Effect of exercise combined with dietary intervention on obese children and adolescents associated with the FTO rs9939609 polymorphism

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Abstract. – OBJECTIVE: Aim of this study was to investigate the association of the FTO rs9939609 polymorphism with the effects of the exercise and dietary intervention on obese adolescents and children in China.

PATIENTS AND METHODS: Total 138 Chinese children and adolescents (77 males and 61 females, aged 10-18 years) were recruited in the 2012 summer camp in Shanghai. Dietary and exercise intervention was performed for four weeks. Obesity related parameters were detected by the physical examination before and after four-week’s intervention. Genotyping of the FTO rs9939609 was performed by using a TaqMan SNP Genotyping Assay. SPSS 19.0 were used to do the statistical analysis.

RESULTS: Finally, 135 campers were investigated in this study. The AA, AT and TT genotype frequencies of rs9939609 were 5.2%, 33.3% and 61.5%, respectively. The BMI in individuals with the genotype AA (or AT) was significantly higher compared with their with TT genotype ($p = 0.044$). The levels of body mass index (BMI), insulin (INS), total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), red blood cell (RBC), Hemoglobin (HB) and hematocrit (HCT) in campers were significantly declined by the combined intervention ($p < 0.05$). Moreover, the levels of TC, low-density lipoprotein (LDL), RBC, HB, and HCT in the camper with genotype AA (or AT) were significantly decreased by the combined intervention compared with the camper with genotype TT ($p < 0.05$).

CONCLUSIONS: The effects of exercise combined with dietary intervention on obesity were associated with the FTO rs9939609 polymorphism in chinese adolescents and children.

Key Words: Adolescents, Obesity, Single nucleotide polymorphism, Exercise combined with dietary intervention.

Introduction

With the economic development and people’s living standards improvement, there is a substantial increase in the incidence of obesity in China¹. This trend is not limited to adults but is also apparent in the children and adolescents²-⁵. A recent statistic showed that the prevalence of obesity increased from 0.4% in 1981-1985 to 7.5% respectively in 2006-2010, with the average annual increase rate of 12.4% in China⁶. The obesity in children and adolescents can not only lead to hypertension, hyper-lipidemia, gout, diabetes/mellitus, cancer, and high prevalence of cardiovascular disease in adult obesity, but also negatively influence the learning, living and social adaptation of them⁷. Thus, it is necessary to better understand the occurrence and development of obesity in children and adolescents, which can provide evidences for drawing up more efficient treatment programs.

Recent studies have demonstrated that genetic factors also exert important roles in the occurrence and development of obesity in addition to diet, lifestyle and other environmental factors⁷,⁸. The fat mass- and obesity-associated gene (FTO) was a gene has been widely reported to be associated with common obesity in adolescents and children from various ethnic backgrounds⁹-¹¹. Thus, the success of obesity prevention and treatment may partly depend on the genetic make-up of the individual. It was reported that the rs9939609 polymorphism of the FTO gene was associated with weight regain after a lifestyle intervention in overweight children¹⁰. Mean-
while, the dietary fatty acid distribution can influence the effect of the rs9939609 polymorphism of the FTO gene on children and adolescents’ obesity risk. Therefore, the mutual influence between genetic factor, especially FTO (rs9939609), and lifestyle intervention should be considered in the research of obesity prevention and treatment.

The previous studies have been reported that an exercise combined with dietary intervention had beneficial effects on obese adolescents and children. However, it is still unknown whether the influence of FTO rs9939609 polymorphism on the effects of this combined intervention existed. Therefore, we performed this study to explore the association between FTO rs9939609 polymorphism and the effect of this combined intervention on obesity and provided insights into the treatment of obesity in Chinese adolescents and children.

**Patients and Methods**

**Subjects**

A total of 138 children and adolescents, including 77 males and 61 females, aged 10-18 years were recruited in 2012 summer camp in Shanghai. Campers will undergo physical examination and history medical inquiry before being accepted into the summer camp. Physical examination including fasting blood tests and generally health indexes were performed by an endocrinologist or a trained nurse practitioner. Each participants’ weight and height were measured by using calibrated electronic instruments as described previously. Body mass index (BMI) was calculated as weight (kg) divided by the square of the height (m).

The children and adolescents were selected according to the pre-established criteria based on the results of physical examination and history medical inquiry. The individuals were included if they were Chinese Han people with a body mass index (BMI) ≥ 25 kg/m² and without history of smoking and diseases of cardiovascular, liver, kidney, lung and others. Individuals were excluded if: i) they were taking medication to affect body weight; ii) they had a psychiatric disorder that might impede protocol compliance, or had abnormal hepatic, renal, or thyroid function; iii) they had lost over 5 lb (2.3 kg) in the past 3 months or were undergoing weight-loss treatment. In addition, pregnant girls were not eligible for the study. The study was approved by the Shanghai institute of Physical Education Ethics Committee. The children and their parents, written informed assent and consent for their participation and genetic analysis were obtained.

**Dietary and Exercise Intervention**

In order to ensure the normal growth and development of all the campers, the diet was supplied according to the basal metabolic rate and arranged by nutrition professionals. Based on the health status and development characteristics of the children and adolescents, dietary intervention was conducted as follows: i) energy supply ratio of sugar, fat and protein was 60% to 70%, 10% to 15%, 20% to 25%, respectively; ii) daily salt intake was less than 6 g; iii) adequate diversification of food sources were used to ensure a balance of energy intake. In addition, the regular health education was performed during the dietary intervention.

Moreover, exercise intervention was carried out simultaneously with the dietary intervention. In order to make a reasonable exercise prescription, an incremental exercise for each participant was required before formal exercise. The incremental exercise was carried out in the flat treadmill with three levels (4 km/h, 6 km/h, and 8 km/h), each level for 2 min. The electrocardiography (ECG) tracing was simultaneously recorded. If the ECG appeared abnormality, the heart rate surpassed 80% of the maximum heart rate, or the participants were unable to continue to the test, the examination was terminated. After the incremental exercise, a recovery ECG was recorded during 1 min after exercise. Exercise intensity and individualized exercise prescription was determined according to the exercise stress. Target heart rate (THR) = resting heart rate (RHR) + heart rate reserve (maximum heart rate, HR R) × 20%-40%. The exercise prescription in this camp was aerobic exercise. The frequency of exercise intervention was six days a week. The duration time was 120 min every day (morning: 10:00-12:00; afternoon: 15:00-17:00), including time of organization, arrangements, preparatory activities, official campaign, and 2-3 times short break. Exercise forms were those easy to control intensity and easy to learn (such as ball games, swimming, and aerobics). Each exercise was guided by professionals. In addition, professionals of medical and human movement science provided the guideline for the intensity monitoring of real-time exercises.
The duration of the dietary combined with exercise intervention was 4 weeks. The gene polymorphism determination was performed after a two-day dietary adaptation. The physical examination was performed again after the four-week intervention. In order to avoid the influence of the intensive exercise, the physical examination was conducted at the next morning after aerobic exercise (18-20 hours after exercise).

**Results**

**Analysis of FTO rs9939609 Polymorphism**

Finally, 135 campers were genotyped and investigated in this study. Seven (5.19%) were homozygous for the obesity risk allele (AA) for FTO rs9939609, 45 (33.33%) were heterozygous (AT) and 83 (61.48%) were wild type (TT). The overall frequencies of the A and T allele were 21.85% and 78.15%, respectively. The genotype frequencies deviate from the Hardy-Weinberg predictions (AA: 14.6%; AT: 49.2%; TT: 36.2%) due to single population and small sample size.

**Association Between FTO rs9939609 Polymorphism and Obesity**

As shown in Table I, the basic information and obesity associated blood parameters were summarized. As has been done in previous studies, homozygous (AA) and heterozygous (AT) risk allele youth were grouped together. The results showed that the parameter BMI was significantly associated with the FTO rs9939609 genotype ($p = 0.044$), suggesting that the children and adolescents with genotype AA (or AT) had significantly higher BMI than that with genotype TT in China.

**Effect of Exercise Combined with Dietary Intervention on Obesity**

The levels of BMI, TG, TC, HDL, INS, RBC, HB, and HCT of campers were significantly declined by the combined intervention after summer camp (Table II), indicating the exercise combined with dietary intervention had an obvious therapeutic effect for obesity in children and adolescents ($p < 0.05$).

**Association of FTO rs9939609 Genotype with the Effect of the Exercise Combined with Dietary Intervention on Obesity**

Different genotypes of FTO rs9939609 had been shown to influence the therapeutic effect of exercise combined with dietary intervention. The
levels of TC, LDL, RBC, HB, and HCT in the camper with genotype AA (or AT) were significantly decreased by the combined intervention compared with the camper with genotype TT \((p < 0.05)\). These results indicated the effect of the exercise combined with dietary intervention was significantly associated with the FTO rs9939609 genotype in Chinese children and adolescents (Table III).

**Discussion**

The association between FTO rs9939609 polymorphisms and obesity in children and adolescents has been reported in many previous studies\(^{11,12,19}\). Children and adolescents with at least one A allele at rs9939609 were at substantially increased risk of obesity compared with that with only the low-risk T allele\(^{16,18}\). In this study, a significantly higher BMI was found in individuals with at least one A allele compared with individuals with only T allele, which was consistent with the results of previous studies. It has been reported that children and adolescents with at least one risk allele (A) showed more frequent loss of control eating episodes and select foods higher in fat at a buffet meal\(^{17,20}\), which may be the mechanisms of the association between FTO rs9939609 polymorphisms and obesity in children and adolescents.

In addition, we also found that the exercise combined with dietary intervention significantly decreased the levels of obesity related parameters, suggesting that this combine intervention effectively inhibited the development of obesity in Chinese children and adolescents. Meanwhile, the association between the FTO rs9939609 polymorphism and the effect of this intervention on obesity in Chinese children and adolescents was found. It indicated that the levels of some obesity related parameters (TC, LDL, RBC, HB, and HCT) in carriers of FTO genotype AA (or AT) could significantly be reduced by the combined intervention compared with the TT carriers.

### Table I. Association between FTO rs9939609 polymorphism and obesity related parameters (mean ± SD).

<table>
<thead>
<tr>
<th>Factors</th>
<th>TT (n = 83)</th>
<th>AT or AA (n = 55)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>14.2 ± 3.11</td>
<td>14.30 ± 3.33</td>
<td>0.897</td>
</tr>
<tr>
<td>Gender</td>
<td>83</td>
<td>55</td>
<td>0.800</td>
</tr>
<tr>
<td>BMI</td>
<td>29.63 ± 4.50</td>
<td>30.94 ± 5.13</td>
<td>0.044*</td>
</tr>
<tr>
<td>BG</td>
<td>3.84 ± 0.55</td>
<td>3.84 ± 0.51</td>
<td>0.352</td>
</tr>
<tr>
<td>TG</td>
<td>1.20 ± 0.47</td>
<td>1.23 ± 0.35</td>
<td>0.403</td>
</tr>
<tr>
<td>TC</td>
<td>4.31 ± 0.82</td>
<td>4.81 ± 1.12</td>
<td>0.795</td>
</tr>
<tr>
<td>HDL</td>
<td>1.18 ± 0.20</td>
<td>1.20 ± 0.20</td>
<td>0.458</td>
</tr>
<tr>
<td>LDL</td>
<td>2.53 ± 0.59</td>
<td>2.92 ± 0.87</td>
<td>0.660</td>
</tr>
<tr>
<td>INS</td>
<td>88.64 ± 43.02</td>
<td>98.20 ± 53.72</td>
<td>0.381</td>
</tr>
<tr>
<td>RBC</td>
<td>5.07 ± 0.29</td>
<td>5.05 ± 0.32</td>
<td>0.555</td>
</tr>
<tr>
<td>HB</td>
<td>145.23 ± 9.45</td>
<td>143.92 ± 8.21</td>
<td>0.417</td>
</tr>
<tr>
<td>HCT</td>
<td>43.06 ± 3.16</td>
<td>42.67 ± 2.69</td>
<td>0.701</td>
</tr>
</tbody>
</table>

Note: \(^*(p < 0.05)\) represents a significantly statistical difference between the people with genotype TT and AT or AA, which suggests that the presence of at least one copy of the A allele was significantly associated with the higher BMI, body mass index; TG, triglyceride; TC, cholesterol; HDL, high-density lipoprotein; INS, insulin; RBC, red blood cell; HB, Hemoglobin; HCT, hematocrit.

### Table II. Exercise combined with diet intervention and its association with obesity related parameters.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Standard error</th>
<th>p-value</th>
<th>95% CI Upper</th>
<th>95% CI Lower</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>1.20198</td>
<td>-0.0108</td>
<td>0.1906</td>
<td>0.001</td>
<td>0.7792</td>
<td>1.5456</td>
</tr>
<tr>
<td>BG</td>
<td>0.1489</td>
<td>0.0024</td>
<td>0.0578</td>
<td>0.008</td>
<td>0.0420</td>
<td>0.2750</td>
</tr>
<tr>
<td>TG</td>
<td>0.21318</td>
<td>0.0003</td>
<td>0.0334</td>
<td>0.001</td>
<td>0.1502</td>
<td>0.2799</td>
</tr>
<tr>
<td>TC</td>
<td>0.996916</td>
<td>0.0009</td>
<td>0.0510</td>
<td>0.001</td>
<td>0.8686</td>
<td>1.0688</td>
</tr>
<tr>
<td>HDL</td>
<td>0.11063</td>
<td>0.0001</td>
<td>0.0149</td>
<td>0.001</td>
<td>0.0808</td>
<td>0.1395</td>
</tr>
<tr>
<td>INS</td>
<td>34.61105</td>
<td>0.2251</td>
<td>3.2416</td>
<td>0.001</td>
<td>28.4791</td>
<td>41.291</td>
</tr>
<tr>
<td>RBC</td>
<td>0.12889</td>
<td>-0.0006</td>
<td>0.0178</td>
<td>0.001</td>
<td>0.0915</td>
<td>0.1613</td>
</tr>
<tr>
<td>HB</td>
<td>5.78206</td>
<td>-0.0120</td>
<td>0.4780</td>
<td>0.001</td>
<td>4.8110</td>
<td>6.6750</td>
</tr>
<tr>
<td>HCT</td>
<td>1.36050</td>
<td>-0.0029</td>
<td>0.1570</td>
<td>0.001</td>
<td>1.0315</td>
<td>1.6664</td>
</tr>
</tbody>
</table>

Note: \(^*(p < 0.05)\) represent a significantly statistical difference between the people with genotype TT and AT or AA, which suggest that the presence of at least one copy of the A allele was significantly associated with the higher BMI, body mass index; TG, triglyceride; TC, cholesterol; HDL, high-density lipoprotein; INS, insulin; RBC, red blood cell; HB, Hemoglobin; HCT, hematocrit.
Therefore, FTO rs9939609 polymorphism may be a factor that affects the therapeutic effect of the exercise combined with dietary intervention on obesity in Chinese children and adolescents.

Although many previous studies have reported the association between FTO rs9939609 polymorphisms and obesity in children and adolescents, the precise mechanism of this association remains unknown. It was reported that FTO rs9939609 polymorphism contributes to variation of the plasma C-reactive protein (CRP) level in obesity middle-aged German individuals and Chinese Han people. Meanwhile, obesity is associated with higher level of high sensitivity-CRP in children and adolescents. Therefore, we inferred there may be also some associations between the FTO rs9939609 polymorphism and the CRP levels in children and adolescents. Moreover, the CRP level has been reported could be reduced by dietary or physical exercise in obesity patients. Thus, the CRP may play crucial roles in the effect of the exercise combined with dietary intervention on obesity in Chinese children and adolescents; the FTO rs9939609 polymorphism may influence this effect through regulating the levels of CRP.

In addition, it was reported that the minor A allele of the FTO rs9939609 was significantly associated with the higher levels of serum leptin concentrations independently of potential confounders including adiposity in European adolescents.

Leptin is produced by adipocytes and plays a key role in the regulation of appetite and body weight. Some publications reported that leptin concentration could be decreased by dietary and/or exercise intervention. Thus, there may be a link between the FTO rs9939609 polymorphism and serum leptin in the control of energy balance by the combined intervention in this study.

Furthermore, it was reported that daily physical activity may modify the effect of the FTO rs9939609 polymorphism on obesity-related traits in adolescents. Dietary fatty acid intake distribution could interact with this FTO genetic variation and obesity. On the contrary, the FTO rs9939609 minor allele A benefits in reduction of dietary intake. Combined with the results of this study, the effect of the exercise combined with dietary intervention on obesity was significantly influence by FTO rs9939609 polymorphism, the evidence of mutual influence between FTO rs9939609 polymorphism and the dietary or/and exercise intervention has been provided. However, given the limitation of sample size and single population, the deviation of genotype frequencies from the Hardy-Weinberg predictions was found. Thus, more studies were required to further investigate the association between FTO rs9939609 polymorphism and this exercise combined with dietary intervention in Chinese obese children and adolescents.

**Conclusions**

The effect of exercise combined with dietary intervention on obesity, which has a good therapy effect on the development of obesity, was associated with the FTO rs9939609 genotype in Chinese adolescents and children. The results offer guidance for the excess body weight loss of Chinese adolescents and children with genetic predisposition.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

Reference


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