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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 China[1]. This trend is not limited to adults but is also apparent in the children and adolescents[2-5]. 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 China[5]. 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 them[6]. 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 factors[7,8]. The fat mass- and obesity-associated gene (*FTO*) was a gene has been wildly reported to be associated with common obesity in adolescents and children from various ethnic backgrounds[9-11]. 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 children[10]. Mean-

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while, the dietary fatty acid distribution can influence the effect of the *rs9939609* polymorphism of the *FTO* gene on children and adolescents' obesity risk[12]. 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[13-15]. 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 participates' 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) $\geq$ 25 kg/m^2 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 1min 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, HRR) $\times$ 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).

Genomic DNA Extraction and FTO Genotyping

Genomic DNA was isolated from a whole peripheral blood sample of each camper by using the Qiagen DNA Blood Maxi Kit (Qiagen Inc, Valencia, CA, USA). Genotyping of the *FTO* SNP *rs9939609* was performed by using a TaqMan SNP Genotyping Assay (Applied Bio-Systems Inc, Foster City, CA, USA). All assays were performed in duplicate, and an automatic allele calling quality value of 0.95 was used to determine genotype assignment. Samples with indeterminate genotyping results by the TaqMan SNP Genotyping Assay were reanalyzed by PCR-amplified DNA using forward primer 5'-CTATGGTTCTACAGTTCCAGTCATTT-3' and reverse primer 5'-AGGATAGTTTCGATC-TATTGACCTC-3'.

Detection of Obesity Related Blood Parameters

Blood parameters including blood glucose (BG), insulin (INS), total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), red blood cell (RBC), Hemoglobin (HB) and hematocrit (HCT) were measured routinely by fasting blood tests in physical examination.

Statistical Analysis

All analyses were performed with SPSS 19.0. (SPSS Inc., Chicago, IL, USA) Logarithmic transformation was used to normalize all the measurement variables that were skewed. Departure of genotype distribution from Hardy-Weinberg equilibrium was assessed by using chi-square analysis. The two independent samples t-test and chi-square analyses were used to analyze the demographics of participant based on genotype (age, gender). Analyses of one-way variance (ANOVA) were used to examine the association of *FTO rs9939609* (AA/AT and TT) with the obesity related parameters. Paired sample T test was used to examine the difference between obesity related parameters before and after intervention. Two independent samples t-test was used to access the association between the outcomes of intervention and the genotype. Differences were considered significant with p-value less than 0.05. Values are expressed as means (S) ± standard deviation (SD).

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[16-18]. 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 chinese 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

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

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

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. BMI, body mass index; TG, triglyceride; TC, cholesterol; HDL, high-density lipoprotein; INS, insulin; RBC, red blood cell; HB, Hemoglobin; HCT, hematocrit.

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

Factors	Bootstrap					
	Mean	Standard deviation	Standard error	*p*-value	95% CI Upper	95% CI Lower
BMI	1.20198	- 0.0108	0.1906	0.001	0.7792	1.5456
BG	0.15689	0.0024	0.0578	0.008	0.0420	0.2750
TG	0.21318	- 0.0003	0.0334	0.001	0.1502	0.2799
TC	0.96916	- 0.0009	0.0510	0.001	0.8686	1.0688
HDL	0.11063	- 0.0001	0.0149	0.001	0.0808	0.1395
INS	34.6110	0.2251	3.2416	0.001	28.4791	41.291
RBC	0.12889	- 0.0006	0.0178	0.001	0.0915	0.1613
HB	5.78200	- 0.0120	0.4780	0.001	4.8110	6.6750
HCT	1.36050	- 0.0029	0.1570	0.001	1.0315	1.6664

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. BMI, body mass index; TG, triglyceride; TC, cholesterol; HDL, high-density lipoprotein; INS, insulin; RBC, red blood cell; HB, Hemoglobin; HCT, hematocrit.

Table III. Effect of Exercise combined with dietary intervention on obesity associated with FTO rs9939609 polymorphism (mean ± SD).

Factors	Mean difference (I-J)	
	AT or AA	TT
BG	0.19 ± 0.01	0.21 ± 0.06
TG	0.30 ± 0.18	0.20 ± 0.19
TC	**1.52 ± 0.29***	0.69 ± 0.12
HDL	0.28 ± 0.01*	0.28 ± 0.03
LDL	**1.10 ± 0.60***	0.45 ± 0.15
INS	33.69 ± 8.33	32.8 ± 16.69
RBC	**1.55 ± 0.31***	0.49 ± 0.38
HB	**7.85 ± 0.30***	4.96 ± 1.92
HCT	**2.29 ± 0.19***	1.14 ± 0.56

Note: Independent T test was used to examine the association of FTO rs9939609 polymorphism (AA/AT and TT) with the mean difference of TG, TC, HDL, INS, RBC, HB and HCT before and after intervention. *$p < 0.05$, significant difference compared with TT genotype. "I" represents the value before intervention and "J" represents the value after intervention.

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[21,22]. Meanwhile, obesity is associated with higher level of high sensitivity-CRP in children and adolescents[23]. 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[24-27]. 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[28]. Leptin is produced by adipocytes and plays a key role in the regulation of appetite and body weight[29,30]. Some publications reported that leptin concentration could be decreased by dietary and/or exercise intervention[31-33]. 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[34-36]. Dietary fatty acid intake distribution could interact with this *FTO* genetic variation and obesity[12]. On the contrary, the *FTO rs9939609* minor allele A benefits in reduction of dietary intake[37,38]. 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

1) Sun Z, Zheng L, Detrano R, Zhang X, Xu C, Li J, Hu D, Sun Y. Incidence and predictors of hypertension among rural Chinese adults: results from Liaoning province. Ann Fam Med 2010; 8: 19-24.
2) Ji CY, Cheng TO. Epidemic increase in overweight and obesity in Chinese children from 1985 to 2005. Int J Cardiol 2009; 132: 1-10.
3) Cui Z, Huxley R, Wu Y, Dibley MJ. Temporal trends in overweight and obesity of children and adolescents from nine Provinces in China from 1991-2006. Int J Pediatr Obes 2010; 5: 365-374.
4) Li Y, Schouten EG, Hu X, Cui Z, Luan D, Ma G. Obesity prevalence and time trend among youngsters in China, 1982-2002. Asia Pac J Clin Nutr 2008; 17: 131-137.
5) Yu Z, Han S, Chu J, Xu Z, Zhu C, Guo X. Trends in overweight and obesity among children and adolescents in China from 1981 to 2010: a meta-analysis. PLoS One 2012; 7: e51949.
6) Dietz WH. Health consequences of obesity in youth: childhood predictors of adult disease. Pediatrics 1998; 101: 518-525.
7) Wardle J, Carnell S, Haworth CM, Plomin R. Evidence for a strong genetic influence on childhood adiposity despite the force of the obesogenic environment. Am J Clin Nutr 2008; 87: 398-404.
8) Moleres A, Martinez J, Marti A. Genetics of obesity. Curr Obes Rep 2013; 2: 23-31.
9) Sentinelli F, Incani M, Coccia F, Capoccia D, Cambuli VM, Romeo S, Cossu E, Cavallo MG, Leonetti F, Baroni MG. Association of FTO polymorphisms with early age of obesity in obese Italian subjects. Exp Diabetes Res 2012; 2012.
10) Reinehr T, Wolters B, Roth CL, Hinney A. FTO Gene: association to weight regain after lifestyle intervention in overweight children. Horm Res Paediatr 2014; 81: 391-396.
11) Xi B, Shen Y, Zhang M, Liu X, Zhao X, Wu L, Cheng H, Hou D, Lindpaintner K, Liu L. The common rs9939609 variant of the fat mass and obesity-associated gene is associated with obesity risk in children and adolescents of Beijing, China. BMC Med Genet 2010; 11: 107.
12) Moleres A, Ochoa MC, Rendo-Urteaga T, Martínez-González MA, Azcona San Julián MC, Martínez JA, Marti A. Dietary fatty acid distribution modifies obesity risk linked to the rs9939609 polymorphism of the fat mass and obesity-associated gene in a Spanish case–control study of children. Br J Nutr 2012; 107: 533-538.
13) Eliakim A, Kaven G, Berger I, Friedland O, Wolach B, Nemet D. The effect of a combined intervention on body mass index and fitness in obese children and adolescents–a clinical experience. Eur J Pediatr 2002; 161: 449-454.
14) Chen AK, Roberts CK, Barnard RJ. Effect of a short-term diet and exercise intervention on metabolic syndrome in overweight children. Metabolism 2006; 55: 871-878.
15) Nemet D, Barkan S, Epstein Y, Friedland O, Kowen G, Eliakim A. Short-and long-term beneficial effects of a combined dietary-behavioral-physical activity intervention for the treatment of childhood obesity. Pediatrics 2005; 115: e443-e449.
16) Lee H-J, Kang JH, Ahn Y, Han B-G, Lee J-Y, Song J. Effects of common< i> FTO</i> gene variants associated with BMI on dietary intake and physical activity in Koreans. Clin Chim Acta 2010; 411: 1716-1722.
17) Tanofsky-Kraff M, Han JC, Anandalingam K, Shomaker LB, Columbo KM, Wolkoff LE, Kozlosky M, Elliott C, Ranzenhofer LM, Roza CA. The FTO gene rs9939609 obesity-risk allele and loss of control over eating. Am J Clin Nutr 2009; 90: 1483-1488.
18) Wardle J, Carnell S, Haworth CM, Farooqi IS, O'rahilly S, Plomin R. Obesity associated genetic variation in FTO is associated with diminished satiety. J Clin Endocrinol Metab 2008; 93: 3640-3643.
19) Zhang M, Zhao X, Cheng H, Wang L, Xi B, Shen Y, Hou D, Mi J. Age-and sex-dependent association between FTO rs9939609 and obesity-related traits in chinese children and adolescents. PLoS One 2014; 9: e97545.
20) Cecil JE, Tavendale R, Watt P, Hetherington MM, Palmer CN. An obesity-associated FTO gene variant and increased energy intake in children. N Engl J Med 2008; 359: 2558-2566.
21) Sun Y, Sun J, Wang X, You W, Yang M. Variants in the fat mass and obesity associated (FTO) gene are associated with obesity and C-reactive protein levels in Chinese Han populations. Clin Invest Med 2010; 33: E405-E412.
22) Fisher E, Schulze MB, Stefan N, Häring HU, Döring F, Joost HG, Al-Hasani H, Boeing H, Pischon T. Association of the FTO rs9939609 single nucleotide polymorphism with creactive protein levels. Obesity 2009; 17: 330-334.
23) Yang S, Gong C, Cao B, Yan C. [Relationship between serum high-sensitivity C-reactive protein and obesity and impaired glycose metabolism in children and adolescents]. Zhonghua Er Ke Za Zhi 2006; 44: 933-936.
24) Seshadri P, Iqbal N, Stern L, Williams M, Chicano KL, Daily DA, Mcgrory J, Gracely EJ, Rader DJ, Samaha FF. A randomized study comparing the effects of a low-carbohydrate diet and a conventional diet on lipoprotein subfractions and C-reactive protein levels in patients with severe obesity. Am J Med 2004; 117: 398-405.
25) Neuhouser ML, Schwarz Y, Wang C, Breymeyer K, Coronado G, Wang C-Y, Noar K, Song X, Lampe JW. A low-glycemic load diet reduces serum C-reactive protein and modestly increases

adiponectin in overweight and obese adults. J Nutr 2012; 142: 369-374.

26) Plaisance EP, Grandjean PW. Physical activity and high-sensitivity C-reactive protein. Sports Med 2006; 36: 443-458.

27) Shaharyar S, Roberson LL, Jamal O, Karim A, Blaha MJ, Martin SS, Agatston AS, Blumenthal RS, Conceicao RD, Meneghelo RS. Physical activity is associated with lower prevalence of elevated high sensitivity C-reactive protein in overweight and obese, but not in normal weight individuals. In: Circulation. Lippincott Williams & Wilkins, Philadelphia, USA, 2013.

28) Labayen I, Ruiz J, Ortega F, Dalongeville J, Jiménez-Pavón D, Castillo M, De Henauw S, González-Gross M, Bueno G, Molnar D. Association between the FTO rs9939609 polymorphism and leptin in European adolescents: a possible link with energy balance control. The HELENA study. Int J Obes 2010; 35: 66-71.

29) Havel PJ. Role of adipose tissue in body-weight regulation: mechanisms regulating leptin production and energy balance. Proc Nutr Soc 2000; 59: 359-371.

30) Tataranni P. Mechanisms of weight gain in humans. Eur Rev Med Pharmacol Sci 2000; 4: 1-8.

31) Gutin B, Ramsey L, Barbeau P, Cannady W, Ferguson M, Litaker M, Owens S. Plasma leptin concentrations in obese children: changes during 4-mo periods with and without physical training. Am J Clin Nutr 1999; 69: 388-394.

32) Kraemer RR, Chu H, Castracane VD. Leptin and exercise. Exp Biol Med 2002; 227: 701-708.

33) Abbenhardt C, Mctiernan A, Alfano CM, Wener MH, Campbell KL, Duggan C, Foster-Schubert KE, Kong A, Toriola AT, Potter JD. Effects of individual and combined dietary weight loss and exercise interventions in postmenopausal women on adiponectin and leptin levels. J Intern Med 2013; 274: 163-175.

34) Scott RA, Bailey ME, Moran CN, Wilson RH, Fuku N, Tanaka M, Tsiokanos A, Jamurtas AZ, Grammatikaki E, Moschonis G. FTO genotype and adiposity in children: physical activity levels influence the effect of the risk genotype in adolescent males. Eur J Hum Genet 2010; 18: 1339-1343.

35) Andreasen CH, Stender-Petersen KL, Mogensen MS, Torekov SS, Wegner L, Andersen G, Nielsen AL, Albrechtsen A, Borch-Johnsen K, Rasmussen SS. Low physical activity accentuates the effect of the FTO rs9939609 polymorphism on body fat accumulation. Diabetes 2008; 57: 95-101.

36) Ruiz JR, Labayen I, Ortega FB, Legry V, Moreno LA, Dallongeville J, Martínez-Gómez D, Bokor S, Manios Y, Ciarapica D. Attenuation of the effect of the FTO rs9939609 polymorphism on total and central body fat by physical activity in adolescents: the HELENA study. Arch Pediatr Adolesc Med 2010; 164: 328-333.

37) Johnson L, Van Jaarsveld CH, Emmett PM, Rogers IS, Ness AR, Hattersley AT, Timpson NJ, Smith GD, Jebb SA. Dietary energy density affects fat mass in early adolescence and is not modified by FTO variants. PLoS One 2009; 4: e4594.

38) Lear SA, Deng WQ, Pare G, Sulistyoningrum DC, Loos RJ, Devlin A. Associations of the FTO rs9939609 variant with discrete body fat depots and dietary intake in a multi-ethnic cohort. Genet Res (Camb) 2011; 93: 419-426.