and significance was set at $P < 0.05$.

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 in the **Supplemental Methods** and elsewhere (27). The first 1607 volunteers who met the inclusion criteria were recruited to the RCT and were randomly assigned to 1 of 4 intervention arms (**Figure 1**) (26). Only participants who were advised to reduce their body weight or WC at baseline (levels 1–3) or control subjects who would have been advised to do so if they had not been in level 0 were included ($n = 683$) (Figure 1). Baseline characteristics of these participants by intervention arm are shown in **Table 2**. In summary, 51% of participants were women, the mean age of subjects was 43.3 y (range: 18–73 y), and mean BMI was 29.3 (range: 25.0–61.7). After 3 and 6 mo, 10% and 14% of participants, respectively, who were randomly assigned to the intervention were lost to follow-up (Figure 1). However, intention-to-treat analyses were performed, and therefore, missing data for body weight and WC at months 3 and 6 were imputed as described in Methods.

Changes in adiposity marker in risk carriers and nonrisk carriers of the *FTO* genotype

For the overall cohort, irrespective of the intervention arm (analyses that included all participants from levels 0–3 are shown in **Table 3**), risk carriers of the *FTO* genotype (AT/AA: $n = 491$) achieved significantly ($P = 0.023$) greater weight reductions (−2.10 kg; 95% CI: −2.49, −1.70 kg) than did nonrisk carriers (TT: $n = 192$) (−1.19 kg; 95% CI: −1.79, −0.59 kg) at month 6. Similarly, significant differences ($P = 0.016$) were observed between the *FTO* genotype for WC (−3.85 compared with −2.46 cm in risk and nonrisk carriers, respectively). However, no significant differences in changes of either body weight or WC between carriers and noncarriers of the risk allele were observed at month 3 (**Supplemental Table 1**).

Effect of knowledge of *FTO* genotype on changes in obesity-related markers

These findings were restricted to participants who were randomly assigned to level 3 and received personalized advice to reduce their body weight or WC. At month 3, body weight and WC were reduced significantly for both risk and nonrisk carriers of the *FTO* gene in level 3 (**Supplemental Table 2**). However, there were no significant effects of the disclosure of *FTO* risk on changes in obesity-related markers at month 3 (Supplemental Table 2, **Supplemental Figure 3**). Furthermore, in level 3, compared with nonrisk carriers, nearly twice as many participants who carried the risk allele lost ≥5% of

TABLE 4
Percentages of participants who achieved a weight loss or WC reduction of 2.5%, 5%, and 10% by intervention arm at month 6[1]

	Level				
	1 (control)	1 (diet)	2 (diet + phenotype)	3 [*FTO* nonrisk (TT)]	3 [*FTO* risk (AT/AA)]
Weight, kg					
n	171	153	173	47	139
2.5–4.9%	20.5	20.4	15.4	21.6	21.7
5.0–9.9%	13.0	11.8	18.8	16.2	21.8
≥10%	4.8	8.7	4.0	0	5.6
WC, cm					
n	84	82	96	27	71
2.5–4.9%	20.0	16.7	24.2	13.5	16.3
5.0–9.9%	14.5	16.7	24.2	13.5	22.6
≥10%	6.2	9.5	6.8	2.7	8.1

[1] No formal comparisons between groups were made for results shown in the table. Analyses were restricted to participants who were advised to lose body weight or to reduce their WC. *FTO*, fat mass and obesity associated; WC, waist circumference.

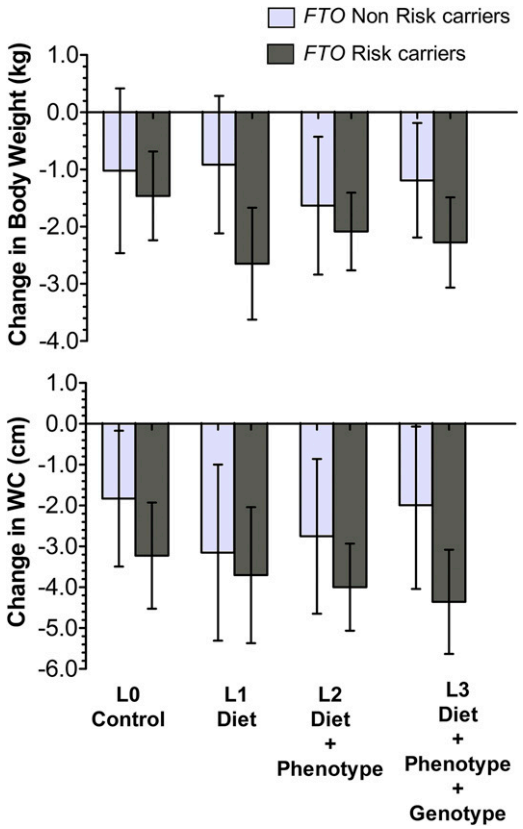

FIGURE 2 Mean δ (95% CIs) changes from baseline in obesity-related markers at month 6 by intervention arm and *FTO* genotype. Nonrisk and risk carriers across all intervention Ls reduced their waist circumference at month 6 compared with at month 0 ($P < 0.001$). Similar reductions were observed for body weight except for nonrisk carriers in L0 and L1. No significant interactions were observed between the intervention arm and *FTO* genotype for any of the outcomes. Analyses were adjusted for age, sex, country, and outcome values at baseline. The interaction between intervention arm and *FTO* genotype was tested with the use of regression analysis ($P = 0.641$ and $P = 0.523$ for body weight and WC, respectively). Participants who were included in the analysis were restricted to those who were advised to reduce their body weight or WC. Numbers of participants included for body weight of nonrisk and risk carriers were as follows: L0, $n = 46$ and 124, respectively; L1, $n = 50$ and 101, respectively; L2, $n = 48$ and 125, respectively; and L3, $n = 47$ and 139, respectively. Numbers for WC of nonrisk and risk carriers were as follows: L0, $n = 24$ and 59, respectively; L1, $n = 28$ and 54, respectively, L2, $n = 28$ and 68, respectively; and L3, $n = 27$ and 71, respectively. *FTO*, fat mass and obesity associated; L, level; WC, waist circumference.

body weight (7.6% and 14.2%, respectively) (Supplemental Table 2).

Similarly, body weight and WC were significantly reduced from baseline to month 6 in both risk and nonrisk carriers of the *FTO* risk allele who were randomly assigned to level 3 (Table 3). Moreover, significant differences were shown between level 3 risk and nonrisk carriers of the *FTO* gene for each of the obesity-related outcomes; reductions in body weight and WC were almost twice as large in risk carriers in level 3 (−2.28 kg and −4.34 cm, respectively) than in nonrisk carriers in level 3 (−1.19 kg and −1.99 cm, respectively) (Table 3). Furthermore, 16.2% of level 3 nonrisk carriers compared with 27.4% of risk carriers achieved a weight loss >5% at month 6. Similar results were observed for WC (**Table 4**). Although there was no significant interaction between the *FTO* genotype and intervention arm for body weight ($P = 0.641$) or WC ($P = 0.523$), greater reductions in obesity-related traits were observed in *FTO* risk carriers than in nonrisk carriers in levels 0–2 in which participants had no knowledge of their genotype (**Figure 2**).

Effects of *FTO*-based personalized advice on obesity-related markers compared with those of other forms of personalization

Significant reductions in WC were observed at month 3 in participants in level 0 (−1.67 cm), level 1 (−2.10 cm), and level 2 (−2.14 cm) who were not stratified by *FTO* genotype. However, these changes were lower than those observed for level 3 risk carriers (−3.47 cm). The WC reduction in level 3 risk carriers was significantly greater than that for participants in level 0 ($P = 0.015$), level 1 ($P = 0.039$), and level 2 ($P = 0.046$) who were not stratified by their *FTO* genotype. However, none of these findings remained significant after correction for multiple testing ($P < 0.01$). Participants in levels 0, 1, and 2 also showed significant reductions in weight (**Supplemental Table 3**). At month 6, there were significant reductions in body weight and WC for participants in all intervention groups (**Table 5**).

DISCUSSION

Main findings

The main findings of this study were as follows: *1*) both nonpersonalized and personalized forms of advice were effective at reducing body weight and WC after a 6-mo intervention, and *2*) compared with the control group, subjects in level 3 who were *FTO* risk carriers had significantly greater reductions in body weight (−1.34 compared with −2.28 kg, respectively; $P = 0.045$) and WC (−2.82 compared with −4.34 cm, respectively; $P = 0.046$). However, the magnitude of changes that were observed in level 1 and 2 participants who received non–genetic-based personalized advice for body weight (−2.08 and −1.96 kg, respectively) and WC (−3.51 and −3.63 cm, respectively) was similar to those observed in level 3 *FTO* risk carriers ($P > 0.05$).

Comparison with other studies

In the past decade, there has been growing interest in tailoring lifestyle interventions with the use of personal DNA information (30). It has been hypothesized that providing lifestyle advice on the basis of genetic information would motivate people to make behavioral changes that are favorable for disease prevention beyond what could be achieved with non–gene-based tailored programs. In a recent meta-analysis, Hollands et al. (31) reported no effect of the addition of DNA-based disease-risk estimates compared with that of a non–DNA-based approach for interventions that were aimed at smoking cessation (6 studies; $n = 2663$), improving diet (7 studies; $n = 1784$), and increasing PA (6 studies; $n = 1704$). The authors concluded that evidence to support gene-based interventions for a behavior change is lacking. Existing data have come from studies with predominantly high or unclear risk of bias and in which the evidence was typically of low quality. Therefore, larger and better-quality

TABLE 5
Changes in obesity-related markers at month 6 in participants in level 3 (*FTO* risk and nonrisk carriers) compared with in levels 0, 1, or 2 who did not receive genotype advice[1]

	Intervention arm, level					*P*			
	1 (control)	1 (diet)	2 (diet + phenotype)	3 [*FTO* nonrisk (TT)]	3 [*FTO* risk (AT/AA)]	Level 3 *FTO* risk compared with control	Level 3 *FTO* risk compared with level 1	Level 3 *FTO* risk compared with level 2
Weight, kg								
n	171	153	173	47	139	—	—	—
δ (95% CI)	−1.34 (−2.02, −0.66)	−2.08 (−2.83, −1.31)	−1.96 (−2.54, −1.37)	−1.19 (−2.19, −0.19)	−2.28 (−3.06, −1.48)	0.045	0.752	0.602
WC, cm								
n	84	82	96	27	71	—	—	—
δ (95% CI)	−2.82 (−3.86, −1.78)	−3.51 (−4.82, −2.21)	−3.63 (−4.54, −2.72)	−1.99 (−4.04, −0.05)	−4.34 (−5.63, −3.08)	0.046	0.290	0.361

[1] Models were adjusted for country, age, sex, and baseline outcome measures. δ Values were calculated as month 6 minus baseline values. Significant changes in the outcomes from baseline and differences within each level were tested with the use of multiple regression analysis. These analyses were restricted to participants in levels 0, 1 and 2 who were advised to lose body weight and/or to reduce their WC and who were not stratified by *FTO* genotype for comparison with participants in level 3 who were further stratified as *FTO* risk and nonrisk carriers. All δ (95% CI) changes between baseline and month 6 were significant at $P < 0.001$. *P* values were corrected for multiple testing, and significant differences were set as $P < 0.01$. *FTO*, fat mass and obesity associated; WC, waist circumference.

studies should be performed to elucidate the effect of personalized advice on the basis of genetic information (31).

The evidence in favor of gene-based lifestyle advice has been limited. Arkadianos et al. (32) reported that participants in a traditional weight-management diet group and participants who received a nutrigenetically tailored diet both lost similar amounts of weight at 100–300 d of follow-up. Thereafter, participants in the nutrigenetic group were significantly more likely to maintain their weight loss than were subjects in the control group. In contrast, there were no short-term (∼3-mo) or longer-term (∼1-y) changes in self-reported anxiety or exercise in generally healthy adults who received information from a commercial direct-to-consumer genome-wide risk test (33, 34). However, Bloss et al. (33) reported changes in fat intake for individuals who received increased obesity risk feedback (33). Frankwich et al. (35) observed no between-group differences in weight loss in a small study of American veterans who were randomly assigned either to a genetics-guided therapy group in which participants received one of 4 diets (a balanced, low-carbohydrate, low-fat, or Mediterranean diet) on the basis of their risk status for 7 obesity-related SNPs [*ApoA2*, Adiponectin, C1Q And Collagen Domain Containing (*ADIPOQ*), *FTO*, Potassium Channel Tetramerization Domain Containing 10 (*KCTD10*), Lipase C, Hepatic Type (*LIPC*), Methylmalonic Aciduria (Cobalamin Deficiency) CbIB Type (*MMAB*), and Peroxisome Proliferator Activated Receptor Gamma (*PPARG*)] or to a standard therapy group in which participants consumed a balanced diet. Furthermore, Meisel et al. (25) showed that healthy individuals who received feedback on their *FTO* status in the weight-control advice felt more prepared to control their weight, but this feedback had no greater effect on behavior than that of weight-control advice alone. Our results are in line with the studies that were previously outlined. We observed that the magnitude of weight and WC reductions was similar in all 3 groups who received personalized advice; the addition of gene-based advice did not seem to promote adiposity changes beyond what were achieved with the use of tailored feedback on the basis of diet or diet and phenotype alone.

Although differences in weight and WC reductions were almost twice as large in individuals who were informed of their risk of *FTO* than in subjects who were informed of their absence of *FTO*-related risk, there was no clear evidence that risk knowledge played a role. Surprisingly, *FTO* risk carriers, irrespective of their intervention group, had greater improvements in obesity-related markers than did nonrisk carriers. This was an unexpected and rather counterintuitive finding. All other factors being equal (same environment), individuals who are genetically (or epigenetically) predisposed to obesity would be expected to make greater efforts to counter this predisposition and to achieve a similar weight loss as other obese individuals would who are not genetically predisposed. Alternatively, the fact that carriers of the *FTO* risk allele were slightly heavier than were nonrisk carriers may have meant that the form group had a greater motivation to lose weight than did participants with no copies of the *FTO* risk variant who were lighter at baseline. For example, in a relatively small study of 51 obese or overweight US veterans, Frankwich et al. (35) observed that participants who had low-risk polymorphisms for obesity lost more weight than did all other participants at 8 wk and had significantly greater reductions in BMI and WC at 24 wk. However, these

findings are in disagreement with a recent meta-analysis that was conducted with the use of 9563 individual participant data from 8 RCTs (36). The study showed that the *FTO* genotype had no detectable effect on weight loss in overweight and obese adults in response to lifestyle- or drug-based intervention (36).

Strengths and limitations

To our knowledge, the Food4Me study is the largest Internet-based intervention on personalized nutrition to date. Innovative aspects of the Food4Me Study include the creation of algorithms for delivering tailored lifestyle advice on the basis of participant characteristics including behavioral, phenotypic, and genotypic information. Another strength of the study is the delivery of the intervention across 7 European countries via the Internet and the application of a remote system for data and biological sample collection. Our Internet-based platform was effective in retaining participants; 85% of subjects completed month 6 of follow-up, and there was >98% compliance with the DNA testing, which was high compared with that in previous web-based survey research (37) and web-based (34) or face-to-face (25) genetic-based interventions. In a study of direct-to-consumer genomic testing, Bloss et al. (33, 34) reported 44% and 63% dropouts at months 3 and 12, respectively. Moreover, the profile of subjects who were interested in participating in the Food4Me intervention study was similar to that of European adults (26), most of whom would benefit from an improved diet and more PA. Finally, we used multiple-imputation procedures to address missing data and, thus, maximized the amount of useful information that was available from 683 participants in the Food4Me study.

Our limitations include that we did not investigate how participants perceived the DNA-based feedback. Because the Food4Me study was an intervention that targeted multiple dietary and lifestyle behaviors, the impact of the genotypic results might have been diluted by the volume of other information provided. Moreover, the genetic feedback was only a positive reinforcement (i.e., participants with the higher-risk genotype benefited more by reducing their weight and WC). Greater risks of obesity and associated comorbidities were not stressed in the reports, and it is possible that the impact of such feedback would have been stronger. In addition, some of the analyses that were performed by intervention arm and *FTO* genotype in this investigation of secondary outcomes may not have had the statistical power to detect biologically or clinically relevant differences in adiposity. Larger studies are needed to corroborate these findings. Finally, height, weight, and WC were self-reported, but a concurrent validation study showed that the self-reported anthropometric measures were reliable (38).

In conclusion, there are larger reductions in body weight and WC in risk carriers of the *FTO* gene than in nonrisk carriers of the *FTO* gene. However, changes in these obesity-related traits are similar in all groups receiving personalized advice. The addition of genetic information to the tailored feedback does not enhance the effectiveness of the intervention compared with that achieved through personalization on the basis of diet or diet and phenotype alone. Our personalized Internet-based intervention is effective at recruiting and retaining participants. This intervention is promising as a scalable and sustainable route to improve behaviors with important public health benefits (11).

The authors' responsibilities were as follows—JCM: coordinated the Food4Me intervention study; HD, YM, IT, CAD, MJG, ERG, LB, JAL, JAM, WHMS, and JCM: contributed to the research design; CC-M, CFMM, SN-C, RS-C, RF, ALM, CO, CW, HF, SK, GM, AS, MCW, and JCM: conducted the intervention; CFMM, WHMS, and CC-M: contributed to the PA measurements; CC-M, CFMM, and KML: performed the statistical analyses for the manuscript; CC-M, CFMM, KML, WHMS, and JCM: drafted the manuscript; and all authors: contributed to a critical review of the manuscript during the writing process and read and approved the final version to be published. None of the authors reported a conflict of interest related to the study.

REFERENCES

1. OECD/EU. Health at a Glance: Europe 2016 – State of Health in the EU Cycle [Internet]. Paris; OECD Publishing [cited 2016 Dec 10]. Available from: http://dx.doi.org/10.1787/9789264265592-en.
2. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, Biryukov S, Abbafati C, Abera SF, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014;384:766–81.
3. WHO. Global health risk: mortality and burden of disease attributable to selected major risk. Geneva, Switzerland; World Health Organization. 2009.
4. Ezzati M, Riboli E. Behavioral and dietary risk factors for noncommunicable diseases. N Engl J Med 2013;369:954–64.
5. Ekelund U, Ward HA, Norat T, Luan J, May AM, Weiderpass E, Sharp SJ, Overvad K, Ostergaard JN, Tjonneland A, et al. Physical activity and all-cause mortality across levels of overall and abdominal adiposity in European men and women: the European Prospective Investigation into Cancer and Nutrition Study (EPIC). Am J Clin Nutr 2015;101:613–21.
6. Hurling R, Catt M, Boni MD, Fairley BW, Hurst T, Murray P, Richardson A, Sodhi JS. Using internet and mobile phone technology to deliver an automated physical activity program: randomized controlled trial. J Med Internet Res 2007;9:e7.
7. Alexander GL, McClure JB, Calvi JH, Divine GW, Stopponi MA, Rolnick SJ, Heimendinger J, Tolsma DD, Resnicow K, Campbell MK, et al. A randomized clinical trial evaluating online interventions to improve fruit and vegetable consumption. Am J Public Health 2010; 100:319–26.
8. Hansen AW, Gronbaek M, Helge JW, Severin M, Curtis T, Tolstrup JS. Effect of a web-based intervention to promote physical activity and improve health among physically inactive adults: a population-based randomized controlled trial. J Med Internet Res 2012;14:e145.
9. Livingstone KM, Celis-Morales C, Navas-Carretero S, San-Cristobal R, Macready AL, Fallaize R, Forster H, Woolhead C, O'Donovan CB, Marsaux CFM, et al. Effect of an internet-based, personalized nutrition randomized trial on dietary changes associated with the Mediterranean diet: the Food4Me Study. Am J Clin Nutr 2016; 104:288–97.
10. Celis-Morales C, Marsaux CFM, Livingstone KM, Navas-Carretero S, San-Cristobal R, O'Donovan CB, Forster H, Woolhead C, Fallaize R, Macready AL, et al. Physical activity attenuates the effect of the FTO genotype on obesity traits in European adults: the Food4Me study. Obesity (Silver Spring) 2016;24:962–9.
11. Celis-Morales C, Lara J, Mathers JC. Personalising nutritional guidance for more effective behaviour change. Proc Nutr Soc 2015; 74:130–8.
12. Hutchesson MJ, Rollo ME, Krukowski R, Ells L, Harvey J, Morgan PJ, Callister R, Plotnikoff R, Collins CE. eHealth interventions for the prevention and treatment of overweight and obesity in adults: a systematic review with meta-analysis. Obes Rev 2015;16:376–92.
13. Levine DM, Savarimuthu S, Squires A, Nicholson J, Jay M. Technology-assisted weight loss interventions in primary care: a systematic review. J Gen Intern Med 2015;30:107–17.
14. Celis-Morales C, Livingstone KM, Marsaux CFM, Macready AL, Fallaize R, O'Donovan CB, Woolhead C, Forster H, Walsh MC, Navas-Carretero S, et al. Effect of personalized nutrition on health-related behaviour change: evidence from the Food4me European randomized controlled trial. Int J Epidemiol 2016 Aug 14 (Epub ahead of print; DOI: 10.1093/ije/dyw186).

15. Collins FS, Varmus H. A new initiative on precision medicine. N Engl J Med 2015;372:793–5.
16. Marteau TM, Lerman C. Genetic risk and behavioural change. BMJ 2001;322:1056–9.
17. Marteau TM, French DP, Griffin SJ, Prevost AT, Sutton S, Watkinson C, Attwood S, Hollands GJ. Effects of communicating DNA-based disease risk estimates on risk-reducing behaviours. Cochrane Database Syst Rev 2010;10:CD007275.
18. Loos RJ, Bouchard C. FTO: the first gene contributing to common forms of human obesity. Obes Rev 2008;9:246–50.
19. Loos RJ, Yeo GS. The bigger picture of FTO: the first GWAS-identified obesity gene. Nat Rev Endocrinol 2014;10:51–61.
20. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, Powell C, Vedantam S, Buchkovich ML, Yang J, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature 2015;518:197–206.
21. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, Perry JR, Elliott KS, Lango H, Rayner NW, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 2007;316:889–94.
22. Kilpeläeinen TO, Qi L, Brage S, Sharp SJ, Sonestedt E, Demerath E, Ahmad T, Mora S, Kaakinen M, Sandholt CH, et al. Physical activity attenuates the influence of FTO variants on obesity risk: a meta-analysis of 218,166 adults and 19,268 children. PLoS Med 2011;8: e1001116.
23. Young AI, Wauthier F, Donnelly P. Multiple novel gene-by-environment interactions modify the effect of FTO variants on body mass index. Nat Commun 2016;7:12724.
24. Marsaux CFM, Celis-Morales C, Livingstone KM, Fallaize R, Kolossa S, Hallmann J, San-Cristobal R, Navas-Carretero S, O'Donovan CB, Woolhead C, et al. Changes in physical activity following a genetic-based internet-delivered personalized intervention: randomized controlled trial (Food4Me). J Med Internet Res 2016;18:e30.
25. Meisel SF, Beeken RJ, van Jaarsveld CH, Wardle J. Genetic susceptibility testing and readiness to control weight: results from a randomized controlled trial. Obesity (Silver Spring) 2015;23:305–12.
26. Celis-Morales C, Livingstone KM, Marsaux CF, Forster H, O'Donovan CB, Woolhead C, Macready AL, Fallaize R, Navas-Carretero S, San-Cristobal R, et al. Design and baseline characteristics of the Food4Me study: a web-based randomised controlled trial of personalised nutrition in seven European countries. Genes Nutr 2015; 10:450.
27. Livingstone KM, Celis-Morales C, Navas-Carretero S, San-Cristobal R, O'Donovan C, Forster H, Woolhead C, Marsaux CM, Macready A, Fallaize R, et al. Profile of European adults interested in internet-based personalised nutrition: the Food4Me study. Eur J Nutr 2016;55:756–69. Erratum in: Eur J Nutr 2016;55:1811–2.
28. Henry CJ. Basal metabolic rate studies in humans: measurement and development of new equations. Public Health Nutr 2005;8:1133–52.
29. Liu Y, De A. Multiple imputation by fully conditional specification for dealing with missing data in a large epidemiologic study. Int J Stat Med Res 2015;4:287–95.
30. Nielsen DE, El-Sohemy A. Applying genomics to nutrition and lifestyle modification. Per Med 2012;9:739–49.
31. Hollands GJ, French DP, Griffin SJ, Prevost AT, Sutton S, King S, Marteau TM. The impact of communicating genetic risks of disease on risk-reducing health behaviour: systematic review with meta-analysis. BMJ 2016;352.
32. Arkadianos I, Valdes AM, Marinos E, Florou A, Gill RD, Grimaldi KA. Improved weight management using genetic information to personalize a calorie controlled diet. Nutr J 2007;6:29.
33. Bloss CS, Schork NJ, Topol EJ. Effect of direct-to-consumer genomewide profiling to assess disease risk. N Engl J Med 2011;364: 524–34.
34. Bloss CS, Wineinger NE, Darst BF, Schork NJ, Topol EJ. Impact of direct-to-consumer genomic testing at long term follow-up. J Med Genet 2013;50:393–400.
35. Frankwich KA, Egnatios J, Kenyon ML, Rutledge TR, Liao PS, Gupta S, Herbst KL, Zarrinpar A. Differences in weight loss between persons on standard balanced vs nutrigenetic diets in a randomized controlled trial. Clin Gastroenterol Hepatol 2015;13:1625–32.e1; quiz e145–6.
36. Livingstone KM, Celis-Morales C, Papandonatos GD, Erar B, Florez JC, Jablonski KA, Razquin C, Marti A, Heianza Y, Huang T, et al. FTO genotype and weight loss: systematic review and meta-analysis of 9563 individual participant data from eight randomised controlled trials. BMJ 2016;354.
37. Yetter G, Capaccioli K. Differences in responses to web and paper surveys among school professionals. Behav Res Methods 2010;42: 266–72.
38. Celis-Morales C, Livingstone KM, Woolhead C, Forster H, O'Donovan CB, Macready AL, Fallaize R, Marsaux CFM, Tsirigoti L, Efstathopoulou E, et al. How reliable is internet-based self-reported identity, socio-demographic and obesity measures in European adults? Genes Nutr 2015;10:476.