FTO genotype and weight loss in diet and lifestyle interventions: a systematic review and meta-analysis

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ABSTRACT

Background: Studies have suggested that the fat mass and obesity–associated (FTO) genotype is associated with individual variability in weight loss in response to diet/lifestyle interventions, but results are inconsistent.

Objective: We aimed to provide a summary of the literature evaluating the relation between the FTO genotype and weight loss in response to diet/lifestyle interventions.

Design: A search of English-language articles in the PubMed and Embase databases (through 30 April 2015) was performed. Eligible studies were diet/lifestyle weight-loss intervention studies conducted in adults that reported changes in body weight or body mass index (BMI) by the FTO variant rs9939609 (or its proxy). Differences in weight loss between FTO genotypes across studies were pooled with the use of fixed-effect models.

Results: A meta-analysis of 10 studies (comprising 6915 participants) that reported the results of additive genetic models showed that individuals with the FTO TA genotype and AA genotype (those with the obesity-predisposing A allele) had 0.18-kg (95% CI: −0.09, 0.45-kg; \( P = 0.19 \)) and 0.44-kg (95% CI: 0.09, 0.79-kg; \( P = 0.015 \)) greater weight loss, respectively, than those with the TT genotype. A meta-analysis of 14 studies (comprising 7700 participants) that reported the results of dominant genetic models indicated a 0.20-kg (95% CI: −0.43, 0.04-kg) greater weight loss in the TA/AA genotype than in the TT genotype (\( P = 0.10 \)). In addition, differences in weight loss between the AA genotype and TT genotype were significant in studies with a diet intervention only, adjustment for baseline BMI or body weight, and several other subgroups. However, the relatively small number of studies limited these stratified analyses, and there was no statistically significant difference between subgroups.

Conclusions: This meta-analysis suggests that individuals carrying the homozygous FTO obesity-predisposing allele may lose more weight through diet/lifestyle interventions than noncarriers. Our data provide evidence for genetic variability in response to diet/lifestyle interventions on weight loss, although clinical applications of these findings need further investigations.

Keywords: FTO genotype, lifestyle intervention, weight loss, meta-analysis, diet

INTRODUCTION

Obesity and its comorbidity have become major public health problems throughout the world (1). It is well established that diet/lifestyle interventions can achieve weight loss (2). However, individual variability in response to interventions has long been noted in weight-loss trials (3, 4). Besides behavioral and psychological characteristics, genetic factors may explain why diet/lifestyle interventions are more effective for some individuals than for others (2, 5). Thus, a better understanding of the modification effects of genetic variation on weight loss in response to diet/lifestyle interventions may help to develop more effective strategies for weight loss, such as individualized interventions based on one’s genetic background (5, 6).

With the advent of genome-wide association studies, many genetic loci have been identified as associated with obesity and related traits (7). Given its strong effect on obesity and possible biological function in regulating energy balance (8), there is great interest in the fat mass and obesity–associated (FTO) gene. Recent large-scale analyses found that the obesity-risk allele (A allele) of the FTO variant is associated with increased food intake (9, 10), and previous studies also reported that the FTO obesity-risk allele was associated with a reduced response in hunger and satiety after the meal in adults and children (11, 12). A number of studies have examined whether diet/lifestyle–induced weight loss differs between the FTO genotype groups (13–21). However, results from these previous studies remain contradictory, and discrepancies might be due to small sample size, moderate genetic effect, types of interventions, variation in study duration, and other characteristics. Therefore, to increase statistical power and achieve a more precise estimation...
of effects, we conducted a systematic review and meta-analysis of randomized weight-loss trials in adults to provide a summary of the literature evaluating the relation between FTO genotype and weight loss in response to diet/lifestyle interventions.

METHODS

Literature search

This meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) and MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines (22, 23). We searched the PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and Embase (http://www.embase.com) databases through 30 April 2015 for diet/lifestyle intervention studies examining the relation between FTO genotype and weight loss in adults.

Two search themes are specified. The first theme identified relevant terms for FTO, and combined exploded versions of the MeSH terms “fat mass and obesity–associated genes” and “FTO.” The second theme identified relevant terms for weight and BMI, and combined exploded versions of the MeSH terms “body weight” and “body mass index.” Two search terms were combined with the use of the Boolean operator “and.” Additional articles were identified from reference lists of selected studies. Our search strategy included terms for BMI because some of these studies also report change in BMI. Details regarding search terms are shown in Supplemental Table 1.

Study selection

Articles were included if they met the following criteria: 1) they were diet/lifestyle weight-loss intervention studies; 2) they were conducted in adults aged ≥18 y; 3) they did not involve medication interventions; 4) they reported changes in body weight or BMI by FTO genotypes; 5) they included peer-reviewed publications with sufficient information for the analysis; and 6) they were in the English language. Two investigators independently screened all of the studies by title or abstract and then by a full-text review. Discrepancies of screening results between the 2 investigators were solved by discussing with a senior investigator.

Data extraction

We extracted the following information from each identified article: basic information from studies (authors, publication year, study duration, number of participants, and FTO variant and its minor allele frequency), demographics of participants (mean age, sex ratio, mean BMI, race, and ethnicity), intervention methods, analysis strategy (statistical models, with covariates included in the models), and mean weight changes and their corresponding SDs. SDs were calculated with the use of SEs or 95% CIs when necessary. For articles with missing SDs for measurement of change (20, 24–26), change-from-baseline SDs were imputed by using the correlation coefficient method presented in the Cochrane Handbook for Systematic Reviews of Interventions (27). We used a correlation coefficient of 0.9 between baseline and follow-up weight because the correlation between body weights at the 2 time points was assumed to be very high. One study presented the results (mean weight changes) in a figure (24), and we extracted the estimates carefully from the given figure. For studies with an initial weight-loss phase followed by a weight-maintenance phase (16, 17, 24), we used data on long-term weight loss. For studies that reported results of weight change without exactable data (14, 28, 29), we contacted the first or corresponding authors to request detailed data; 2 authors replied with the requested data (14, 28). We also contacted the authors of the studies that only reported data in dominant genetic models and requested data on additive genetic models (13, 15, 25, 26), although none of them replied to our request. Thus, we did not include these 4 studies in our primary meta-analysis of studies reporting data in additive genetic models.

Data synthesis and statistical analysis

The difference in weight loss (in kg) between the FTO genotype groups in response to diet/lifestyle interventions was designated as our principal effect. In this meta-analysis, each selected study was considered to be a single study unit, and mean weight loss by the FTO genotype groups in the overall sample, regardless of intervention differences, was taken into account. For studies that reported weight loss for intervention groups separately (15, 18, 27), we combined the results of different groups with the use of the combining method recommended by the Cochrane Handbook for Systematic Reviews of Interventions (30). We used the same method to combine results of the FTO TA and AA genotype groups for studies that provided results of additive genetic models (16–21, 24, 31). All of the data synthesis was conducted after the data collecting and data requesting process.

A heterogeneity test was conducted with the use of 2 different methods, the Cochran’s Q test and the $I^2$ statistic (32, 33). A $P$ value <0.1 and $I^2 >50\%$ were defined to indicate statistically significant heterogeneity in meta-analysis, in accordance with the Cochrane Handbook for Systematic Reviews of Interventions. Because no significant heterogeneity was detected in our analysis, results were presented in the fixed-effect model. In addition, the possibility of publication bias was evaluated by using a Begg’s test and funnel plots (34, 35). Moreover, stratified analyses were performed to evaluate the influence of study characteristics on results. STATA software (version 12.0) was used to perform the meta-analysis.

RESULTS

Results of literature search

A total of 1248 unique citations were identified by our search strategy (792 from PubMed and 1039 from Embase, with 583 duplicates), of which 42 were accepted for full text review after screening by titles and abstracts. From the remaining 42 articles, we excluded papers with results stratified by genotypes other than FTO ($n = 2$) (36, 37), conference abstracts ($n = 11$) (38–48), studies in children ($n = 8$) (49–56), those that did not have weight or BMI change as the main outcome ($n = 3$) (57–59), those with data not available ($n = 1$) (29), and studies that were not in the English language ($n = 1$) (60). Ultimately, 14 articles were eligible and included in our meta-analysis (13–21, 24–26, 28, 31). A detailed screening flow is shown in Figure 1. Of the 14 selected articles, 10 reported the results of an additive genetic
model (TA compared with TT, AA compared with TT) (6, 7, 11, 12, 16–21), whereas the other 4 articles reported the results of a dominant genetic model (TA/AA compared with TT) (13, 15, 25, 26), which was mainly the result of limited sample size in these 4 studies. Given the known additive genetic effect of FTO variant on BMI and obesity risk, our primary analyses focused on the 10 studies that reported additive genetic model results.

Study characteristics
The primary characteristics of the 14 studies included in our meta-analysis are shown in Table 1. Overall, 7700 participants were included in this meta-analysis, with 33.1% (n = 2547) having the TT genotype (reference group). The sample size varied from 75 to 3756 in the 14 studies. Nine studies were conducted in European countries, 3 studies were conducted in the United States, 1 study was conducted in Brazil, and 1 study was conducted in Japan. The age of participants ranged from 18 to 80 y, and the mean baseline BMI (in kg/m²) of each study ranged from 28.5 to 41.8. Three studies recruited female participants exclusively (20, 24, 31), and the remaining 11 studies recruited both sexes. Thirteen studies investigated the FTO single-nucleotide polymorphism rs9939609, and one study examined a perfect proxy single-nucleotide polymorphism (rs8050136; $r^2 = 1$) (20).

The intervention methods were diverse. Diet modification was used in 12 trials (13–19, 21, 24–26, 28), and 4 of them combined interventions on diet with physical activity (14, 25, 26, 28). One study only used physical activity modulation (20), and the other study involved only nutritional education to encourage people to consume a balanced and healthy diet (31). The interventions varied in length from 3 mo to 4 y, with a median duration of 9 mo.

In 9 studies, changes in body weight were calculated from multivariable-adjusted models (14, 17–21, 24, 28, 31). One study explicitly mentioned that the model was unadjusted (25). For the other 4 studies (13, 15, 16, 18), no information was provided regarding the statistical adjustment.

FTO genotype and weight loss
We first conducted a meta-analysis of 10 studies (including 6951 subjects) with data from additive genetic models to compare weight loss across the FTO genotype groups. Greater weight loss induced by diet/lifestyle interventions was observed in the FTO TA genotype [$-0.18$ kg (95% CI: $-0.45$, 0.09 kg); $P = 0.19$; NS] and AA genotype [$-0.44$ kg (95% CI: $-0.09$, $-0.79$ kg); $P = 0.015$] groups than in the TT genotype group (Q Qi, unpublished data, 2014) (Figure 2). No heterogeneity was observed in either comparison (AA compared with TT: $I^2 = 0.0$%; TA compared with TT: $I^2 = 0.0$%).

When carrying out a meta-analysis of 14 studies that reported dominant genetic model results as a secondary analysis, a tendency for greater weight loss was observed in the TA/AA genotype with TT genotype groups [$-0.20$ kg (95% CI: $-0.43$, 0.04 kg), $P = 0.10$; $I^2 = 0.0$%] (Supplemental Figure 1).
<table>
<thead>
<tr>
<th>Study first author and year (ref)</th>
<th>Enrollment or completers, n</th>
<th>Country or region</th>
<th>Age, y</th>
<th>Male, %</th>
<th>BMI, kg/m²</th>
<th>Intervention</th>
<th>Energy restricted</th>
<th>Duration</th>
<th>FTO SNP</th>
<th>MAF</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curti 2013 (26)²</td>
<td>134Brazil</td>
<td>56.6 (18–80)³</td>
<td>34</td>
<td>30.4 (NA)</td>
<td>Diet and exercise</td>
<td>Yes</td>
<td>9 mo</td>
<td>rs9939609</td>
<td>0.42</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>de Luis 2012 (15)²</td>
<td>305Spain</td>
<td>43.5 (NA)</td>
<td>26</td>
<td>36.6 (&gt;30)</td>
<td>Diet and exercise</td>
<td>Yes</td>
<td>3 mo</td>
<td>rs9939609</td>
<td>0.44</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>de Luis 2013 (13)²</td>
<td>106Spain</td>
<td>49.5 (NA)</td>
<td>34</td>
<td>34.8 (&gt;30)</td>
<td>Low-fat hypocaloric diet</td>
<td>Yes</td>
<td>3 mo</td>
<td>rs9939609</td>
<td>0.45</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Grau 2009 (18)</td>
<td>618Europe</td>
<td>NA (20–50)</td>
<td>25</td>
<td>35.5 (≥30)</td>
<td>Two low-energy diets with either low or high fat content</td>
<td>Yes</td>
<td>2 y</td>
<td>rs9939609</td>
<td>0.40</td>
<td>Age, sex, baseline weight, fat-free mass, fat mass, WC, fat oxidation</td>
<td></td>
</tr>
<tr>
<td>Haupt 2008 (25)²</td>
<td>204Germany</td>
<td>45.9 (NA)</td>
<td>40</td>
<td>29.1 (&gt;27)</td>
<td>Diet and exercise</td>
<td>Yes</td>
<td>9 mo</td>
<td>rs8050136</td>
<td>NA</td>
<td>Unadjusted</td>
<td></td>
</tr>
<tr>
<td>Lappalainen 2009 (28)</td>
<td>412Finland</td>
<td>55.3 (40–56)</td>
<td>33</td>
<td>31.2 (≥25)</td>
<td>Diet and exercise</td>
<td>Yes</td>
<td>4 y</td>
<td>rs9939609</td>
<td>0.42</td>
<td>Age, sex, baseline BMI</td>
<td></td>
</tr>
<tr>
<td>Matsuo 2012 (31)</td>
<td>204Japan</td>
<td>51.9 (24–66)</td>
<td>0</td>
<td>28.5 (≥25)</td>
<td>Dietary lectures</td>
<td>No</td>
<td>14 wk</td>
<td>rs9939609</td>
<td>0.26</td>
<td>Age, menstrual status, baseline values</td>
<td></td>
</tr>
<tr>
<td>McCaffery 2013 (14)</td>
<td>3756United States</td>
<td>59.0 (45–76)</td>
<td>44</td>
<td>36.2 (≥25)</td>
<td>Diet and exercise</td>
<td>Yes</td>
<td>1 y</td>
<td>rs9939609</td>
<td>0.49</td>
<td>Age, sex, study site, ancestry informative markers</td>
<td></td>
</tr>
<tr>
<td>Mitchell 2010 (20)</td>
<td>234United States</td>
<td>58.1 (45–75)</td>
<td>0</td>
<td>31.6 (25–43)</td>
<td>Three groups of different exercise intensity</td>
<td>No</td>
<td>6 mo</td>
<td>rs8050136</td>
<td>0.43</td>
<td>Exercise assignment</td>
<td></td>
</tr>
<tr>
<td>Rauhio 2013 (24)</td>
<td>75Finland</td>
<td>39.6 (25–45)</td>
<td>0</td>
<td>34.0 (&gt;30)</td>
<td>Very low-energy diet followed by weight maintenance</td>
<td>Yes</td>
<td>1 y</td>
<td>rs9939609</td>
<td>0.45</td>
<td>Age, sex</td>
<td></td>
</tr>
<tr>
<td>Razquin 2010 (19)</td>
<td>776Spain</td>
<td>67.8 (55–80)</td>
<td>45</td>
<td>29.2 (NA)</td>
<td>Two Mediterranean diets and one conventional low-fat diet</td>
<td>Yes</td>
<td>3 y</td>
<td>rs9939609</td>
<td>0.45</td>
<td>Age, sex, baseline BMI, diabetes status</td>
<td></td>
</tr>
<tr>
<td>Verhoeof 2014 (17)</td>
<td>148Netherlands</td>
<td>NA (20–50)</td>
<td>35</td>
<td>32 (27–38)</td>
<td>Very low-energy diet followed by weight maintenance</td>
<td>Yes</td>
<td>5 mo</td>
<td>rs9939609</td>
<td>0.39</td>
<td>Age, sex, baseline weight, short-term weight loss</td>
<td></td>
</tr>
<tr>
<td>Woehning 2013 (16)</td>
<td>125Germany</td>
<td>44.6 (18–72)</td>
<td>33</td>
<td>41.8 (≥30)</td>
<td>Very low-energy diet followed by weight maintenance</td>
<td>Yes</td>
<td>52 wk</td>
<td>rs9939609</td>
<td>0.48</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Zhang 2012 (21)</td>
<td>603United States</td>
<td>51 (30–70)</td>
<td>40</td>
<td>33 (25–40)</td>
<td>Four low-energy diets with different compositions of macronutrients</td>
<td>Yes</td>
<td>2 y</td>
<td>rs1558902</td>
<td>0.40</td>
<td>Age, sex, race, baseline BMI, intervention group</td>
<td></td>
</tr>
</tbody>
</table>

¹FTO, fat mass and obesity–associated; MAF, minor allele frequency; NA, not available; ref, reference; SNP, single-nucleotide polymorphism; WC, waist circumference.
²Not included in the primary meta-analysis of studies that reported results of additive genetic models because they reported only results of dominant genetic models.
³Mean; range in parentheses (all such values).
Stratified analysis

Because studies included in the meta-analysis varied in intervention methods and many other characteristics, we then performed subgroup analyses to investigate the influences of study characteristics on pooled results. Studies were classified according to age (mean age <50 or ≥50 y), sex (mixed or women only), BMI (mean baseline BMI <35 or ≥35), baseline adjustments (adjusted for baseline BMI or body weight, or not adjusted for baseline BMI or body weight), regions in which studies were conducted (America, Europe, or Asia), methods of intervention (diet only or other interventions), and study duration (<1 y or ≥1 y).

A total of 10 studies with 6951 participants were included in the stratified analyses. No statistically significant difference between subgroups was observed for any of these stratified analyses (Table 2), although some significant results were observed in several subgroups. Specifically, a significantly greater weight change was observed in those with the AA genotype (−0.40 kg [95% CI: −0.79, −0.01 kg]; P = 0.04) and AA genotype (−0.72 kg [95% CI: −1.21, −0.23 kg]; P = 0.004) than in those with the TT genotype group in studies that used diet intervention only (all energy-restricted). In studies with adjustment for baseline BMI or body weight, we also found significantly greater weight loss in the AA genotype group than in the TT genotype group (−0.70 kg [95% CI: −1.16, −0.23 kg]; P = 0.003). In addition, significantly greater weight change was observed in the AA genotype group than in the TT genotype group in studies with participants who were ≥50 y old (−0.44 kg [95% CI: −1.12, −0.28 kg]; P = 0.003), those with participants who had a baseline mean BMI <35 (−0.70 kg [95% CI: −1.16, −0.23 kg]; P = 0.003), studies with men and women combined (mixed) (−0.46 kg [95% CI: −0.83, 0.10 kg]; P = 0.013), and studies conducted in Europe (−0.42 kg [95% CI: −0.79, −0.05 kg], P = 0.026).

Sensitivity analysis

We conducted a sensitivity analysis in the 10 primary studies by excluding one study at a time to examine the individual effect of each study on the overall results. The estimates (differences in weight loss) comparing the FTO AA and TT genotypes ranged from −0.66 kg to −0.27 kg, with the biggest influence coming from the study by McCaffery et al. (14) (Supplemental Figure 2). The results became even more significant after the exclusion of this study [AA compared with TT, −0.66 kg (95% CI: −1.10, −0.21 kg); P = 0.004]. In addition, we repeated the meta-analysis by excluding studies without reporting SDs for measurements of weight change, and the results were similar [TA compared with TT: −0.19 kg (95% CI: −0.46, 0.08 kg); P = 0.19]. AA compared with TT: −0.44 kg (95% CI: −0.80, −0.08 kg); P = 0.016].

Publication bias

On the basis of funnel plots (Supplemental Figure 3) and Egger’s tests, no significant publication bias was observed in this meta-analysis (TA compared with TT: P = 0.78; AA compared with TT: P = 0.75).

DISCUSSION

In this meta-analysis of weight-loss trials, we found that individuals carrying the homozygous FTO obesity-predisposing allele (AA genotype) had greater weight loss than did non-carriers (TT genotype) after diet/lifestyle interventions. Furthermore, differences in weight loss between the FTO AA and TT genotype groups became more significant in several subgroups stratified by various study and participant characteristics.

To the best of our knowledge, no previous meta-analysis has been conducted to investigate the effect of the FTO variant on...
Table 2: Stratified analysis of FTO genotype and weight-loss according to study characteristics

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Mean age</th>
<th>Duration</th>
<th>Intervention</th>
<th>Sex</th>
<th>Region</th>
<th>Adjusted for baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sample size, n</td>
<td>966</td>
<td>4</td>
<td>-0.21 (-0.73, 0.31)</td>
<td>0.0</td>
<td>-0.42 (-1.12, 0.28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5985</td>
<td>6</td>
<td>-0.17 (-0.48, 0.15)</td>
<td>0.0</td>
<td>-0.44 (-0.85, -0.04)</td>
</tr>
<tr>
<td>Mean BMI at baseline</td>
<td>&lt;35</td>
<td>2452</td>
<td>7</td>
<td>-0.25 (-0.64, 0.14)</td>
<td>0.0</td>
<td>-0.79 (-1.33, -0.26)</td>
</tr>
<tr>
<td></td>
<td>≥35</td>
<td>4499</td>
<td>3</td>
<td>-0.11 (-0.48, 0.26)</td>
<td>0.0</td>
<td>-0.17 (-0.63, 0.30)</td>
</tr>
<tr>
<td>Duration</td>
<td>&lt;1 y</td>
<td>1204</td>
<td>4</td>
<td>-0.07 (-0.49, 0.35)</td>
<td>0.0</td>
<td>-0.53 (-1.18, 0.12)</td>
</tr>
<tr>
<td></td>
<td>≥1 y</td>
<td>5747</td>
<td>6</td>
<td>-0.25 (-0.60, 0.09)</td>
<td>0.0</td>
<td>-0.40 (-0.82, 0.02)</td>
</tr>
<tr>
<td>Diet intervention only</td>
<td>2345</td>
<td>6</td>
<td>-0.40 (-0.79, -0.01)</td>
<td>0.0</td>
<td>-0.72 (-1.21, -0.23)</td>
<td>0.0</td>
</tr>
<tr>
<td>Other</td>
<td>4606</td>
<td>4</td>
<td>0.02 (-0.35, 0.39)</td>
<td>0.0</td>
<td>-0.15 (-0.65, 0.49)</td>
<td>0.0</td>
</tr>
<tr>
<td>Sex</td>
<td>Mixed</td>
<td>6438</td>
<td>7</td>
<td>-0.24 (-0.53, 0.05)</td>
<td>0.0</td>
<td>-0.46 (-0.83, -0.10)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>513</td>
<td>3</td>
<td>0.17 (-0.52, 0.86)</td>
<td>0.0</td>
<td>-0.09 (-1.48, 1.30)</td>
</tr>
<tr>
<td></td>
<td>America</td>
<td>4593</td>
<td>3</td>
<td>-0.07 (-0.51, 0.37)</td>
<td>0.0</td>
<td>-0.22 (-0.75, 0.32)</td>
</tr>
<tr>
<td></td>
<td>Europe</td>
<td>2154</td>
<td>6</td>
<td>-0.34 (-0.72, 0.03)</td>
<td>0.0</td>
<td>-0.66 (-1.14, -0.18)</td>
</tr>
<tr>
<td></td>
<td>Asia</td>
<td>204</td>
<td>20</td>
<td>-0.60 (-1.00, NA)</td>
<td>0.0</td>
<td>0.30 (-0.79, -0.09)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>2761</td>
<td>6</td>
<td>-0.26 (-0.60, 0.08)</td>
<td>0.0</td>
<td>-0.70 (-1.16, -0.23)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>4190</td>
<td>4</td>
<td>-0.04 (-0.51, 0.43)</td>
<td>0.0</td>
<td>-0.09 (-0.63, 0.46)</td>
</tr>
</tbody>
</table>

1 Differences in weight loss after intervention between FTO genotypes across studies were pooled with the use of fixed-effect models. The heterogeneity between studies for each group was tested by $I^2$. P values between groups were tested with the use of Cochran’s Q test. FTO, fat mass and obesity–associated; NA, not available; WMD, weighted mean difference.

2 Includes studies with exercise interventions, both exercise and diet interventions, or nutritional education.

weight loss in response to diet/lifestyle interventions. All previous meta-analyses were based on observational studies investigating interrelations between FTO variant, diet/lifestyle factors, and obesity. For example, a large meta-analysis suggested that greater physical activity attenuates the association of FTO genotype and obesity in adults (61). Moreover, our prior meta-analysis indicated that the obesity-predisposing allele of FTO is associated with higher total energy intake in adults and higher protein intake in children (9, 10), although whether there is an interaction between FTO genotype and dietary intake on obesity remains controversial. In the current meta-analysis, we examined the FTO genetic effect on weight loss in randomized intervention trials, which provided more reliable evidence because the study conditions were prescribed and the confounding effects were maximally reduced. Taken together, these findings support the interactive roles of the FTO gene and diet/lifestyle factors in the regulation of body weight.

It is not surprising that the observed difference in weight loss between the FTO genotype groups is modest, which is consistent with the modest effect of the FTO variant on BMI ($\sim 0.35$ allele) (61). In addition, although the result was not significant when comparing the TA and TT genotype groups, the trend of weight loss increased across the 3 genotype groups, which is in line with the additivity of the FTO genetic effect. Admittedly, the observed difference in weight loss between the FTO genotype groups may not translate into a clinically important benefit; however, the true effect might be underestimated because of heterogeneity of intervention modality. For example, the effect size is greater with diet interventions [$-0.72$ kg (95% CI: $-1.21, -0.22$ kg)] than with other interventions [$-0.15$ kg (95% CI: $-0.65, -0.49$ kg)], although there is no statistically significant difference between subgroups, which might be due to the limited number of studies and participants in this stratified analysis. Thus, more studies are needed to examine whether intervention modality may influence the FTO genetic effect on weight loss, and the clinical relevance of our findings needs further investigations.

It is interesting that the homozygous FTO obesity-predisposing genotype is associated with greater weight loss induced by diet/lifestyle interventions. Several other previous studies also reported that individuals carrying risk alleles exhibited greater improvement of respective traits than did noncarriers after diet interventions (62–65). One may argue that this may reflect baseline weight difference for different genotypes: heavier people (the risk allele carriers) tend to lose more weight. However, the significant FTO genotype effect on weight loss was observed in the meta-analysis of 6 studies with adjustment for baseline BMI or body weight [$-0.70$ kg (95% CI: $-1.16, -0.23$ kg)] between the TA and TT genotypes, and there was no significant difference between groups with and without adjustment for baseline BMI or body weight. In addition, it is possible that individuals carrying the FTO obesity genotype may have attempted more frequently to lose body weight and are therefore more successful in weight loss, at least in the short term.
However, in the long term, their genetic predisposition to obesity could result in a cycle of weight loss and regain. This might explain a previously reported association between the FTO genotype and variation in BMI (66). Nevertheless, further studies are needed to investigate whether the observed genetic influence on diet/lifestyle–induced weight loss could be maintained in the long term.

The mechanisms underlying our findings are unknown but might be related to the potential role of FTO in regulating energy homeostasis. FTO expression in the hypothalamus is regulated by feeding, fasting, and energy restriction (67–73). Both animal and human studies support the association between FTO and food intake (9, 10, 74), and FTO also has been linked to habitual apetite behaviors (11, 12) and appetite-related hormones (ghrelin and leptin) (75, 76). Moreover, a recent study reported that the obesity-predisposing allele of the FTO variant was associated with a reduction in food cravings and appetite during an intervention with hypocaloric weight-loss diets (44). Consistently, our subgroup analysis also indicates a stronger effect of FTO on weight loss in response to energy-restricted diet interventions than with other interventions. In addition, it should be noted that the FTO variants may affect the functions of other genes rather than the FTO itself. A recent study reported that the FTO obesity-associated variants are associated with expression of the homeobox gene Iroquois-class homeobox protein 2 (IRX3) (77).

Several limitations of this meta-analysis should be acknowledged. First, we were unable to include 4 studies (13, 15, 25, 26) in our primary analysis because of difficulty in obtaining additive genetic model results. However, a secondary meta-analysis of 14 studies based on the dominant genetic model showed similar but nonsignificant results. Second, studies included in our meta-analysis varied in intervention methods and duration, sample size, study setting, race/ethnicity, and other participant characteristics, although there was no significant heterogeneity in results across individual studies or subgroups. We had a limited sample size in the stratified analyses, and more studies are needed. Third, we examined the FTO genetic effect on weight loss regardless of the various diets and other interventions applied in the individual trials, although some specific FTO–diet intervention interactions have been reported (19, 21). However, there are insufficient numbers of published studies with a similar design for the meta-analysis. Moreover, we only included papers published in the English language, and may have missed some eligible studies published in other languages.

In conclusion, this study provides some evidence from a meta-analysis that weight loss varies between the FTO genotypes in response to diet/lifestyle interventions. Our findings provide some support for considering genetic variability in response to diet/lifestyle interventions in the development of more effective strategies for weight loss. Nevertheless, more studies are needed to explore which types of diet/lifestyle interventions most powerfully facilitate the FTO genetic effect on weight loss.

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