Nutrition, Metabolism & Cardiovascular Diseases (2019) **29**, 474–480

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Evaluating the interaction of common FTO genetic variants, added sugar, and trans-fatty acid intakes in altering obesity phenotypes

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Received 26 August 2018; received in revised form 21 November 2018; accepted 14 January 2019
Handling Editor: A. Siani
Available online 1 February 2019

KEYWORDS
Trans-fatty acids;
Added sugar;
FTO polymorphisms;
Obesity;
Interaction

Abstract *Background and aims:* The results of studies on the effect of trans-fatty acids (TFAs) and added sugars on obesity are not consistent. This study aimed to investigate whether the association of changes in general and central obesity with added sugar and TFA intakes is modified by common fat mass and obesity-associated gene (FTO) polymorphisms, in isolation or in a combined-form genetic risk score (GRS).

Methods and results: Subjects of this cohort study were selected from among adult participants of the Tehran Lipid and Glucose Study (n = 4292, 43.2% male). Dietary data were collected using a valid and reliable food frequency questionnaire. The genotypes of selected polymorphisms (rs1421085, rs1121980, and rs8050136) were determined. Genetic risk score (GRS) was calculated using the dominant weighted method.

The mean age of participants was 42.6 ± 14 and 40.4 ± 13 years in men and women, respectively. FTO rs8050136 polymorphisms and TFAs have a significant interaction in changing body mass index (BMI) (P interaction = 0.01). There were no changes in waist circumference (WC) and BMI among FTO risk allele carriers, across quartiles of added sugar intake. GRS and TFA intakes significantly interacted in altering the BMI and WC; thus, a higher intake of TFAs was associated with higher changes of BMI and WC in subjects with high GRS (P trend<0.05) compared to individuals with low GRS.

Conclusion: Our findings suggest that TFA intake can increase the genetic susceptibility of FTO SNPs to BMI or WC change.

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https://doi.org/10.1016/j.numecd.2019.01.005

Introduction

Increasing rates of obesity have stimulated investigations revealing specific dietary components as contributing factors. Among dietary factors, food constituents that contribute to the calories of food and beverages, such as fatty acids and sugars, are more suspected than others; this is because they are readily available, highly palatable, and inexpensive [1]. It has also been shown that body weight and the distribution of adipose tissue, are regulated by many genes. One of the most significant genes making individuals prone to obesity is fat mass and obesity-associated gene (FTO). Each FTO risk allele increases ~0.84–2.1 kg of body weight in a person of height 180 cm [2].

The results of studies on the effect of trans-fatty acids (TFAs) and simple sugars (SS) on the incidence of obesity are not consistent [3–5]. These contradictory results suggest that genetic predisposition to weight gain is modulated by TFAs and SS. Fried foods and sugar-sweetened beverages magnified the association of genetic predisposition and obesity [6,7].

The aim of the current study was to investigate whether common FTO gene polymorphisms (rs1121980, rs1421085, and rs8050136), in isolation or in a combined-form genetic risk score (GRS), interact with added sugar and TFA intakes in relation to changes in general and central obesity, over a mean of 3.6 years follow-up. These results can be used to develop personalized dietary recommendations for the prevention and treatment of obesity.

Methods

Study population

Subjects of this cohort study were selected from TLGS participants [8], a population-based prospective study performed to determine the risk factors for non-communicable diseases, in a sample of Tehran's (capital of Iran) 13th district residents. The first examination survey was performed from 1999 to 2001 on 15,005 individuals aged ≥3 years, and follow-up examinations were conducted every 3 years (2002–2005; 2005–2008; 2008–2011, and 2011–2014) to identify recently developed diseases.

In the current study, among the 12823 participants who entered the fourth survey (2008–2011), 7812 were randomly selected for dietary assessment; of these 7812 participants, 6874 adult participants aged ≥18 years were included and followed for a mean period of 3.6 years. Subjects who did not complete data on the follow up survey (n = 950) were excluded. Also, individuals without DNA sample or lacking DNA purification in the range of $1.7 < A260/A280 < 2$ (n = 1182), those whose reported energy intake divided by the predicted energy intake did not meet the ±3SD range, those with missing anthropometric data, pregnant or lactating women, and those using drugs that affect weight were excluded (n = 480); ultimately, 4292 subjects remained for data analysis.

A written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the ethical committee of the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Measurements

Usual dietary intakes were assessed using a valid and reliable, 168-item semi-quantitative food frequency questionnaire (FFQ) during the previous year before the examination by expert nutritionists [9]. The frequency of each food item was changed to daily intakes; portion sizes were then converted to grams using household measures. The Iranian food composition table (FCT) [10] was used for calculating the TFA content of foods (biscuits, dairies, oils, and sweets); the United States Department of Agriculture (USDA) FCT [11] was used for food items that were not included in the Iranian FCT (fried vegetables and meats). Because there are no databases for added sugar content of Iranian food products, added sugar was estimated using the mean of the most popular food brand labels; these foods include, biscuits, cakes, chocolate and flavored milk, ice-cream, canned fruits, synthetic fruit juices, all kinds of sugar sweetened carbonated soft drinks, candy, chocolates, and Iranian deserts and sweets. Added sugar includes all kinds of sugars (e.g., white sugar, malt syrup, honey, and invert fructose sweetener) added to foods during their preparation and processing; and also the sugar added to foods at the table. The percentage of energy from TFAs and added sugar was calculated.

Body weight of subjects was measured to the nearest 100 g using digital scales (model 707, range 0.1–150 kg; Seca, Hamburg, Germany) while they were lightly clothed, and not wearing shoes. Height was measured to the nearest 0.5 cm with a tape measure (model 208 Portable Body Meter Measuring Device; Seca) while the subjects were in standing position, with their head in the Frankfort horizontal plane, and without shoes. Waist Circumference (WC) was measured to the nearest 0.1 cm, using a flexible tape at the end of a normal expiration, over light clothing, with the un-stretched tape meter positioned at the level of umbilicus, without exerting any pressure on the body surface.

BMI (kg/m^2) and WC (cm) changes were calculated by subtracting the BMI and WC at baseline, from their measurements at follow up; increase in BMI and WC was defined as BMI or WC change being positive or >0.

Physical activity level was assessed with high reliability and moderate validity, using the Persian translated modifiable activity questionnaire (MAQ). The frequency and time spent on light, moderate, hard, and very hard intensity activities were obtained, according to the list of common daily life activities over the past year; and these

data were converted into metabolic equivalent hours per week (METs/h/week) [12].

Genotyping

Seventeen single nucleotide polymorphisms (SNPs) were selected within the region of the FTO gene, based on the validated catalog of published genome-wide association studies and the Phenotype-Genotype Integrator [13,14], considering minor allele frequency (MAF) > 0.2 and P values $< 10^{-7}$. The selected SNPs were associated with dietary intake or obesity phenotypes [15,16]; of which 6 SNPs (rs1421085, rs1121980, rs17817449, rs8050136, rs9939973, and rs3751812) were available in our data; among these, three SNPs (rs8050136, rs3751812, and rs17817449) had a strong correlation (r^2 [2]>0.8) with the other three SNPs and moderate correlation ($r^2 < 0.7$) with each other (Table 1).

Genomic DNA was extracted from peripheral blood using a standard Proteinase K salting-out method. The quality and quantity of the extracted DNA were evaluated. A Thermo Scientific Nano Drop 1000 Spectrophotometer was used for qualitative assessment of the extracted DNA. Samples without DNA purification in the range of $1.7 <$ A260/A280 < 2 were excluded due to low quality and concentration. Extracted DNAs were aliquoted into 1.5-ml tubes and stored in -80 °C ultra-freezers, for future studies. Portions of DNA samples were genotyped with HumanOmniExpress-24-v1-0 bead chips, containing 649,932 SNP loci, with an average mean distance of 4 kb at the deCODE genetics company (Reykjavik, Iceland), according to the manufacturer's specifications (Illumina Inc., San Diego, CA, USA). For quality control procedures, PLINK program (V 1.07) and R statistic (V 3.2) were used, with the total genotyping rate of 0.9774. After quality control procedures, the genotyping data of FTO polymorphisms were used for data analysis [17].

Obesity GRS calculation GRS was calculated based on the three SNPs, using the dominant weighted method [18], assigning point 1 to the risk allele carriers, and sum of the unweighted GRS was calculated. The standardized weighted GRS was determined from coefficients obtained from the logistic regression analysis in our population (Table 1); with the lowest coefficients being assigned a value of 1. The lowest coefficient was 0.21, so the other two coefficients were multiplied by 4.76 (1 divided by 0.21 equal to 4.76). The range of GRS in our population was 0–3.23.

Statistical analysis

Statistical analyses were carried out using the Statistical Package for Social Sciences (version 21.0; SPSS). P value < 0.05 was considered as significant. The descriptive analysis consisted of comparing qualitative and quantitative variables, across quartiles of the percentages of energy from TFA and added sugar intakes using the Chi square and ANOVA tests, respectively. Pearson's Chi-square test was used to calculate the Hardy–Weinberg equilibrium. Logistic regression analysis was used to obtain coefficients and odds ratio of the association between the three SNPs (dominant model) and obesity (BMI$\geq$30 and BMI$<$30) [19].

To evaluate how diet and FTO gene variants or GRS interact in altering the BMI and WC, general linear models were used, including the corresponding main effects and interaction effects. Subjects were divided into eight groups, based on the combined role of quartiles of TFA or added sugar (percentage of energy intakes), and dominant model of FTO SNP genotypes in estimating mean $\pm$ SE changes of BMI and WC. Models were adjusted for sex, age, education levels ($>$14 and $\leq$ 14 years), smoking (never smoked, ex-smoker, and current smoker), baseline physical activity (light, moderate, high), baseline body mass index (BMI), and energy intake.

Table 1 Genotype information of FTO polymorphisms, among the population of Tehran Lipid and Glucose Study.

Polymorphisms		Frequency	Risk allele	HWE P value	Coefficients	OR (CI)	P	Unweighted risk score	Weighted risk score
rs1121980			T	0.89					
Allele	C	59.0							
	T	41.0							
Genotype	CC	37.4			0.21	1.23 (1.06–1.42)	0.008	0	0
	CT + TT	62.6						1	1
rs1421085			C	0.87					
Allele	T	62.0							
	C	38.0							
Genotype	TT	38.9			0.23	1.25 (1.09–1.45)	0.002	0	0
	TC + CC	61.1						1	1.09
rs8050136			A	0.96					
Allele	G	64.0							
	A	36.0							
Genotype	GG	40.7			0.24	1.27 (1.10–1.46)	0.001	0	0
	GA + AA	59.3						1	1.14

HWE: Hardy–Weinberg Equilibrium.
Odds ratio (OR) and confidence intervals (CI) obtained from logistic regression analysis, three SNPs (dominant model) as independent variables and obesity (BMI$\geq$30 and BMI$<$30) as dependent variable.

Participants were separated into two groups based on the median of GRS (≥3.23 and < 3.23). General linear models were performed to estimate the interactions of GRS with quartiles of TFA and added sugar intakes, in changing WC or BMI. All models were adjusted for variables proven to be associated with obesity; including age, gender, educational level, smoking, physical activity, and energy intake. The P value for trend across quartiles of dietary factors was determined using logistic regression, with the median of each quartile as a continuous variable.

Results

Frequency of genotypes or alleles, coefficients, odds ratio, and risk allele of each SNP for obesity traits is demonstrated in Table 1. Genotype frequencies did not deviate from the Hardy–Weinberg equilibrium.

Table 2 shows the baseline characteristics and dietary intakes of participants in the TLGS across quartiles of TFA and added sugar intakes. Individuals with higher quartiles of TFA and added sugar intakes were younger ($P < 0.001$) compared to the lower quartiles. Higher quartiles of TFA intake were associated with increase in BMI ($P = 0.01$). WC changes increased across quartiles of TFA ($P = 0.02$) and added sugar intakes ($P = 0.03$). Energy and dietary fat intakes were higher in the highest quartile of TFA intake compared to the lowest quartile ($P < 0.001$).

Changes in BMI, according to quartiles of TFA and added sugar intakes by FTO genotypes and GRS, are shown in Table 3. FTO rs8050136 and TFA intakes had a significant interaction in changing the BMI (p-value for interaction or $Pi = 0.01$). No statistically significant interaction was observed between FTO polymorphisms and added sugar intake, regarding BMI change. Individuals with a higher GRS had higher changes in BMI across quartiles of TFA intake (Q1: 1.68 ± 0.3 vs Q4: 20.6 ± 0.3, P trend<0.05) compared to individuals with low GRS.

The difference in WC change between individuals in the fourth quartile of TFA compared to the first quartile was significant for FTO rs1421085 and rs8050136 ($P < 0.05$) (Table 4). GRS and TFA intake had a statistically significant interaction in WC change ($Pi = 0.04$); a higher intake of TFAs was associated with higher changes in WC in subjects with high GRS compared to individuals with low GRS.

Discussion

Our study showed that TFA intake modified the association of some FTO SNPs with changes in general and abdominal obesity, in a prospective cohort study on the Tehranian population. Higher TFA intake by risk allele carriers of rs8050136 was associated with about a two fold increase in BMI and WC change. Our findings are of importance in public health, considering that based on MAF, these SNPs are common and a high percentage of people carry these risk alleles. Further, added sugar intake and FTO polymorphisms did not interact in altering obesity phenotypes, which may be due to consuming added sugar in our population in accordance with dietary recommendations (less than 10% of energy intake) [20].

Individuals with an unhealthy diet or lifestyle tend to have more TFA intake [21]; so the interaction term between genetic variants and TFAs, in relation to obesity, was further adjusted for physical activity, cigarette smoking, and energy intake.

To date, a few studies have focused on identifying the effect of interaction between FTO polymorphisms and dietary intakes on BMI [22,23]. Interaction of FTO polymorphisms and various dietary macronutrients (especially dietary fat), in relation to obesity; has been investigated in previous studies. The results of these studies were not consistent; consuming a high-fat diet in A allele carriers of rs9939609 (in high linkage disequilibrium with rs8050136, rs3751812, and rs17817449), was related to increase in BMI [24]. De Luis et al. [25] revealed that a diet rich in MUFA, had a positive effect on body weight loss in risk allele (A) carriers of rs9939609. Furthermore, it was shown that compared to C allele (rs1121980) carriers, those with TT genotypes had a higher BMI with high saturated fat diet [24]. The A allele of rs8050136 was associated with higher body fat and BMI, in a cross-sectional study [26]. In the multiethnic cohort study, the percentage of calories from fat, mediated the rs8050136 effect on BMI, during 10 years of follow-up [27].

Our findings showed that A allele (rs8050136) carriers had higher changes in BMI and WC, in the last quartile of TFA. It seems that A allele carriers of rs8050136 may be more susceptible to high BMI and WC than the CC genotype, when dietary TFAs are high. Qi et al. demonstrated that individuals with higher genetic predisposition to obesity, had a higher risk of obesity with over-consumption of fried foods (containing high TFAs) [6] and sugar-sweetened beverages, compared to individuals with lower genetic predisposition [7]; among 32 BMI associated variants, FTO polymorphism showed the strongest interaction with fried foods, in relation to obesity. The findings of two prospective US cohort studies showed that higher adherence to healthy eating index-2010 and dietary approach to stop hypertension diet scores decreased BMI predominantly in individuals with genetic predisposition to obesity compared to those with low genetic risk. Consuming low TFAs and added sugars are two components of these indices [28].

The main mechanisms of our findings are yet unclear, but might be related to the role of FTO in regulating satiety signals. Energy restriction, feeding, and fasting regulate the expression of FTO in the hypothalamus [29]. Fried food, containing high TFAs are palatable; resulting in high fat intake, high energy density, and low satiety index [6]. In a group of overweight/obese Caucasian adults, the risk allele of rs1421085 and rs17817449 polymorphisms were associated with poorer eating habits; including higher interpretation of hunger and greater emotional disinhibition, which was regulated internally [30].

Our study had some limitations.Iit has been shown that the effects of FTO minor alleles on BMI, decrease as the age

Table 2 Characteristics of the study population, according to dietary trans-fatty acids and added sugars; among adult participants of the Tehran Lipid and Glucose Study (n = 4292).

	Trans fatty acids					Added sugars				
	Q1	Q2	Q3	Q4	P	Q1	Q2	Q3	Q4	P
Median (% of energy)	0.86	1.58	2.35	4.07		1.71	3.53	5.33	9.22	
Age	45.1 ± 14.2[a]	41.0 ± 13.6	39.9 ± 13.0	38.1 ± 13.4	0.00	43.8 ± 13.7	41.1 ± 13.8	39.7 ± 13.6	39.5 ± 13.7	0.00
Current smokers (%)	13.4	16.2	16.4	15.2	0.09	12.0	12.6	15.7	21.0	0.00
Physical activity (MET/min/week)[c]	613 ± 850	577 ± 836	583 ± 900	563 ± 955	0.63	607 ± 837	589 ± 820	607 ± 1005	531 ± 869	0.17
Education level (%)[b]	32.6	34.4	33.9	35.5	0.25	29.4	32.5	37.2	38.5	0.00
Baseline BMI (Kg/m^2)	27.6 ± 4.5	27.7 ± 4.8	27.3 ± 4.8	26.9 ± 4.8	0.15	28.1 ± 4.9	27.4 ± 4.8	27.1 ± 4.7	27.8 ± 4.7	0.52
Delta BMI (Kg/m2)	1.01 ± 7.5	1.64 ± 7.4	1.81 ± 7.3	2.50 ± 8.0	0.01	1.45 ± 7.8	1.83 ± 7.2	1.66 ± 7.7	1.83 ± 7.2	0.57
Baseline WC (cm)	93.3 ± 11.5	93.1 ± 12.1	92.0 ± 12.3	93.1 ± 12.6	0.32	91.9 ± 12.1	91.9 ± 12.0	91.9 ± 12.1	91.9 ± 12.3	0.81
Delta WC	0.30 ± 7.07	0.91 ± 6.98	0.94 ± 6.90	1.17 ± 7.69	0.02	0.31 ± 7.09	0.93 ± 7.24	1.09 ± 7.37	0.98 ± 6.97	0.03
Energy intake (Kcal/day)	2470 ± 1179	2554 ± 1064	2628 ± 454	2676 ± 1080	0.00	2586 ± 1246	2561 ± 959	2590 ± 1022	2591 ± 1109	0.90
Carbohydrate (% of energy)	62.1 ± 7.5	59.7 ± 6.2	57.7 ± 5.7	55.4 ± 6.6	0.00	58.5 ± 7.9	58.5 ± 7.0	58.5 ± 6.7	59.4 ± 6.4	0.00
Protein intake (% of energy)	15.7 ± 3.7	15.2 ± 2.7	14.7 ± 2.7	13.7 ± 2.6	0.00	15.0 ± 3.3	15.2 ± 3.4	14.7 ± 2.7	13.8 ± 2.6	0.00
Total fat (% of energy)	26.2 ± 6.6	28.6 ± 4.9	31.0 ± 5.2	34.2 ± 6.4	0.00	29.7 ± 7.4	30.0 ± 6.5	30.2 ± 6.1	30.1 ± 6.1	0.24
Total fiber intake (g/1000 Kcal)	11.1 ± 4.1	10.4 ± 3.4	9.63 ± 3.0	9.54 ± 3.9	0.00	11.0 ± 3.9	10.4 ± 3.5	10.0 ± 3.0	9.15 ± 3.9	0.00
Saturated fat (% of energy)	8.58 ± 2.6	9.54 ± 2.6	10.1 ± 2.7	10.7 ± 2.9	0.00	9.32 ± 2.8	9.74 ± 2.8	9.87 ± 2.7	9.28 ± 2.9	0.18
MUFA (% of energy)	8.53 ± 2.8	9.26 ± 2.0	10.3 ± 2.2	11.7 ± 3.1	0.00	9.83 ± 3.0	9.98 ± 2.8	9.98 ± 2.5	9.98 ± 2.8	0.49
PUFA (% of energy)	5.15 ± 3.2	5.36 ± 1.4	6.21 ± 1.5	7.39 ± 2.3	0.00	6.07 ± 3.3	6.04 ± 2.2	6.03 ± 1.9	5.98 ± 1.9	0.86

Q: quartiles of tans-fatty acids and added sugars, MET: Metabolic Equivalent, BMI: body mass index, WC: waist circumference, MUFA: Mono-unsaturated fatty acids. PUFA: Poly-unsaturated fatty acids.

[a] Values are mean ± SD unless otherwise listed.

[b] Educational level ≥14 years.

[c] MET/min/week: Metabolic Equivalent minutes per each week.

Table 3 Changes in BMI, according to quartiles of trans-fatty acid and added sugar intakes by FTO genotypes and GRS; in adult participants of the Tehran Lipid and Glucose Study[a].

	Trans fatty acids						Added sugars					
	Q1	Q2	Q3	Q4	P trend	Pi	Q1	Q2	Q3	Q4	P trend	Pi
rs1121980						0.57						0.84
CC	1.37 ± 0.4[b]	1.41 ± 0.4	0.92 ± 0.4	1.69 ± 0.4	0.17		1.54 ± 0.4	1.46 ± 0.4	1.20 ± 0.4	1.19 ± 0.4	0.49	
CT + TT	1.80 ± 0.3	2.12 ± 0.3	1.50 ± 0.3	0.3 ± 1.86	0.43		1.76 ± 0.3	2.08 ± 0.3	1.54 ± 0.3	1.94 ± 0.3	0.89	
rs1421085						0.66						0.96
TT	0.97 ± 0.4	1.55 ± 0.4	1.50 ± 0.4	1.39 ± 0.4	0.19		1.42 ± 0.4	1.67 ± 0.4	1.08 ± 0.4	1.27 ± 0.4	0.94	
TC + CC	1.79 ± 0.3	2.11 ± 0.3	1.53 ± 0.3	1.98 ± 0.3	0.11		1.88 ± 0.3	1.99 ± 0.3	1.71 ± 0.3	1.86 ± 0.3	0.44	
rs8050136						0.01						0.94
GG	1.54 ± 0.4	1.49 ± 0.4	1.47 ± 0.3	1.53 ± 0.4	0.69		1.55 ± 0.4	1.53 ± 0.4	1.14 ± 0.4	1.42 ± 0.4	0.67	
GA + AA	0.92 ± 0.3	1.88 ± 0.3	1.86 ± 0.3	0.3 ± 2.15	0.04		1.79 ± 0.3	2.11 ± 0.3	1.70 ± 0.3	1.78 ± 0.3	0.90	
GRS						0.05						0.18
GRS<3.23	1.62 ± 0.3	1.44 ± 0.3	1.53 ± 0.4	1.42 ± 0.4	0.51		1.82 ± 0.4	1.18 ± 0.3	1.62 ± 0.4	1.91 ± 0.43	0.73	
GRS≥3.23	1.68 ± 0.3	1.51 ± 0.3	1.90 ± 0.3	2.06 ± 0.3	0.02		1.76 ± 0.3	1.78 ± 0.3	1.55 ± 0.3	2.08 ± 0.3	0.31	

[a] BMI (body mass index) change was calculated by subtracting the BMI at baseline, from their measurements over a mean of 3 years follow up; increase in BMI was defined if BMI change was positive or >0. Participants were jointly classified (eight groups), according to quartiles of dietary pattern scores and dominant model of FTO polymorphism genotypes or genetic risk score (GRS) ≥ median and < median.
[b] Data are Means ± SEM (Kg/m^2). Models were adjusted for age, sex, baseline BMI, educational level, smoking status, physical activity and energy intake. Q: quartiles of trans-fatty acids and added sugars, Pi: P interaction, GRS: Genetic risk score.

Table 4 Changes in WC, according to quartiles of trans-fatty acid and added sugar intakes by FTO genotypes and GRS; in adult participants of the Tehran Lipid and Glucose Study[a].

	Trans-fatty acids						Added sugars					
	Q1[b]	Q2	Q3	Q4	P trend	Pi	Q1	Q2	Q3	Q4	P trend	Pi
rs1121980												0.61
CC	0.94 ± 0.4	0.85 ± 0.4	0.95 ± 0.4	0.84 ± 0.4	0.71	0.34	0.30 ± 0.38	0.55 ± 0.37	1.05 ± 0.38	0.80 ± 0.38	0.83	
CT + TT	0.62 ± 0.3	1.09 ± 0.3	0.43 ± 0.3	0.70 ± 0.3	0.87		0.53 ± 0.3	0.85 ± 0.3	0.58 ± 0.29	0.88 ± 0.29	0.48	
rs1421085						0.03						0.57
TT	0.67 ± 0.3	0.40 ± 0.3	0.82 ± 0.4	0.72 ± 0.3	0.19		0.23 ± 0.4	0.65 ± 0.4	1.09 ± 0.4	0.91 ± 0.4	0.77	
TC + CC	−0.22 ± 0.4	1.14 ± 0.3	0.92 ± 0.4	1.17 ± 0.4	0.01		0.64 ± 0.3	0.80 ± 0.3	0.65 ± 0.3	0.80 ± 0.3	0.51	
rs8050136						0.01						0.48
GG	0.66 ± 0.3	0.42 ± 0.3	0.99 ± 0.4	0.78 ± 0.3	0.82		0.19 ± 0.4	0.56 ± 0.4	1.01 ± 0.4	0.95 ± 0.4	0.85	
GA + AA	−0.14 ± 0.4	0.83 ± 0.4	1.04 ± 0.3	1.27 ± 0.3	0.02		0.63 ± 0.3	0.86 ± 0.3	0.64 ± 0.3	0.71 ± 0.3	0.18	
GRS												0.70
GRS<3.23	0.83 ± 0.3	1.09 ± 0.4	0.91 ± 0.4	0.64 ± 0.4	0.71	0.03	0.46 ± 0.4	0.74 ± 0.4	0.77 ± 0.4	0.71 ± 0.4	0.21	
GRS≥3.23	0.16 ± 0.4	0.92 ± 0.3	0.83 ± 0.3	0.99 ± 0.4	0.03		0.34 ± 0.4	0.92 ± 0.3	0.43 ± 0.3	1.06 ± 0.3	0.84	

[a] Waist circumference (WC) changes were calculated by subtracting the WC at baseline from their measurements over a mean 3 years of follow up; increase in WC was defined if their changes were positive or >0. Participants were jointly classified (eight groups), according to quartiles of dietary pattern scores and dominant model of FTO polymorphism genotypes or genetic risk score (GRS) ≥ median and < median.
[b] Data are Means ± SEM. Models were adjusted for age, sex, baseline WC, educational level, smoking status, physical activity and energy intake. Q: quartiles of trans-fatty acids and added sugars, Pi: P interaction.

of subjects increases [24]; therefore, it is suggested that future studies are designed with a large sample size to cover statistical power for analyzing the interaction effect of FTO GRS with dietary factors on obesity traits, in an age and sex dependent manner. In addition, there are unknown confounding factors, which cannot be included in our analysis. Moreover, multiple gene variants caused the obesity trait, which we did not consider in this study.

The strengths of our study include the cohort design, with 3.6 years of follow up; using a valid and reliable FFQ that gives a better estimate of usual dietary intakes; also, using a GRS based on three tag variants of FTO SNPs that could cover the limited power of each variant, to detect its minor effect.

In conclusion, our findings suggest that TFA could increase the association between genetic susceptibility of FTO SNPs and BMI or WC change. These results support dietary recommendations to reduce the consumption of foods containing TFAs, to prevent obesity; particularly in subjects with more genetic predisposition to obesity.

Author contributions

The authors' contributions are as follows: F. H-E., G. K, and Z. E. designed the study, collected and analyzed the data, and wrote the manuscript; F. A., M-S. D and P. M. supervised the research and critically revised the manuscript for important intellectual content.

Conflicts of interest

The authors declare that they do not have any conflict of interests.

Acknowledgements

The study protocol was approved by the research committee of the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran (Grant Number 840). The authors wish to acknowledge Dr. Forough Ghanbari for critical English editing of the manuscript. The authors thank Iran Science Elites Federation for their enthusiastic support.

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