

# association of fat mass and obesity-associated

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## Research Article

# Association of Fat Mass and Obesity-associated rs9939609 Polymorphisms and Eating Behaviour and Food Preferences in Adolescent Minangkabau Girls

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## Abstract

**Background and Objective:** There are pros and cons surrounding the relationship between fat mass obesity associated (FTO) rs9939609 variants and the occurrence of obesity with regards to ethnicity and race. The Minangkabau ethnicity is unique compared to other ethnicities in Indonesia regarding its dietary pattern, in that this ethnic diet is high in fat intake and low in fibre intake. This study aimed to investigate the relationship between FTO rs9939609 variants and eating habits and food preferences among adolescent girls of Minangkabau ethnicity. **Methodology:** This study was a case control study and 275 adolescent girls (130 obese and 145 normal) were included. Tetra-primer amplification refractory mutation system-polymerase chain reaction (tetra-ARMS-PCR) was employed to examine genetic variants of FTO rs9939609. Eating habits were determined using an eating habits questionnaire and body mass index (BMI) was computed using the BMI Z-score (WHO). **Results:** This study revealed a significant relationship between genetic variants of FTO rs9939609 (TT, TA and AA genotypes) and higher BMI ( $p = 0.01$ ). Those with the A allele were found to consume more fried food and have a lower intake of fruit ( $p < 0.05$ ) than those with the TT genotype. In the obese group, subjects with the A allele did not have a preference for a fruit-vegetable diet ( $p < 0.05$ ). Based on cooking method, subjects with the A allele preferred to eat less meat curry than those with TA and TT genotypes ( $p = 0.01$ ). **Conclusion:** The genetic variants of FTO rs9939609 are associated with obesity, eating behaviour and food preferences in adolescents of Minangkabau ethnicity.

**Key words:** FTO rs9939609, obesity, eating behaviour, food preferences, adolescents

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**Competing Interest:** The authors have declared that no competing interest exists.

**Data Availability:** All relevant data are within the paper and its supporting information files.

## INTRODUCTION

Despite rigorous effort to prevent obesity by lifestyle changes associated with eating habits and exercise, the occurrence of obesity in all nations is still rising. The aetiology and pathogenesis of obesity are not yet fully understood, which makes therapy and prevention of obesity less effective. The risk of obesity depends on intertwined factors; i.e., genetic variants (polymorphisms) and environmental factors (diet, physical activities)<sup>1</sup>.

The National Basic Health Research<sup>2</sup> study revealed that in West Sumatera, which is predominated by the Minangkabau ethnic group, the prevalence of obesity is 10.8% or similar to the national prevalence, 8.3% obese and 2.5% very obese. In terms of dietary patterns, Lipoeto *et al.*<sup>3</sup> reported that the Minangkabau ethnic group is unique among other ethnicities in Indonesia with diets mainly consisting of steamed rice as a source of carbohydrates, fish, coconut, vegetables and chili, with slight differences between breakfast, lunch and dinner. Almost all Minangkabau food items are cooked with coconut milk and spices (garlic, turmeric, onion, ginger and chili).

Genes can interact with other genes or with external factors (diet) to contribute to increased body fat. Previous studies found that genes play a role in nutrient-specific choices and eating preferences<sup>4</sup>. Genetic variations may explain individual-specificities in food preferences, nutritional requirements and dietary responses among individuals<sup>5</sup>.

The occurrence of obesity tends to be conferred by increased energy intake and increased hunger/reduced satiety instead of changes to energy outflow or less exercise in humans<sup>6</sup>. Fat mass and obesity-associated protein (FTO) is explicitly found in the nucleus of cells in nearly all human tissues<sup>7</sup>. The hypothalamus is the area where its highest expression levels are observed. This appetite-control zone plays an important role in sensitivity to satiety, food responsiveness and eating behaviour<sup>8</sup>.

Time for meals, food intake and food preferences are affected by an intricate relationship among physiological, psychological, social and genetic factors<sup>9</sup>. Food intake and choices are mainly determined by food preferences. Food preferences are the result of a complex relationship between genetic and external factors that drive variations in individuals; for instance, children are dubious and picky about food and their food preferences<sup>10</sup>. This preference is reinforced by a clear genetic stimulus of appetite features in children<sup>11</sup>.

Harbron *et al.*<sup>12</sup> found that in a Caucasian group, unhealthy eating habits, such as growing hunger and shyness or emotional scores as well as higher fat and carbohydrate

consumption are related to the risk of FTO polymorphism alleles. McCaffery *et al.*<sup>3</sup> found that dietary patterns and composition can be affected by risk variants that are related to obesity. Meanwhile, Brunkwall, *et al.*<sup>14</sup> suggested that preference for protein and sucrose is related to risk alleles of the FTO gene and is also related to a high-fat and low-fibre diet<sup>15</sup> and the consumption of carbohydrates and protein<sup>16</sup>.

Despite numerous studies on genetic interactions and environmental variables, the association between the FTO rs9939609 polymorphism and dietary behaviours in obese adolescent has rarely been comprehensively studied. Therefore, this study was conducted to investigate the relationship between the FTO rs9939609 polymorphism and diet patterns and food preferences in an obese Minangkabau population.

## MATERIALS AND METHODS

**Settings and study design:** This study was conducted as a case control study design in four regencies in West Sumatera Province (i.e., Tanah datar, Padang Panjang, Pariaman and Padang). The main study population consisted of adolescent girls aged 12-15 years. The subjects were recruited from schools after informed consent was obtained. Subjects with a history of hormonal disturbances or intestinal diseases were excluded from the study. Obese and normal subjects were selected according to body mass index (BMI). Obesity was defined as a BMI Z score > +1 SD and non-obese was defined as -2 SD < BMI Z score < +1 SD<sup>17</sup>.

### Measurement of anthropometric parameters:

Anthropometric parameters were measured by a professional enumerator. Body height was measured using a roll-up measuring tape (Seca 206, Germany) with a wall attachment. Body weight was measured to the nearest 0.5 kg with a digital scale (Omron, HBF-510W, Japan) while the subjects were wearing normal clothing and no shoes. Body mass index was calculated as weight divided by height squared ( $\text{kg m}^{-2}$ ). Waist circumference was measured to the nearest 0.5 cm with a standard household tape measure. BMI was calculated according to the WHO 2007 growth reference. Subjects were classified as obese if they had a BMI Z score > +2 SD and normal if -2 SD < BMI Z score < +1 SD. All measurements were obtained in duplicate by a team of trained persons.

**Genotyping:** A professional analyst was employed to collect 5 mL blood specimens from each respondent. A DNA isolation kit (Invitrogen, Thermo Fisher Scientific) was used to extract

genomic DNA from EDTA-anticoagulated whole blood specimens and the DNA samples were then stored at -20°C. Tetra-primer amplification refractory mutation system-PCR (tetra-ARMS-PCR) was used to genotype the SNP variant rs9939609. PCR-restriction fragment length polymorphism (RFLP) was employed to genotype the rs9939609 variant, aimed to validate the results of the tetra-ARMS-PCR.

**Eating behaviour and food preferences:** Food intake was measured using a semi-quantitative food frequency questionnaire in a face-to-face interview with an experienced enumerator. The FFQ includes questions on routine consumption of 223 food choices for the last year prior to the study. The food choices were grouped into 15 categories: carbohydrates (rice, fried rice, potatoes and cereal), fresh fish and other seafood, salted fish, meat, poultry, eggs, tofu and tempeh, peanuts and other nuts, fast food, milk and dairy products, vegetables, fruits, snack foods, drinks and beverages. Other questions asked were about how often the sub-items were eaten, the way the food was prepared and any additional information. The subjects were requested to memorize the foods they had eaten during the past year. Several coloured pictures were presented to subjects in order to estimate the serving size of the foods. In general, the questionnaire enabled the approximation of the daily food intake of the 223 food options by further examining sub-items, such as fruits and vegetables, in supplementary questions. Data on the nutrient content of the food items was acquired from the Nutrient Composition of Minangkabau Foods. An identical population was used to validate the questionnaire. Eating habits were explained as a way to choose, consume and use food by a person or group based on social norms and customs. The questionnaire used was Eating, drinking and

smoking habits<sup>18</sup>. The information on diet included the subjects' preference of food type (animal protein diet, plant protein diet, fruit-vegetarian, western and sweet food).

**Ethical approval:** All subjects and their parents or guardians signed informed consent forms that were prepared by the enumerators. Ethical approval was granted by the Ethics Committee of the Medical Faculty of Andalas University, Padang, Indonesia.

**Statistical analysis:** SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) was employed for the statistical analyses. Continuous variables are expressed as the Mean ± SD and categorical variables are expressed as frequencies (%). For normally distributed variables between the obese and non-obese groups, mean differences were examined using a t-test. For non-normally distributed variables, the Mann-Whitney U test was employed. Chi-squared test was used to assess differences in categorical variables (FTO genotype frequency) between the obese and normal groups. An analysis was also conducted to determine the relationships among BMI, eating habits and FTO genotype. Differences were considered significantly different when  $p < 0.05$ .

## RESULTS

**Subjects' characteristics:** Table 1 shows that anthropometric measurements (weight, BMI, waist circumference, hip circumference, systolic and diastolic blood pressure and % body fat) in the obese group were significantly higher than those in the normal group ( $p = 0.01$ ). Average total energy intake was not significantly different between the two groups ( $2649.32 \pm 912.52$  vs  $2678.92 \pm 1286.31$ ;  $p = 0.26$ ).

Table 1: Subjects characteristic

	Normal (n = 145)	Obese (n = 128)	p-value <sup>†</sup>
<b>Anthropometrics</b>			
Weight (kg)	48.14 ± 7.14	66.14 ± 8.22	0.01*
Body mass index ( $\text{kg m}^{-2}$ )	20.82 ± 2.68	28.35 ± 2.79	0.01*
Waist circumference (cm)	69.61 ± 6.62	84.37 ± 6.67	0.01*
Hip circumference (cm)	85.82 ± 5.94	100.12 ± 6.63	0.01*
W/H ratio	0.81 ± 0.05	0.84 ± 0.04	0.01*
Systolic blood pressure (mmHg)	116.71 ± 9.41	129.00 ± 13.07	0.01*
Diastolic blood pressure (mmHg)	71.60 ± 8.12	78.00 ± 11.07	0.01*
Body fat (%)	24.26 ± 3.11	30.62 ± 1.79	0.01*
<b>Dietary intake</b>			
Total energy ( $\text{kcal day}^{-1}$ )	2649.32 ± 912.52	2678.92 ± 1286.31	0.26
Carbohydrate	301.76 ± 110.11	308.92 ± 152.06	0.21
Fat (g)	130.01 ± 53.07	131.17 ± 128.51	0.37
Protein	101.42 ± 42.64	98.64 ± 54.02	0.33
Fiber ( $\text{g day}^{-1}$ )	17.93 ± 7.29	14.96 ± 8.19	0.20

Values are expressed as the Mean ± SD. <sup>†</sup> Independent t-test

Table 3: Association FTO rs9939609 genotype and eating behaviour

Eating behaviour	Normal			p-value	Obese			p-value
	TT (n = 82)	TA (n = 60)	AA (n = 3)		TT (n = 58)	TA (n = 56)	AA (n = 14)	
<b>Regular meal</b>								
Always	33 (40.2%)	20 (33.3%)	1 (33.3%)	0.69	15 (25.9%)	21 (37.5%)	3 (21.4%)	0.30
Seldom	49 (59.8%)	40 (66.7%)	2 (66.7%)		43 (74.1%)	35 (62.5%)	11 (78.6%)	
<b>Breakfast</b>								
Always	41 (50.0%)	21 (35.0%)	1 (33.3%)	0.19	26 (44.8%)	29 (51.8%)	11 (78.6%)	0.076
Seldom	41 (50.0%)	39 (65.0%)	2 (66.7%)		32 (55.2%)	27 (48.2%)	3 (21.4%)	
<b>Meal frequency/day</b>								
1-2 x/d	5 (6.1%)	1 (1.7%)	0 (0.0%)	0.40	2 (3.4%)	1 (1.8%)	0 (0.0%)	0.70
3-4x/d	77 (93.9%)	59 (98.3%)	3 (100.0%)		56 (96.6%)	55 (98.2%)	14 (100.0%)	
<b>Snack frequency/day</b>								
Always	13 (15.9%)	8 (13.3%)	0 (0.0%)	0.70	7 (12.1%)	6 (10.7%)	1 (7.1%)	0.87
Seldom	69 (84.1%)	52 (86.7%)	3 (100.0%)		51 (87.9%)	50 (89.3%)	13 (92.9%)	
<b>Fruit frequency/day</b>								
Always	24 (29.3%)	25 (41.7%)	0 (0.0%)	0.14	33 (56.9%)	19 (33.9%)	6 (42.9%)	0.04
Seldom	58 (70.7%)	35 (58.3%)	3 (100.0%)		25 (43.1%)	37 (66.1%)	8 (57.1%)	
<b>Vegetable frequency/day</b>								
Always	29 (35.4%)	15 (25.0%)	0 (0.0%)	0.21	11 (19.0%)	15 (26.8%)	6 (42.9%)	0.16
Seldom	53 (64.6%)	45 (75.0%)	3 (100.0%)		47 (81.0%)	41 (73.2%)	8 (57.1%)	
<b>Fried frequency/day</b>								
Always	59 (72.0%)	36 (60.0%)	2 (66.7%)	0.32	48 (82.8%)	33 (58.9%)	11 (78.6%)	0.01
Seldom	23 (28.0%)	24 (40.0%)	1 (33.3%)		10 (17.2%)	23 (41.1%)	3 (21.4%)	
<b>Meal with family</b>								
Always	35 (42.7%)	24 (40.0%)	2 (66.7%)	0.76	22 (37.9%)	13 (23.2%)	9 (64.3%)	0.86
Seldom	47 (57.3%)	36 (60.0%)	1 (33.3%)		36 (62.1%)	43 (76.8%)	5 (35.7%)	

\*Significant differences with p-value<0.05. †Chi square test

Table 4: Association FTO rs9939609 and dietary preferences

FTO genotypes	Normal		p-value	Obese		p-value
	Low	High		Low	High	
<b>*Animal protein diet</b>						
TT	12 (14.6%)	70 (85.4%)	0.30	5 (8.6%)	53 (91.4%)	0.13
TA	5 (8.5%)	54 (91.5%)		7 (12.5%)	49 (87.5%)	
AA	1 (33.3%)	2 (66.7%)		4 (28.6%)	10 (71.4%)	
<b>*Plant protein diet</b>						
TT	33 (40.2%)	49 (59.8%)	0.14	18 (31.0%)	40 (69.0%)	0.40
TA	16 (27.1%)	43 (72.9%)		14 (25.0%)	42 (75.0%)	
AA	2 (66.7%)	1 (33.3%)		6 (42.9%)	8 (57.1%)	
<b>*Western diet</b>						
TT	25 (30.5%)	57 (69.5%)	0.39	33 (56.9%)	25 (43.1%)	0.83
TA	21 (35.6%)	38 (64.4%)		33 (58.9%)	23 (41.1%)	
AA	0 (0.0%)	3 (100.0%)		7 (50.0%)	7 (50.0%)	
<b>*Fruit-vegetables diet</b>						
TT	28 (34.1%)	54 (65.9%)	0.50	19 (32.8%)	39 (67.2%)	0.01*
TA	22 (37.3%)	37 (62.7%)		14 (25.0%)	42 (75.0%)	
AA	2 (66.7%)	1 (33.3%)		10 (71.4%)	4 (28.6%)	
<b>*Sweet food</b>						
TT	21 (25.6%)	61 (74.4%)	0.25	27 (46.6%)	31 (53.4%)	0.32
TA	14 (23.7%)	45 (76.3%)		20 (35.7%)	36 (64.3%)	
AA	2 (66.7%)	1 (33.3%)		4 (28.6%)	10 (71.4%)	

\*Animal protein base diet includes meat, beef, lamb, chicken, liver, fish, shrimp and egg, †Plant protein base diet nut, tofu, tempeh, ‡Western base diet includes soft drink, pizza and potato chips and hamburger, §Fruit vegetable diet includes fruit, vegetable and juice, ¶Sweet food diet includes candy, chocolate, ice-cream and soft drinks, \*Chi square test, significant differences with p-value<0.05

and a weight excess of 3 kg has a 1.5 times greater risk of obesity than a person without risk alleles. FTO variants that are frequently found in Europeans are associated with obesity in Chinese people and Malays living in Singapore<sup>20</sup>, as found

elsewhere such as in Chinese<sup>21,23</sup>, Romanian children<sup>24</sup>, Pakistanis<sup>25</sup> and South Asians<sup>26</sup>. However, inconsistencies were found among Pakistanis with obesity<sup>27</sup>.

Risk variants of the fat mass and obesity-associated protein (FTO) rs9939609 gene have been associated with a higher risk of obesity. Nevertheless, the fact that FTO genotype and food intake are related has yet to be confirmed. In this study, we support the finding that there are no significant differences in macronutrient intake between FTO genotypes, as previously found by a meta-analysis study of Livingstone *et al.*<sup>28</sup>. Furthermore, the A allele of the FTO rs9939609 gene is associated with obesity via higher energy intake, i.e., mainly fat<sup>29,30</sup>. However, this finding is inconsistent with the results of a meta-analysis conducted for children and adolescents<sup>31</sup>. The A allele of rs9939609 influenced obesity but did not contribute to the control of energy expenditure. Instead, this allele could be involved in the regulation of food intake and food choices in European children, suggesting a pathway to a hyperphagic phenotype or a preference for high calorie food. However, our study did support this result. This difference was thought to be due to distinction in the studied SNPs, the age of subjects (mainly children), fewer number of subjects and variations in the measurements of dietary intake that is incompatible with our FFQ.

The fundamental molecular interactions between FTO and risk of obesity are still unclear. Based on studies of humans, the appetites and eating habits of children and adolescents are affected by the FTO genotype<sup>32</sup>. Similarly, the FTO genotype influences eating habits, food selection<sup>29</sup> and food preferences<sup>34</sup>. Recent research found that the FTO genotype is associated with a rise in ghrelin hormone (hunger hormone) levels and a decline in leptin hormone (satiety hormone) levels<sup>33</sup>. The A allele of FTO may disrupt the circulating levels of the orexigenic hormone acyl-ghrelin and diminish postprandial appetite reduction<sup>34</sup>.

Many new genes in the brain are well studied and some genes are specifically found in the hypothalamus, which functions in conjunction with central nervous system processes and have an essential role in the control of body weight. The hypothalamus is key in controlling energy homeostasis and food intake. Dysfunction in the hypothalamic area may cause deregulation of body weight due to changes in eating behaviour<sup>35</sup>.

Persons with the A allele were shown to eat considerably more fried food than those with the TT genotype. Moreover, we also found a significant relationship between the A allele and lower fruit intake. This finding is in line with a study of youth in which they had at least one A allele and consumed a considerably higher percentage of energy from fat than the TT

subjects did ( $p = 0.008$ )<sup>36</sup>. The FTO rs9930609 allele is associated with an increase in the consumption of 5 g day<sup>-1</sup> fat and 25 kJ day<sup>-1</sup> energy (based on a 3 day food record) in children<sup>37</sup>. Other research has identified a relationship between FTO genotype and BMI in persons consuming a diet high in fat and, particularly, saturated fat<sup>38</sup>. In Spanish children, the risk allele carriers that consume more than 12.6% SFA (of total energy) had a higher risk of obesity than TT carriers<sup>39</sup>.

Genetic variations may alter how children recognize their preference for fat-rich foods. In adults, there are differences between persons with obesity and with normal weight in their preference for fat and for a blend of sugar and fat<sup>40</sup> and this finding supports a mechanism that may be contained in the aetiology of the variations. Persons with obesity and that are overweight exhibit a predisposition to preference and selection of high-energy foods that could promote these conditions. Despite being an important part of food choice, 'liking' only contributes to general distinction in food choice and eating behaviours to a reasonable extent<sup>41</sup>. Sugar and fat are the two most favourable ingredients in food by children<sup>42</sup>.

These results are in line with a cohort study in the United States in which the variants of FTO were associated with a fried food diet<sup>43</sup>. In our study, it was suggested that fried food and fruit intakes could modify the relationship between FTO variants and obesity, particularly in individuals who consume more fried food or less fruit and have a genetic risk of obesity.

There is substantial similarity in children's preferences of food; high-fat and sweet foods are usually preferred by children, but vegetables are almost universally disliked<sup>44</sup>. In line with these results, a study that investigated food patterns across the FTO genotypes found that A allele carriers consumed a higher number of meals per day and ate more servings of energy-dense foods<sup>13</sup>.

In obese subjects, there is an association between rs9939609 genotype and fruit preference. Participants with the AA genotype did not prefer a fruit-vegetable diet. This finding is in line with a previous study in Chinese Han children and adolescents<sup>45</sup>. There is an interaction between FTO variants and fibre intake in those with general obesity, an effect that was more prominent in those who consumed high levels of dietary fibre and had a high number of risk alleles<sup>46</sup>.

Based on cooking method, in obese subjects, there was a significant association between FTO genotype and a preference for meat curry. Participants with the A allele had a lower intake of meat curry than those with other genotypes. Meat curry consists of meat (fish, chicken and beef) with coconut and many spices, especially phenolic compounds. Phenolic compounds, as secondary metabolites in plants, present the greatest evidence of effective obesity treatment.

Polyphenols may provide beneficial effects on adipose tissue under obese conditions by reducing intracellular oxidative stress and chronic low-grade inflammation and by suppressing adipogenesis, lipogenesis and the differentiation of preadipocytes to mature adipocytes<sup>47</sup>. As one of the spices in curry, turmeric contains curcumin, which is an active ingredient that can be utilized to reduce weight.

### CONCLUSION

Obese subjects with the A allele consume more fried food and less fruit than those with the T allele. Furthermore, obese subjects with the A allele do not prefer a diet including fruits-vegetables and meat curry. High fried food intake and low fruit, vegetable and curry intake may increase obesity prevalence in subjects with the A allele.

The strength of this research is that the study has been conducted in numerous samples and various geographic distributions comprising rural and urban subjects. The limitation of this study is that the study was a cross-sectional study, which cannot trace causal mechanisms. Based on this limitation, future research will include an intervention study.

### SIGNIFICANCE STATEMENT

This research found a relationship between the FTO rs9939609 polymorphism and obesity. The results of this study could be used by health care professionals to set weight management goals and provide dietary assistance for people with a genetic tendency for obesity.

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