Can genetic-based advice help you lose weight? Findings from the Food4Me European randomized controlled trial


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% Cl: −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 = 0.046).

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.

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.
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that were observed in other interventions groups who received
whether changes in obesity markers were different from those
ation on changes in obesity-related markers and to investigate
non–genotype-based personalized nutrition advice.

trition that was conducted across 7 European countries (Germany,

METHODS

Study design

Subjects were participants in the Food4Me proof-of-principle
study, which was a 6-mo web-based RCT on personalized nu-
trition that was conducted across 7 European countries (Germany;

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 per-
sonalized 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 infor-
mation (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 associ-
ated 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 disclo-
sure 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 in-
creased 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 infor-

19 Abbreviations used: FTO, fat mass and obesity associated; PA, physical
activity; RCT, randomized controlled trial; SNP, single nucleotide poly-
morphism; WC, waist circumference.
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.

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.

TCF7L2 Reduce 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.

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.

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.

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/m²) 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.
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

<table>
<thead>
<tr>
<th>Level</th>
<th>1 (control)</th>
<th>1 (diet)</th>
<th>2 (diet + phenotype)</th>
<th>3 [FTO nonrisk (TT)]</th>
<th>3 [FTO risk (AT/AA)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI ≥25.0, total n</td>
<td>171</td>
<td>153</td>
<td>173</td>
<td>47</td>
<td>139</td>
</tr>
<tr>
<td>WC, total n</td>
<td>84</td>
<td>82</td>
<td>96</td>
<td>27</td>
<td>71</td>
</tr>
<tr>
<td>Sex, F, (%)</td>
<td>53.8</td>
<td>49.0</td>
<td>47.4</td>
<td>48.9</td>
<td>54.6</td>
</tr>
<tr>
<td>Age, y</td>
<td>42.9 ± 12.2</td>
<td>44.2 ± 11.4</td>
<td>43.9 ± 12.1</td>
<td>42.2 ± 13.3</td>
<td>43.7 ± 11.9</td>
</tr>
<tr>
<td>Anthropometric measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>85.1 ± 12.6</td>
<td>87.5 ± 15.0</td>
<td>87.3 ± 12.8</td>
<td>83.9 ± 12.4</td>
<td>86.1 ± 12.9</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.0 ± 3.8</td>
<td>29.7 ± 4.5</td>
<td>29.8 ± 3.9</td>
<td>28.7 ± 3.1</td>
<td>29.4 ± 4.3</td>
</tr>
<tr>
<td>WC, cm</td>
<td>95.7 ± 11.1</td>
<td>96.0 ± 12.2</td>
<td>96.9 ± 11.6</td>
<td>94.2 ± 10.8</td>
<td>96.1 ± 11.0</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAL4</td>
<td>1.69 ± 0.13</td>
<td>1.72 ± 0.16</td>
<td>1.70 ± 0.16</td>
<td>1.71 ± 0.13</td>
<td>1.69 ± 0.13</td>
</tr>
<tr>
<td>Sedentary time, min/d</td>
<td>761.9 ± 77.5</td>
<td>761.9 ± 73.9</td>
<td>761.0 ± 84.2</td>
<td>756.5 ± 74.7</td>
<td>767.7 ± 79.4</td>
</tr>
</tbody>
</table>

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/m²) ≥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.

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

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

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 WC 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 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 2), 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 cm 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

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

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.
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).

**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 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.

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 studies are needed to confirm these findings.

Supplemental Table 2

<table>
<thead>
<tr>
<th>Intervention Arm</th>
<th>Nonrisk Carriers</th>
<th>Risk Carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>L0 Control</td>
<td>FTO</td>
<td>FTO</td>
</tr>
<tr>
<td>L1 Diet</td>
<td>FTO</td>
<td>FTO</td>
</tr>
<tr>
<td>L2 Diet + Phenotype</td>
<td>FTO</td>
<td>FTO</td>
</tr>
<tr>
<td>L3 Diet + Genotype</td>
<td>FTO</td>
<td>FTO</td>
</tr>
</tbody>
</table>

**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).

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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.  

<table>
<thead>
<tr>
<th>Intervention arm, level</th>
<th>1 (diet)</th>
<th>2 (diet &amp; phenotype)</th>
<th>3 (FTO risk, risk, nonrisk (TT))</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>171</td>
<td>173</td>
<td>139</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>84</td>
<td>82</td>
<td>96</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(82.8, 95.4)</td>
<td>(82.8, 95.4)</td>
<td>(94.8, 95.4)</td>
</tr>
<tr>
<td>WC, cm</td>
<td>3.51</td>
<td>2.21</td>
<td>2.21</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(3.28, 3.73)</td>
<td>(2.21, 3.73)</td>
<td>(2.21, 3.73)</td>
</tr>
</tbody>
</table>

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.

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-yr) 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, CIQ And Collagen Domain Containing (ADIPOQ), FTO, Potassium Channel Tetramerization Domain Containing 10 (KCTD10), Lipase C, Hepatic Type (LIPC), Methylmalonic Aciduria (Cobalamin Deficiency) CblB 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 studies should be performed to elucidate the effect of personalized advice on the basis of genetic information (31).
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.

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