Fat mass- and obesity-associated genotype, dietary intakes and anthropometric measures in European adults: the Food4Me study

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Abstract

The interplay between the fat mass- and obesity-associated (FTO) gene variants and diet has been implicated in the development of obesity. The aim of the present analysis was to investigate associations between FTO genotype, dietary intakes and anthropometrics among European adults. Participants in the Food4Me randomised controlled trial were genotyped for FTO genotype (rs9939609) and their dietary intakes, and diet quality scores (Healthy Eating Index and PREDIMED-based Mediterranean diet score) were estimated from FFQ. Relationships between FTO genotype, diet and anthropometrics (weight, waist circumference (WC) and BMI) were evaluated at baseline. European adults with the FTO risk genotype had greater WC (AA v. TT: +1.4 cm; P = 0.003) and BMI (+0.9 kg/m²; P = 0.001) than individuals with no risk alleles. Subjects with the lowest fried food consumption. However, there was no evidence of interactions between FTO genotype and dietary intakes on BMI and WC, and thus further research is required to confirm or refute these findings.

Key words: Fat mass- and obesity-associated gene: BMI: Fried foods: Dietary intakes

Over the past 30 years, 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 multifactorial condition that is influenced by the complex interplay between diet, physical activity (PA) and genetics(3,4). Recent genome-wide association studies in nearly 400 000 individuals have identified SNP in genes, including the fat mass- and obesity-associated gene (FTO), which are strongly associated with the development of obesity(5–7). A study of 38 759 individuals revealed that those homozygous for the FTO (rs9939609) risk allele weighed on average 3 kg more and had 1.7-fold increased odds of being obese compared with those homozygous for the lower-risk allele(8).
The association between $FTO$ and obesity has been attributed to higher energy intake\(^{(8,9)}\), although findings are equivocal\(^{(10)}\). Furthermore, obese individuals may consume higher amounts of energy-dense foods such as fried foods\(^{(11)}\). The obesogenic influence of $FTO$ may be exacerbated by higher energy and fat intakes\(^{(12,13)}\), although there is little information on links between $FTO$ genotype and total dietary intake, or dietary patterns\(^{(14)}\).

Interactions between obesity-susceptibility genes, intakes of fried foods and sugar-sweetened beverages and measures of adiposity have been reported among US adults\(^{(15,16)}\). Qi et al.\(^{(15)}\) found that BMI increased by 1·1 (se 0·2), 1·6 (se 0·5) and 2·2 (se 0·6) kg/m\(^2\) per ten obesity-related risk alleles with increasing frequency of fried food consumption (less than once, one to three times and four or more times a week, respectively; $P_{\text{linear}} < 0·001$). Furthermore, Qi et al.\(^{(16)}\) reported an interaction between sugar-sweetened beverage intake and genetic predisposition to obesity ($P_{\text{interaction}} < 0·001$). It is also evident that healthier eating patterns – for example, the PREDIMED-based Mediterranean diet (MD) score – may modulate the effect of $FTO$ genotype on adiposity\(^{(17)}\). However, few studies have investigated relationships between $FTO$ genotype, dietary intakes and adiposity in European adults.

The present study investigated the associations of $FTO$ genotype and BMI and waist circumference (WC) with dietary intakes and potential interactions between $FTO$ genotype, dietary intake and adiposity (BMI and WC) in adults participating in the pan-European Food4Me randomised controlled trial (RCT)\(^{(18)}\).

### Methods

#### Study population

The Food4Me proof of principle study was a 6-month, pan-European, RCT including 1607 adults\(^{(18,19)}\). Participants were recruited between August 2012 and August 2013 across seven European recruitment sites: University College Dublin (Ireland); Maastricht University (The Netherlands); University of Navarra (Spain); Harokopio University (Greece); University of Reading (UK); National Food and Nutrition Institute (Poland); and Technical University of Munich (Germany).

#### Dietary intakes

Habitual dietary intake was quantified using an online FFQ and food habits questionnaire, developed and validated for this study\(^{(20,21)}\). The Food4Me FFQ included 157 food items consumed frequently in each of the seven recruitment countries. Intakes of foods and nutrients were computed in real time using a food composition database based on \textit{McCance and Widdowson’s The Composition of Foods}\(^{(22)}\). A ‘fried foods’ category was created by summing the following foods: chips, spring rolls, fried processed chicken or poultry, fried fish in batter and fish fingers/fish cakes. Additional information on fried food consumption was obtained from a questionnaire on dietary habits\(^{(20)}\), which asked how often participants consumed fried food in the past month, with the following options: ‘never’, ‘1–3 times/month’, ‘once a week’, ‘2–4 times/week’, ‘5–6 times/week’ or ‘once a day’. Responses to this question were aggregated into three categories: low = ‘never’ and ‘1–3 times/month’; medium = ‘once a week’ and ‘2–4 times/week’; and high = ‘5–6 times/week’ and ‘once a day’. Participants responded to questions on dietary habits including salt use (i.e. how often do you add salt while cooking? and how often do you add salt at the table?) and fat consumption (i.e. what do you do with visible fat on meat?). Both questions relating to salt were scored on a five-point scale ranging from ‘never’ to ‘always’, which was aggregated to a three-point scale (low = ‘never’ and ‘rarely’, medium = ‘sometimes’, high = ‘usually’ and ‘always’). For fat consumption, respondents could select whether they ate most, some or as little as possible of visible fat on meat or that they did not eat meat, and these responses were aggregated to produce three groups: high = ‘ate most or some of the fat’, medium = ‘ate as little as possible’ or low = ‘did not eat meat’. Categories were also created for ‘sweets and snacks’ and ‘sugar-sweetened beverages’.

‘Sweets and snacks’ included sweet biscuits, cakes, flanpucks, muesli bars, buns, muffins, pastries, waffles, pancakes, crépes, fruit pies, tarts, crumbles, sponge and milk puddings, ice cream, sorbets and jellies, chocolate and chocolate snack bars, sweets, sugar added to tea/coffee/cereal and crisps. ‘Sugar-sweetened beverages’ were restricted to fizzy soft drinks and did not include low-energy content or diet options. A Healthy Eating Index (HEI) was estimated according to the consumption of total and whole fruits, total vegetables, greens and beans, whole grains, dairy products, protein and fatty acids\(^{(23)}\). The MD score was estimated based on an adaptation of the PREDIMED fourteen-point criteria. In brief, participants scored 1 if they met one of the following criteria and 0 if they did not: higher intake of olive oil than other culinary fat and of white meat than red meat, high intake of fruits (including natural fruit juice) and vegetables, legumes, nuts, fish, wine and \textit{sofrito} and a limited intake of red and processed meats, fats and spreads, soft drinks and commercial bakery goods, sweets and pastries\(^{(24)}\). Scores were summed and ranged between 0 and 14\(^{(25)}\). Details of the MD scoring system are provided in online Supplementary Table S1.

#### Assessment of anthropometric and lifestyle measures

Body weight (kg), height (m) and WC (cm) were self-measured and self-reported. Participants were provided with information sheets and online video instructions in their own language on how to complete the measurements. BMI (kg/m\(^2\)) was calculated using measures of body weight and height. Self-reported measurements were validated in a sub-sample of the participants across seven European countries and showed a high degree of reliability\(^{(26)}\). Physical activity level (PAL) and time spent sedentary (min/d) were estimated from triaxial accelerometers (TracmorD; Philips Consumer Lifestyle). Participants self-reported their current smoking status.

#### Genotyping

Participants collected buccal cell samples at baseline using Isolelix SK-1 DNA buccal swabs and Isolelix dried capsules and posted the samples to each recruiting centre for shipment to LGC Genomics. LGC Genomics extracted DNA and genotyped specific loci using KASP\(^{TM}\) genotyping assays to provide
bi-allelic scoring of FTO SNP – rs9939609 and rs1121980. These two SNP showed a high linkage disequilibrium ($\chi^2$ 0.96), and therefore results for rs1121980 are not reported. No significant deviation from the Hardy–Weinberg equilibrium was observed for rs9939609 (0.51; $P=0.48$).

**Ethical approval and participant consent**

This study was conducted according to the guidelines laid down in the 1964 Declaration of Helsinki, and all procedures involving human subjects were approved by the Research Ethics Committees at each University or Research Centre delivering the intervention. All participants who expressed an interest in the study were asked to sign online consent forms at two stages in the screening process. These consent forms were automatically directed to the local study investigators to be counter-signed and archived (18). The Food4Me trial was registered as a RCT (NCT01530159) at Clinicaltrials.gov.

**Statistical analysis**

Data were analysed using Stata (version 13; StataCorp LP). Only baseline data were used for the present analyses. Results from descriptive analyses are presented as means and standard deviations for continuous variables or as percentages for categorical variables. Multinomial logistic regression was used to test for significant differences across categorical variables and multiple linear regression was used for continuous variables. Multiple linear regression analyses were used to test for associations ($P_{\text{trend}}$) between anthropometric measures (BMI and WC) and FTO genotype, stratified according to tertiles of dietary intakes or dietary scores, with the exception of sugar-sweetened beverages, which was a dichotomous variable due to high numbers of non-consumers ($n$ 899). Interactions between categories of dietary intakes and FTO genotype on BMI and WC were investigated by including an interaction term in the model. Analyses were adjusted for age, sex, country, PAL and smoking (smokers, non-smokers). Results were deemed significant at $P<0.05$. Sensitivity analyses were used to test the effects of specific foods within the fried food category (chips, pizza and spring rolls; fried processed chicken and poultry; and fried fish in batter and fish products). Sensitivity analyses also excluded participants who reported energy intake lower than BMR x 1.1 (27), where BMR was calculated using Oxford equations (20), and energy intakes $>18828$ kJ/d ($>4500$ kcal/d) (29). Adjustment for total energy intake (EI) was included in the sensitivity analyses when investigating the relationship between foods, FTO genotype and interactions with BMI and WC. In addition, continuous variables for dietary intakes and anthropometrics were used to test for interactions between dietary intakes and FTO genotype.

**Results**

**Participant characteristics**

Of the 1607 individuals randomised into the Food4Me RCT, data at baseline on FTO genotype, anthropometry and dietary intake were available for 1277 participants. As summarised in Table 1, 30% of individuals were overweight and 16% were obese. In addition, 22% of males and 22% of females had WC above healthy limits (>102 and >88 cm, respectively). Each additional copy of FTO risk allele was associated with an increase in weight, WC and BMI ($P_{\text{trend}}=0.005$, 0.003 and 0.001, respectively). Furthermore, the percentage of participants who were overweight or obese was higher in carriers of the FTO risk allele (TF: 29 vs. AA: 33%; $P=0.036$ and 13 vs. 18-4%; $P=0.019$, respectively) than non-carriers. There were no significant differences in sex distribution, age, PA, smoking prevalence and EI:BMR ratio between FTO genotypes (Table 1).

**Dietary intake and FTO genotype**

No significant differences in total energy and macronutrient intakes were detected between FTO genotypes (Table 2). However, individuals with two risk alleles for FTO consumed more high-fat dairy products ($P=0.001$) and fewer crisps ($P=0.043$) than individuals with no FTO risk alleles. No other significant differences were observed (data not shown). Individuals with no copies of the FTO risk allele added salt less frequently while cooking ($P=0.052$) than those with two copies of the risk allele. MD and HEI scores did not differ between FTO genotypes. The relationships between dietary intake and BMI are presented in the online Supplementary Tables 2 and 3.

**Dietary intakes, FTO genotype and anthropometrics**

On the basis of FFQ responses, individuals with the lowest fried food consumption (first tertile) and two copies of the FTO risk variant had on average 1.4 kg/m² greater BMI ($P_{\text{trend}}=0.028$) and 3.1 cm greater WC ($P_{\text{trend}}=0.045$) compared with individuals with no copies of the risk allele with the lowest fried food consumption. Similarly, individuals with medium fried food consumption (second tertile) and two copies of the FTO risk variant had on average 1.2 kg/m² greater BMI ($P_{\text{trend}}=0.036$) compared with individuals with no copies of the risk allele with the lowest fried food consumption. No significant relationships were identified in individuals with the highest fried food consumption. WC did not differ between genotypes in medium or highest fried food consumers and no significant interactions were observed (Fig. 1). These results were consistent when fried food consumption was estimated from the food habits questionnaire: participants who rarely consumed fried foods and had two copies of the risk allele had 1.3 kg/m² higher BMI compared with those with no risk alleles ($P_{\text{trend}}=0.008$). Similarly, participants who frequently consumed fried foods and had two copies of the risk allele had 5.2 kg/m² higher BMI compared with those with no risk alleles ($P_{\text{trend}}=0.027$). No significant interactions were observed. BMI was higher in individuals with two copies of the FTO risk genotype and lowest sugar-sweetened beverage consumption (lowest consumption; AA v. TF: +1.4 kg/m²; $P_{\text{trend}}=0.003$) and highest sweet and snack consumption (highest consumption; AA v. TF: +1.7 kg/m²; $P_{\text{trend}}=0.009$) compared with individuals with no copies of the FTO risk genotype. BMI was higher in individuals with two copies of the FTO risk genotype and moderate and...
Table 1. Demographic characteristics of participants by fat mass- and obesity-associated (FTO) risk allele* (Mean values and standard deviations; percentages)

<table>
<thead>
<tr>
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<th>FTO_rs9939609</th>
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<tbody>
<tr>
<td></td>
<td>TT</td>
</tr>
<tr>
<td><strong>Total (n)</strong></td>
<td>Mean</td>
</tr>
<tr>
<td><strong>Sex – female (%)</strong></td>
<td>58.0</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>40.4</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>74.8</td>
</tr>
<tr>
<td><strong>Waist circumference (cm)</strong></td>
<td>85.8</td>
</tr>
<tr>
<td><strong>Central adiposity (%)</strong></td>
<td>23.3</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>25.5</td>
</tr>
<tr>
<td><strong>Normal weight (%)</strong></td>
<td>52.7</td>
</tr>
<tr>
<td><strong>Overweight (%)</strong></td>
<td>30.4</td>
</tr>
<tr>
<td><strong>Obese (%)</strong></td>
<td>16.8</td>
</tr>
</tbody>
</table>

PAL, physical activity level (ratio between total energy expenditure:BMR).
* Multinomial logistic regression and multiple linear regression were used to test for significant differences across categorical and continuous variables, respectively; P values were adjusted for age, sex, country and smoking habits. Analyses were also adjusted for BMI with the exception of weight, waist circumference and BMI.

Table 2. Dietary intakes of participants by fat mass- and obesity-associated (FTO) risk allele (Mean values and standard deviations)

<table>
<thead>
<tr>
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<th>FTO_rs9939609</th>
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<tbody>
<tr>
<td></td>
<td>TT</td>
</tr>
<tr>
<td><strong>Total (n)</strong></td>
<td>Mean</td>
</tr>
<tr>
<td><strong>Macronutrient intake</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total energy intake (kJ)</strong></td>
<td>10 594</td>
</tr>
<tr>
<td><strong>Fat (% energy)</strong></td>
<td>36.1</td>
</tr>
<tr>
<td><strong>SFA (% energy)</strong></td>
<td>14.2</td>
</tr>
<tr>
<td><strong>Trans-fat (% energy)</strong></td>
<td>0.5</td>
</tr>
<tr>
<td><strong>MUFA (% energy)</strong></td>
<td>13.8</td>
</tr>
<tr>
<td><strong>PUFA (% energy)</strong></td>
<td>5.8</td>
</tr>
<tr>
<td><strong>n-3 Fatty acids (% energy)</strong></td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Carbohydrates (% energy)</strong></td>
<td>45.9</td>
</tr>
<tr>
<td><strong>Sugar (% energy)</strong></td>
<td>21.1</td>
</tr>
<tr>
<td><strong>Protein (% energy)</strong></td>
<td>16.9</td>
</tr>
<tr>
<td><strong>Alcohol (% energy)</strong></td>
<td>3.5</td>
</tr>
<tr>
<td><strong>Salt (g/d)</strong></td>
<td>7.3</td>
</tr>
<tr>
<td><strong>Contribution from sweets and snacks</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total energy</strong></td>
<td>15.3</td>
</tr>
<tr>
<td><strong>% Energy from fat</strong></td>
<td>18.5</td>
</tr>
<tr>
<td><strong>% Energy from SFA</strong></td>
<td>20.9</td>
</tr>
<tr>
<td><strong>% Energy from sugars</strong></td>
<td>24.7</td>
</tr>
</tbody>
</table>

* Multiple linear regressions were used to test for significant differences across genotypes. Analyses were adjusted for age, sex, physical activity, BMI, country and smoking status.
beverages (risk genotype (Fig. 2). With the exception of sugar-sweetened foods and intake from sugar (P = 0.045) compared with individuals with no copies of the risk allele and with the lowest fried food consumption. However, with the exception of sugar-sweetened beverages, we did not detect any significant interactions between dietary intakes and FTO genotype on BMI or WC. This is the first time that these relationships between genotype, diet and adiposity have been investigated in a pan-European population, and the link between ‘unhealthy’ dietary intakes and higher BMI in subjects with the risk alleles for FTO genotype warrants further investigation. Thus, further studies are required to confirm or to refute these observations.

### Discussion

#### Main findings

Our main finding is that individuals with the FTO risk genotype and the highest intakes of sugar, fat and sweet and snacks had the highest BMI. Furthermore, subjects with the lowest fried food consumption and two copies of the FTO risk variant had on average 1.4 kg/m² greater BMI (P_{trend} = 0.028) and 5.1 cm greater WC (P = 0.045) compared with individuals with no copies of the risk allele and with the lowest fried food consumption. However, with the exception of sugar-sweetened beverages, we did not detect any significant interactions between dietary intakes and FTO genotype on BMI or WC. This is the first time that these relationships between genotype, diet and adiposity have been investigated in a pan-European population, and the link between ‘unhealthy’ dietary intakes and higher BMI in subjects with the risk alleles for FTO genotype warrants further investigation. Thus, further studies are required to confirm or to refute these observations.

#### Comparison with other studies

Our findings support the link between obesity and fried food consumption(11, 30). A recent study in a US cohort reported that individuals with high genetic risk of obesity and high fried food consumption had 2.4 kg/m² higher BMI than individuals with low genetic risk and low fried food intake (P_{interaction} = 0.005)(15). These findings were replicated in two further cohorts with similar results(15). Although the diet–gene interaction was not significant, when only the highest fried food consumers were considered, we demonstrated that European adults at higher genetic risk of obesity had 1.3 kg/m² higher BMI than individuals without the risk allele. Furthermore, with the exception of fried foods and sugar-sweetened beverages, we observed that BMI was significantly higher in the ‘unhealthiest’ tertile of dietary intake or dietary score. This suggests that the presence of the FTO risk allele may only increase BMI in individuals with the poorest diets.

Although we identified a significant interaction between sugar-sweetened beverages and genetic predisposition to obesity, this was the only significant interaction and may be a chance finding(16). Importantly, our cohort of European adults was smaller (1280) compared with the Nurse’s Health Study (9623), Health Professionals Follow-up Study (6379) and the Women’s Genome Health Study (21 421), which may have impact on our ability to detect significant interactions(15, 16). Furthermore, we did not detect any significant differences in macronutrient intakes or levels of PA between FTO genotypes, despite finding significant differences in BMI, WC and weight. Nonetheless, as investigated in a recent systematic review and

### Sensitivity analyses

No significant interactions between specific sub-groups of fried foods and FTO genotype on anthropometric outcomes were observed. In addition, there were no significant interactions between FTO genotype and dietary intakes on BMI or WC when dietary intakes were included as continuous variables. Exclusion of energy misreporters did not change the pattern of the results. Adjustment for EI when investigating the relationship of food intakes with FTO genotype, as well as any interactions with BMI or WC, did not change the pattern of results (data not shown).
meta-analysis, the role of EI in the relationship between FTO and BMI remains unclear\(^\text{10}\) and other measures of PA, such as whether participants met PA recommendations, may have been more informative but were not the focus of the present analysis.

Although there have been a number of investigations of interactions between macronutrients intake, genotype and anthropometric measures, Qi et al.\(^\text{15}\) were one of the first to evaluate relationships between specific food groups, genetic risk and adiposity. Some diet–gene interactions have been supported by findings from RCT\(^\text{31–34}\); however, few large-scale studies have identified any significant interaction between macronutrient intake and FTO genotype on BMI\(^\text{12,35–40}\).

A recent meta-analysis did not detect any interactions between protein intake and genetic predisposition to obesity on BMI, WC or waist:hip ratio\(^\text{41}\). In contrast, a very recent study reported a significant interaction between genetic risk score (based on sixteen obesity-related SNP) and intakes of energy, protein, total fat, SFA, PUFA and carbohydrate on BMI, body fat mass and WC\(^\text{13}\). The inconsistency of current evidence for interactions between macronutrients, FTO and adiposity, as well as the limited research into effects of specific food groups, highlights the need for further research in this area.

Our results support the need for personalising nutritional advice based on the rationale that diet and lifestyle behaviour...
responses will be bigger when individuals are given more accurate and relevant diagnostic feedback\(^\text{[12]}\). Focusing on health risks in the provision of lifestyle-based recommendations may facilitate long-term improvements in diet and PA\(^\text{[4,15,16]}\).

**Potential mechanisms**

Little is known about the mechanisms through which the FTO allele enhances obesity risk\(^\text{[6,43]}\), although recent evidence suggests that manipulation of a pathway for adipocyte thermogenesis regulation may play an important role\(^\text{[34,45]}\). In addition, there is little mechanistic explanation for the reported interaction between specific dietary components, FTO genotype and adiposity\(^\text{[15]}\). Intake of specific foods may be a marker for a less healthy diet and lifestyle\(^\text{[11]}\), and thus apparent relationships may not be causal.

The unhealthy food groups chosen for the present analyses were typically energy-dense foods, with limited nutritional value, low in fibre and with low satiety index\(^\text{[40]}\) but were highly palatable\(^\text{[47]}\). It has been speculated that the more attractive organoleptic properties generating through the frying process may drive associations between fried foods and increased risk of obesity\(^\text{[11]}\). These attributes may encourage higher ad libitum energy intake, and thereby mediate their effects on obesity. Nonetheless, our analyses were adjusted for EI, suggesting that the mechanism of action on adiposity goes beyond higher energy intake alone. To understand the mechanism(s) driving sustained surplus energy intake, it will be important to investigate simultaneous effects on energy expenditure.

**Strengths and limitations**

Strengths of our study include the relatively large number of European adults (1280), broadly representative of the seven countries in the Food4Me study in terms of diet and PA levels. We assessed dietary intakes using a semi-quantitative FFQ, enabling a more detailed appraisal of food groups and individual foods. Furthermore, we included an analysis of overall dietary healthfulness based on the MD score and on the HEI, which improved the richness of our dietary data. In addition, we evaluated the effect of diet-genie interactions on two measures of adiposity, BMI and WC, which have different interpretations and links with health outcomes. A limitation of our study was that it was not powered to detect diet–gene interactions. In contrast, Qi et al.\(^\text{[15]}\) included a much larger sample size of \(n = 37\ 423\), which is likely to have contributed to the statistically significant interactions observed. In addition, we investigated the effect of only one obesity-related gene, although FTO is the gene with the largest association with adiposity, and the study would have been stronger if we had been able to use a risk score based on multiple gene variants\(^\text{[48]}\). Although Qi et al.\(^\text{[15]}\) studied effects of thirty-two SNP, the authors concluded that FTO was primarily responsible for the genetic associations observed. All FFQ-derived food intake data are subject to dietary misreporting\(^\text{[49]}\), although we did not identify any differences in dietary misreporting between FTO genotypes. As a sensitivity analysis, effects of over- and under-reporting of dietary intakes were minimised by excluding individuals with implausible energy intakes, and this exclusion did not alter the findings. Finally, anthropometric measures were self-measured and self-reported, which may introduce measurement errors. However, a validation study embedded within the Food4Me study demonstrated a high degree of correlation between self-reported and measured anthropometric variables (interclass correlation coefficients: height 0.990; weight 0.994; and BMI 0.983)\(^\text{[20]}\).

**Conclusions**

The present study has demonstrated that high consumption of some, but not all, unhealthy foods and the presence of poor dietary patterns in individuals with the FTO risk genotype are associated with greater BMI compared with individuals with no risk alleles. However, there was limited evidence of interactions between FTO genotype and dietary intakes on BMI. Research in larger cohorts is required to confirm or to refute these findings, and RCT will be needed to ascertain whether any associations are causal.

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**Supplementary material**

For supplementary material/s referred to in this article, please visit http://dx.doi.org/10.1017/S0007114515004675

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