European Review for Medical and Pharmacological Sciences 2015; 19: 614-623

Association of fat-mass and obesity-associated gene FTO rs9939609 polymorphism with the risk of obesity among children and adolescents: a meta-analysis

L.-L. QUAN, H. WANG, Y. TIAN, X. MU, Y. ZHANG, K. TAO

Department of Plastic Surgery, General Hospital of Shenyang Military Area Command, Shenhe District, Shenyang, Liaoning, China

Abstract. – OBJECTIVE: To elucidate the association of fat-mass and obesity-associated gene (FTO) rs9939609 polymorphism with obesity among children and adolescents.

METHODS: A literature search was conducted in PubMed, MEDLINE, Springer, and Google scholar to identify eligible studies. The pooled odds ratios (ORs) with 95% confidence intervals (CIs) were used for four models: co-dominant model (AA vs. TT, AT vs. TT), dominant model (AA + AT vs. TT), recessive model (AA vs. AT + TT), and allelic model (A vs. T). Subgroup analyses stratified by ethnicity (Caucasian, others) and participants (children, children and adolescents) were assessed under allelic model. The heterogeneity and publication bias were examined.

RESULTS: This meta-analysis included 12 eligible studies consisting 5,000 cases and 9,853 controls. The results revealed that FTO rs9939609 polymorphism was significantly associated with the increased risk of obesity in co-dominant model (AA vs. TT: OR = 1.91, 95% CI: 1.47-2.48, $p < 0.01$; AT vs. TT: OR = 1.18, 95% CI: 1.02-1.38, $p = 0.03$), dominant model (AA + AT vs. TT: OR = 1.47, 95% CI: 1.35-1.59, $p < 0.01$), recessive model (AA vs. AT + TT: OR = 1.79, 95% CI: 1.47-2.17, $p < 0.01$), and allelic model (A vs. T: OR = 1.39, 95% CI: 1.22-1.58, $p < 0.01$). Similar results were obtained for the subgroup analyses stratified by ethnicity and participants under allelic model.

CONCLUSIONS: FTO rs9939609 polymorphism is associated with the increased risk of obesity among children and adolescents, especially the homozygous carriers.

Key Words:
FTO, rs9939609, Polymorphism, Obesity, Meta-analysis.

Introduction

Obesity, caused by a complex interaction between the environment, genetic predisposition, and human behavior, has become a global epidemic due to increasing incidence worldwide[1]. Currently, at least 300 million people are obese worldwide, according to the World Health Organization (WHO) estimation[2]. Alarmingly, obesity is increasing among children and adolescents worldwide and is a risk factor for various disorders including type 2 diabetes, hypertension, cardiovascular disease, stroke, and cancer[1].

In the past few years, with the progress of genome-wide association studies (GWAS), valid evidence emerged to indicate a significance and involvement of the genetic component in the occurrence and development of obesity[3]. The fat-mass and obesity-associated gene (FTO), since its first discovery by Frayling et al[4], has attracted considerable attention with its potential association with the development of obesity[5-9]. Recent meta-analysis by Peng et al[10] provided significant evidence for a modest increase risk of obesity associated with the five single nucleotide polymorphisms (SNP) (rs9939609, rs1421085, rs8050136, rs17817449, and rs1121980) across various ethnic populations. Among these polymorphisms, the SNP rs9939609 is the most extensively studied (n = 68,856; 29 studies). It is noteworthy that most of the included studies for rs9939609 were based on adults (27 of 29 studies), and two studies did not offer the information on HWE. In addition, the pooled results were obtained only under additive and allelic model. A subsequent mete-analysis was conducted to focus on the association of common genetic variants in FTO (rs9939609, rs1421085, rs1558902, and rs8050136) with overweight and obesity risk among children and adolescents[11]. Again, SNP rs9939609 was the most extensively investigated (n = 30,254; 14 studies), and the pooled results were also obtained under only an

Corresponding Author: Kai Tao, MD; e-mail: kai-tao@tom.com

additive model, revealing that rs9939609 polymorphism was significantly associated with overweight and obesity risk, with an overall odds ratio (OR) of 1.35 (95%CI: 1.27-1.44). Similar result was obtained for obesity with the subgroup analysis which pooled data from 8 studies. In this meta-analysis, we aimed to better elucidate the association of FTO rs9939609 polymorphism with the risk of obesity among children and adolescents, based on the assessment under four genetic models including co-dominant model, dominant model, recessive model, and allelic model.

Methods

Literature Search

Under the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement[12], a literature search was conducted in PubMed, MEDLINE, Springer, and Google scholar with a predesigned protocol up to July 31 2014. The search was limited to English-language publications. The following search terms were used: "rs9939609" and "FTO or fat mass and obesity-associated gene" and "obesity" and "children or adolescents". Additionally, references of eligible studies were also screened for any potential studies.

Study Selection

Studies will be included if they met: (1) study evaluating the relationship between rs9939609 polymorphism and the risk of obesity; (2) using case-control, cross-sectional, or cohort design; (3) the cases were obese and the controls were healthy; (4) participants should be children and/or adolescents; and (5) providing an odds ratio (OR) or relative risk (RR) with 95% confidence interval (CI) or sufficient raw data for calculation of OR/RR and CI.

The exclusion criteria were as follows: (1) the study design was based on family or sibling pairs; (2) the genotype frequency of rs9939609 was not reported; (3) the study did not evaluate the association of rs9939609 with the risk of obesity; (4) studies were excluded if the controls violated the Hardy-Weinberg Equilibrium (HWE); (5) reviews, letters and comments were excluded; (6) duplicate studies were excluded. In the case that multiple publications were from one study cohort, only the publication with the most detailed information was included.

Data Extraction

With the standard protocol, two investigators independently extracted the following data from included studies: name of first author; publication year; country of origin; study design; numbers of cases and controls; characteristics of subjects; allele frequency. Evidence of HWE was collected, and $p > 0.05$ was considered significantly accorded with HWE. Discrepancies were resolved by discussion to reach a consensus.

Statistical Analysis

The association of rs9939609 polymorphism with the risk of obesity was estimated by calculating pooled OR and 95% CI. The pooled ORs with 95%CIs were used for co-dominant model (AA vs. TT or AT vs. TT), dominant model (AA + AT vs. TT), recessive model (AA vs. AT + TT), and allelic model (A vs. T), respectively. Subgroup analyses stratified by ethnicity (Caucasian, others) and participants (children, children and adolescents) were assessed under allelic model. The heterogeneity across studies was examined by the Cochran's Q statistic and the I^2 statistic[13]. The fixed effects model was selected for homogeneous outcomes ($p \geq 0.05$ and $I^2 < 50\%$) and the random effects model was applied for heterogeneous outcomes ($p < 0.05$ or $I^2 \geq 50\%$). Publication bias was observed by the funnel plot, and funnel plot asymmetry was assessed by Egger's regression test[14]. To assess the stability of the results, sensitivity analysis was performed by removing one study at a time and repeating the meta-analysis. $p < 0.05$ was considered to be statistically significant. Statistical analysis was performed with Review Manager 5.2 version software (Cochrane Collaboration) and STATA 12.0 version software (Stata Corporation, College Station, TX, USA).

Results

Characteristics of Included Studies

The process of study selection is depicted in Figure 1. Initially, 1,216 articles were identified according to the search strategy (PubMed: 128; MEDLINE: 127; Springer: 619; Google Scholar: 342), of which 914 were excluded because they were duplicate publication. After screening the titles and abstracts, 248 articles were excluded because they were inconsistent with the inclusion criteria. With further examination, 42 of remaining 54 articles were excluded. No additional eli-

Table I. Characteristics of included studies in the meta-analysis.

Study	Publication year	Country	Ethnicity	Diagnosis criteria	Sample size			Participants	Study design
					Total	Case	Control		
Jacobsson	2008	Sweden	Caucasian	BMI SD values	962	450	512	Children	Case-control study
Moleres	2012	Spain	Caucasian	> 97th percentile for BMI values	354	208	146	Children and adolescents	Case-control study
Wardle	2008	UK	Caucasian	BMI SD values	4948	926	4022	Children	Case-control study
Zhang	2014	China	Asian	the age- and sex- specific BMI by IOTF	3503	757	2746	Children and adolescents	Cross-sectional study
Zavattari	2011	Italy	Caucasian	BMI > 95th percentile according to the reference	1455	912	543	Children	Case-control study
Beata	2013	Poland	Caucasian	> 95th percentile for age and sex reference values the age- and sex- specific cut-off points	160	136	24	Children and adolescents	Cross-sectional study
Olza	2013	Spain	Caucasian		534	292	242	Children	Case-control study
Riffo	2012	Chile	Amerindian	BMI > 95th percentile	374	238	136	Children	Case-control study
Mangge	2011	Austria	Caucasian	> 95th percentile and BMI values	371	268	103	Adolescents	Case-control study
Luczynski	2012	Polish	Caucasian	BMI SD values	833	199	634	Children	Cross-sectional study
González	2012	Spain	Caucasian	> 95th percentile for age and sex reference values	386	202	184	Children	Case-control study
Ibba	2013	Italy	Caucasian	> 95th percentile for age and sex reference values	955	412	543	Children and adolescents	Case-control study

BMI, body mass index.

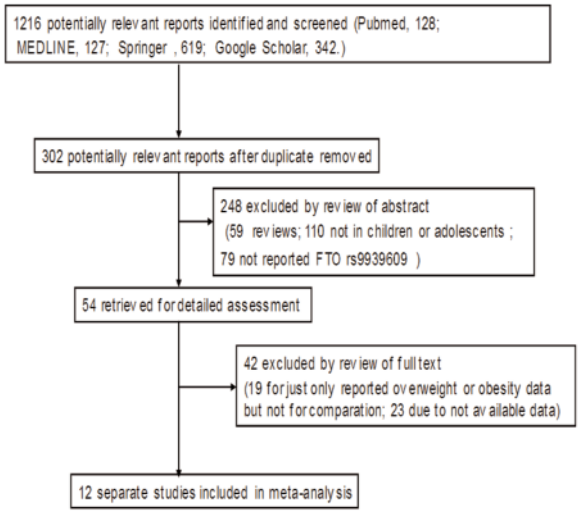

Figure 1. Process of the study selection.

gible articles were obtained via manual literature searches. Thus, 12 articles were finally included in current meta-analysis [15-26].

The characteristics of included studies are shown in Table I. A total of 12 articles (published from 2008 to 2014) comprising 14,835 participants (5,000 cases and 9,853 controls) were selected for present study. All included studies were case-control study or cross-sectional study, varied in sample size (from 160 to 4948), and enrolled children or both children and adolescents. In addition, most of included studies were performed on Europe population except for two studies whose participants were form Asian[26] or South America[21]. The genotypes in the controls of all included studies were accorded with HWE ($p > 0.05$, Table II).

Meta-Analysis Results

Table III lists the main results of the meta-analysis. ORs with 95% CIs were used to assess the strength of association of rs9939609 polymorphism with obesity. The results revealed that FTO rs9939609 polymorphism was significantly associated with increased risk of obesity. The pooled ORs (95% CIs) for the genetic model comparison were as follows: co-dominant model (AA vs. TT: OR = 1.91, 95% CI: 1.47-2.48, $p < 0.01$; AT vs. TT: OR = 1.18, 95% CI: 1.02-1.38, $p < 0.01$), dominant model (AA + AT vs. TT: OR = 1.47, 95% CI: 1.35-1.59, $p < 0.01$), recessive model (AA vs. AT + TT: OR = 1.79, 95% CI: 1.47-2.17, $p < 0.01$), and allelic model (A vs. T: OR = 1.39, 95% CI: 1.22-1.58, $p < 0.01$). Fur-

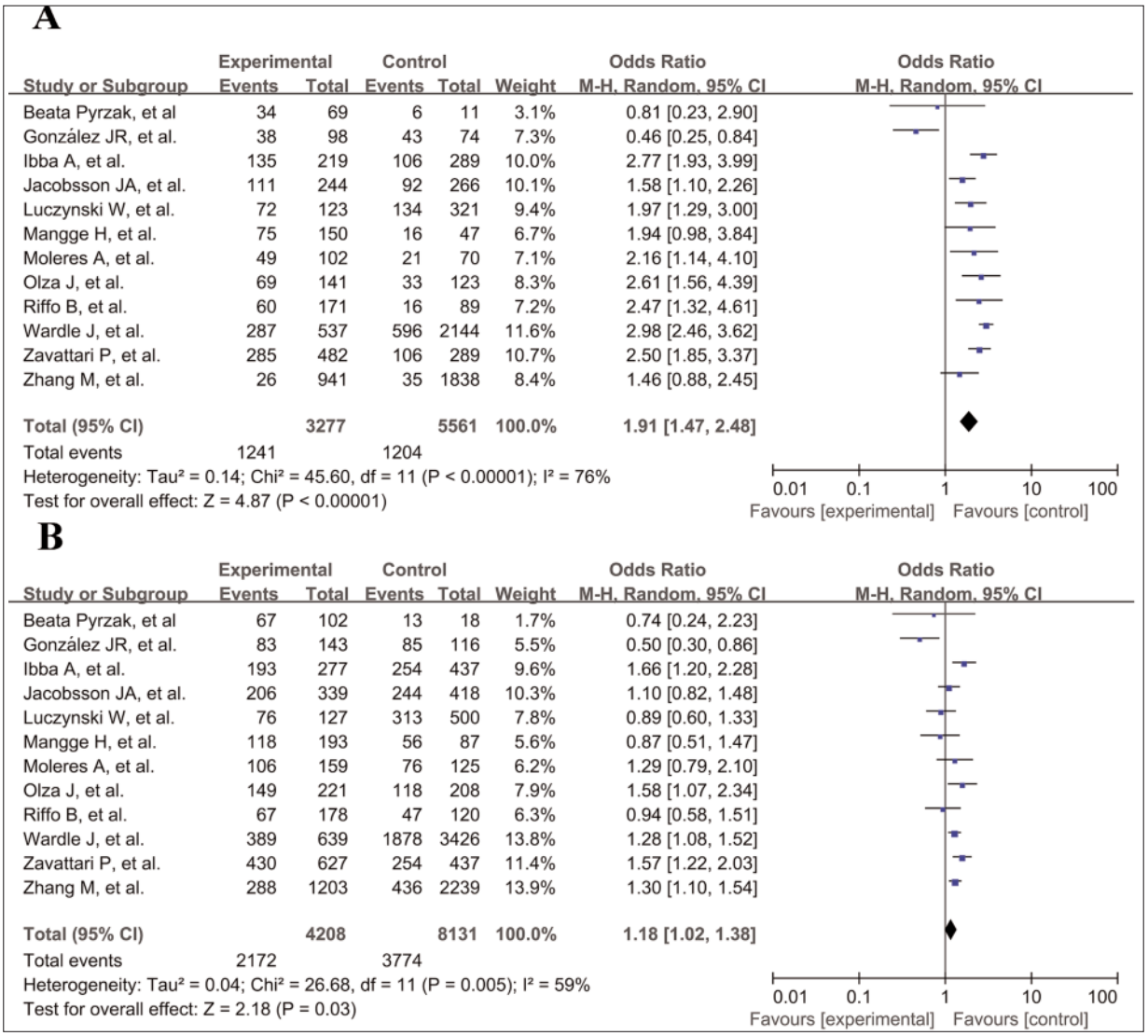

Figure 2. Forest plot of the association between obesity and the rs9939609 polymorphism under co-dominant model: (A): AA vs. TT; (B): AT vs. TT.

thermore, we performed subgroup analyses stratified by ethnicity and participants under allelic model; and the results are presented in Table IV. Significant association between rs9939609 polymorphism and obesity risk was found in Caucasians (OR = 1.38, 95% CI: 1.19-1.61, $p < 0.01$) and others (OR = 1.33, 95% CI: 1.17-1.52, $p < 0.01$). The overall pooled OR in children group, and in children and adolescents group was 1.39 (95% CI: 1.15-1.68, $p < 0.01$) and 1.40 (95% CI: 1.15-1.71, $p < 0.01$), respectively.

Sensitivity Analysis

The influence of a single study on the overall meta-analysis was examined by excluding each study at a time. The result confirmed the significant association between rs9939609 polymorphism and the risk of obesity.

Heterogeneity

Statistically significant heterogeneity was observed for A vs. T ($p < 0.01$, $I^2 = 62\%$), AA vs. TT ($p = 0.02$, $I^2 = 52\%$) and AA vs. TT+AT (P = 0.02, $I^2 = 55\%$), but there was no significant heterogeneity for AA+AT vs. TT ($p = 0.12$, $I^2 = 35\%$) and AT vs. TT ($p = 0.75$, $I^2 = 0.0\%$). In the subgroup analyses, significant heterogeneity was also existed ($p < 0.05$, $I^2 > 50\%$).

Publication Bias

As shown in Figure 6, the shapes of the funnel plots did not reveal any evidence of obvious

Table II. Genotype frequencies of rs9939609 in studies included in the meta-analysis.

Study	Year of publication	Case genotype			Control genotype			HWE chi-square test	*p* value
		TT	AT	AA	TT	AT	AA		
Jacobsson	2008	133	206	111	174	244	92	0.16	0.69
Moleres	2012	53	106	49	49	76	21	0.95	0.33
Wardle	2008	250	389	287	1548	1878	596	0.46	0.50
Zhang	2014	915	288	26	1803	436	35	2.11	0.15
Zavattari	2011	197	430	285	183	254	106	1.11	0.29
Beata	2013	35	67	34	5	13	6	0.17	0.68
Olza	2013	72	149	69	90	118	33	0.34	0.56
Riffo	2012	111	67	60	73	47	16	3.55	0.06
Mangge	2011	75	118	75	31	56	16	1.28	0.26
Luczynski	2012	51	76	72	187	313	134	0.02	0.88
González	2012	60	83	38	31	85	43	0.90	0.34
Ibba	2013	84	193	135	183	254	106	1.11	0.29

HWE: Hardy-Weinberg equilibrium, it was evaluated using the goodness-of-fit chi-square test. p-values were presented. $p < 0.05$ was considered representative of a departure from HWE.

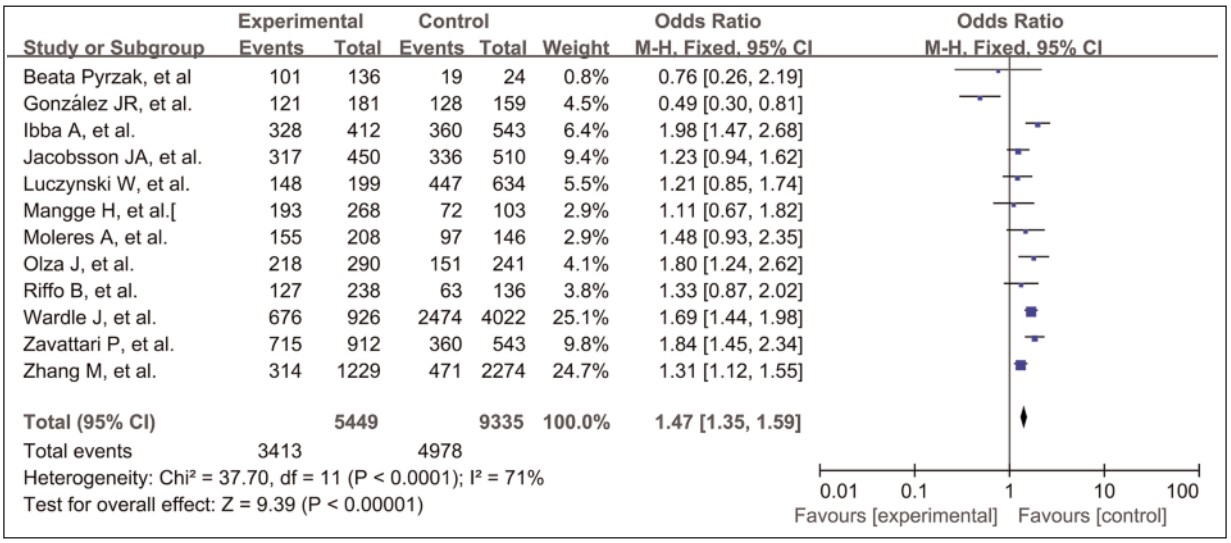

Figure 3. Forest plot of the association between obesity and the rs9939609 polymorphism under dominant model.

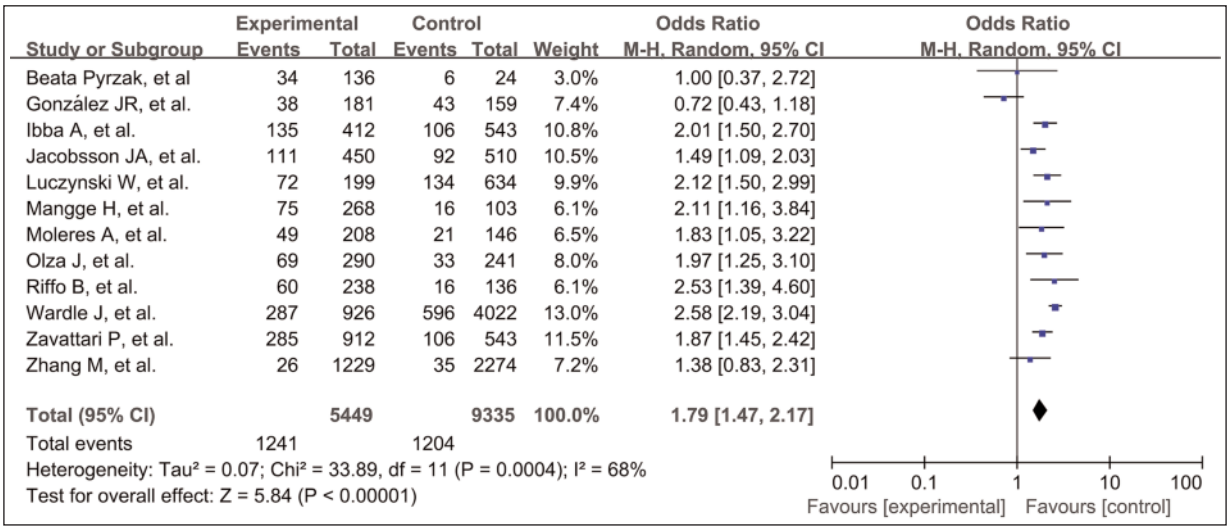

Figure 4. Forest plot of the association between obesity and the rs9939609 polymorphism under recessive model.

Table III. Results of meta-analysis for rs9939609 polymorphism with obesity.

rs9939609	Sample size		Test of association			Model	Test of heterogeneity			Bgger's test for publication bias[c]	
	Cases	Control	OR (95%CI)	Z	*p* value		Q	*p* value	I^2 (%)	z	*p* value
A vs. T	10898	18670	1.39 (1.22, 1.58)	4.94	<0.01	Random	50.52	<0.01	78	1.17	0.244
AA vs. TT	3277	5561	1.91 (1.47, 2.48)	4.87	<0.01	Random	45.60	<0.01	76	0.89	0.373
AT vs. TT	4208	8131	1.18 (1.02, 1.38)	2.18	0.03	Random	26.68	0.01	59	1.58	0.115
AA vs. TT+AT	5449	9335	1.79 (1.47, 2.17)	5.84	<0.01	Random	33.89	<0.01	68	1.85	0.064
AA+AT vs. TT	5449	9335	1.47 (1.35, 1.59)	9.39	<0.01	Random	37.70	<0.01	71	0.21	0.837

OR: Odds ratio; CI: confidence interval.

asymmetry. Also there was no statistical evidence of publication bias among studies by using Egger's regression test for all models (p = 0.298 for A vs. T, p = 0.636 for AA vs. TT, p = 0.884 for AT vs. TT, p = 0.338 for AA vs. TT+AT, p = 0.961 for AA+AT vs. TT, respectively).

Discussion

In current meta-analysis, a total of 12 studies consisting 14,835 (5,000 cases and 9,853 controls) participants were included. The pooled result confirmed that FTO rs9939609 polymorphism was significantly associated with the increased risk of obesity among children and adolescents; and similar results were obtained for the subgroup analyses stratified by ethnicity and participants under allelic model. Although there was a significant heterogeneity across studies, sensitivity analysis did not alter this significant association. Furthermore, we found the allele A of rs9939609 might increase the risk of obesity among children and adolescents.

Similarly, several previous meta-analyses[10,11,27,28] also identified the significant association of FTO rs9939609 polymorphism with the increased risk of obesity, although these studies did not exclusively focused on the role of FTO rs9939609 polymorphism in obesity among children and adolescents. Nevertheless, the results should be interpreted with caution. As a multi-factorial disease, obesity is considered largely attributed to environmental interaction in subjects with obesity susceptibility genes[29,30]. On the other hand, although accumulating evidence have consistently confirmed the role of FTO gene polymorphism for the occurrence and development of obesity across multiple populations, especially in Caucasian populations[31-33], a remarkable fact is that FTO polymorphism do not appear to affect BMI or the risk of obesity in several other populations such as African Americans[6], Chinese Hans[34], Japanese[35] or Oceanic populations (Melanesians, Micronesians and Polynesians)[36]. However, there was limited data on these populations, and only two studies enrolled these populations were included in present study. What should be accounted for the difference among ethnicities? An acceptable explanation may be the differences in minor allele frequency (MAF) or linkage disequilibrium (LD) patterns across various ethnic populations, which is based on the truth that MAF in Asian populations and

Table IV. Results of subgroup analyses.

Subgroup	No. of studies	Sample size		Test of association				Test of heterogeneity		
		Cases	Controls	OR (95%CI)	Z	*p* value	Model	Q	*p* value	I^2 (%)
Ethnicity										
Caucasian	10	7964	13850	1.38 (1.19, 1.61)	4.17	<0.01	Random	45.65	<0.01	80
Others	2	2934	4820	1.33 (1.17, 1.52)	4.21	<0.01	Fixed	1.36	0.24	26
Participants										
Children	7	6392	12490	1.39 (1.15,1.68)	3.39	<0.01	Random	40.65	<0.01	85
Children and adolescents	4	3970	5974	1.40 (1.15,1.71)	3.30	<0.01	Random	7.77	0.05	61

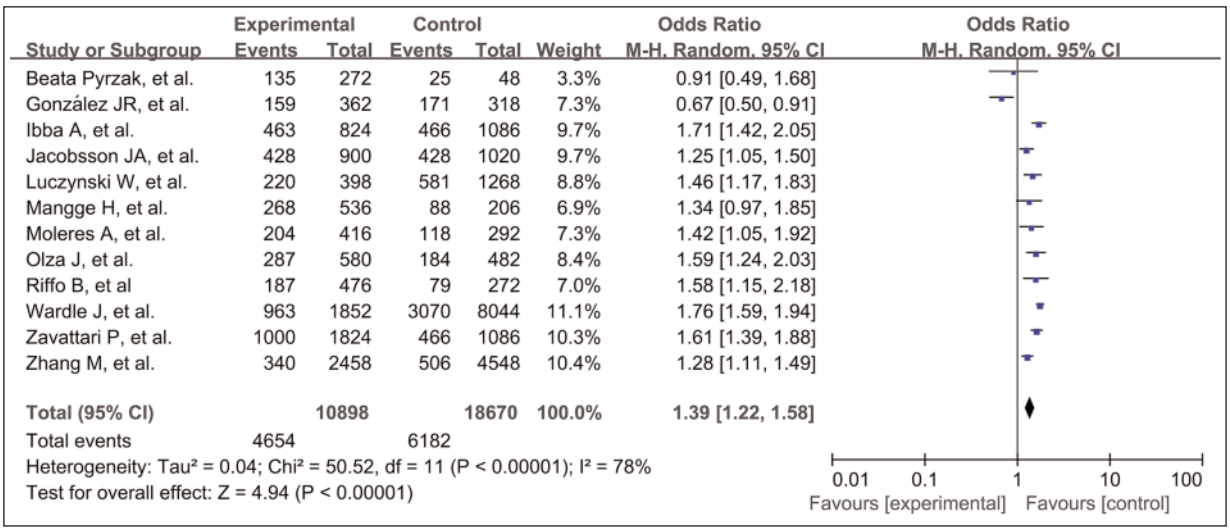

Figure 5. Forest plot of the association between obesity and the rs9939609 polymorphism under allelic model.

South Americans is less than half of that reported for populations of European descent and the patterns of LD are also distinct[9].

Our finding that the allele A of rs9939609 might increase the risk of obesity among children and adolescents is consistent with the study by Wardle et al[18]. They found that the FTO rs9939609 polymorphism might impair satiety responsiveness and thus have a direct effect on appetite, which may naturally influence adiposity. On the other hand, they considered that except for the effects on appetite, other obesogenic effects of the FTO A allele might exist. Cecil et al[37] found that the children carrying the FTO A allele have a preference for energy-dense foods. Although the underlying mechanism is needed to be further investigated, these studies have provided important evidence on the complex system governing the regulation of energy balance. A central role for FTO may involve the way through an effect on cerebrocortical insulin sensitivity, which was supported by the finding that individuals homozygous for the risk allele have a reduced insulin response in the brain[38]. Additionally, there may exist a peripheral role for FTO, as indicated by the finding that FTO mRNA levels in adipose tissue increased with BMI, and carriers of the risk-allele had reduced lipolytic activity, independent of BMI[39] We considered that understanding the etiology of obesity and the biology of the FTO gene may bring more valuable information in this regard.

Some limitations of this study should be discussed. First, only published studies were included in the present meta-analysis, which may bring publication bias although it was not detected. Second, significant heterogeneity was observed across studies, which may attribute to differences

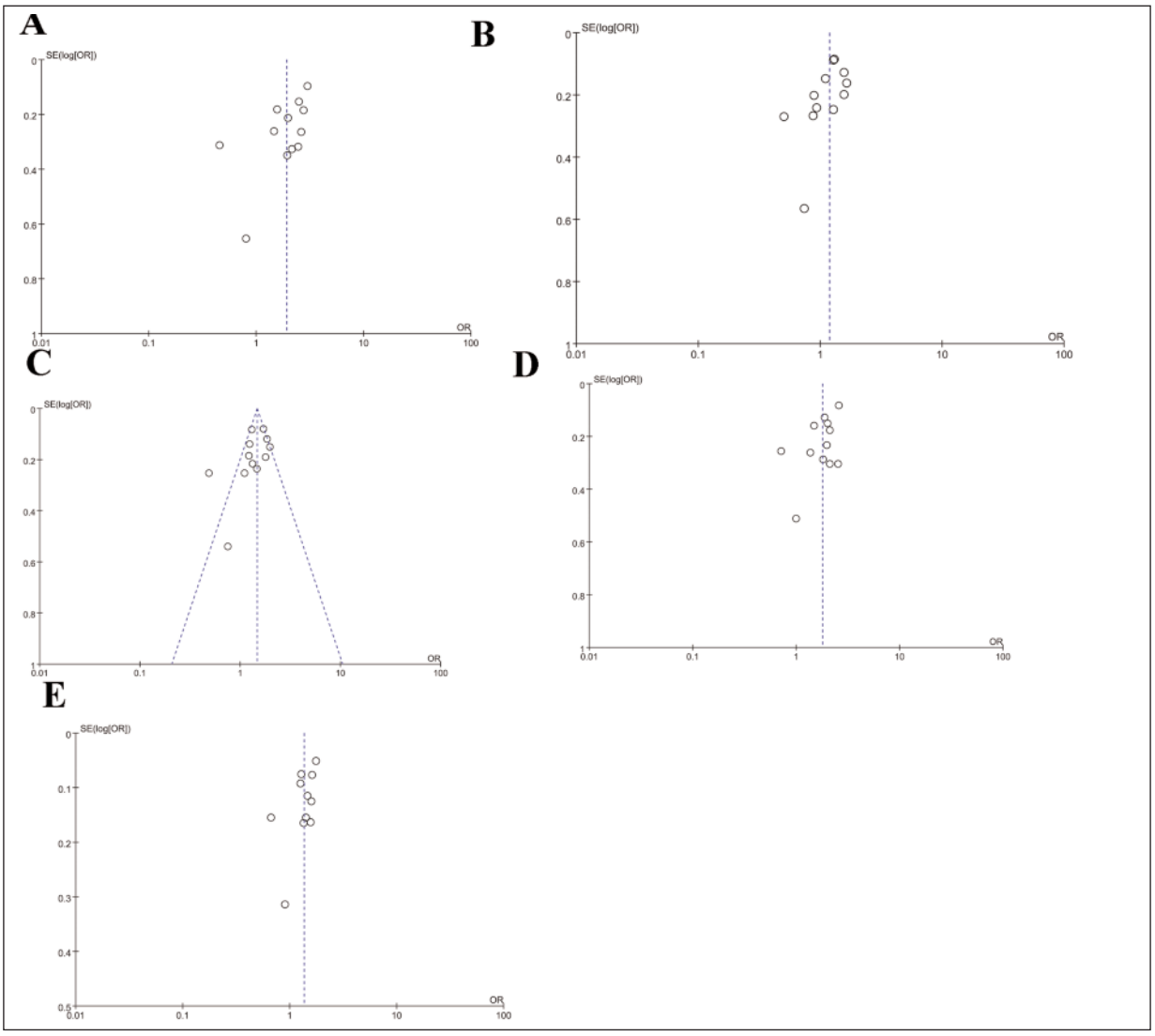

Figure 6. Funnel plots of publication bias for four models. ***A,*** AA vs. TT; ***B,*** AT vs. TT; ***C,*** AA+TT vs. TT; ***D,*** AA vs. TT+AT; ***E,*** A vs. T.

in genetic susceptibility across various populations, participant characteristics and in the sample size. Furthermore, either the study design of included studies was case-control or cross-sectional with limited sample, more high-quality studies are required to verify the result of this meta-analysis.

Conclusions

This meta-analysis reveals that the FTO rs9939609 polymorphism significantly associated with the risk of obesity among children and adolescents, and the allele A of rs9939609 might increase the risk. Larger and well-designed studies based on different populations are needed to confirm our results.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Nguyen DM, El-Serag HB. The epidemiology of obesity. Gastroenterol Clin North Am 2010; 39: 1-7.
2) Westley RL, May FE. A twenty-first century cancer epidemic caused by obesity: the involvement of insulin, diabetes, and insulin-like growth factors. Int J Endocrinol 2013; 2013: 632461.

3) González Jiménez E. Genes and obesity: a cause and effect relationship. Endocrinología y Nutrición (English Edition) 2011; 58: 492-496.

4) Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, Perry JR, Elliott KS, Lango H, Rayner NW. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 2007; 316: 889-894.

5) Kring SI, Holst C, Zimmermann E, Jess T, Berentzen T, Toubro S, Hansen T, Astrup A, Pedersen O, Sørensen TI. FTO gene associated fatness in relation to body fat distribution and metabolic traits throughout a broad range of fatness. PLoS ONE 2008; 3: e2958.

6) Scuteri A, Sanna S, Chen W-M, Uda M, Albai G, Strait J, Najjar S, Nagaraja R, Orrú M, Usala G. Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits. PLoS Genet 2007; 3: e115.

7) Dušátková L, Zamrazilova H, Sedlá ková B, V elák J, Hlavatý P, Aldhoon HI, Korenkova V, Bradnova O, Bendlova B, Kunešová M. Association of obesity susceptibility gene variants with metabolic syndrome and related traits in 1,443 czech adolescents. Folia Biologica (Praha) 2013; 59: 123-133.

8) Meng XR, Song JY, Ma J, Liu FH, Shang XR, Guo XJ, Wang HJ. Association study of childhood obesity with eight genetic variants recently identified by GWAS. Pediatr Res 2014; 76: 310-315.

9) Loos R, Bouchard C. FTO: the first gene contributing to common forms of human obesity. Obes Rev 2008; 9: 246-250.

10) Peng S, Zhu Y, Xu F, Ren X, Li X, Lai M. FTO gene polymorphisms and obesity risk: a meta-analysis. BMC Med 2011; 9: 71.

11) Liu C, Mou S, Cai Y. FTO Gene variant and risk of overweight and obesity among children and adolescents: a systematic review and meta-analysis. PLoS One 2013; 8: e82133.

12) Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009; 151: 264-269.

13) Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Br Med J 2003; 327: 557.

14) Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj 1997; 315: 629-634.

15) Zavattari P, Loche A, Pilia S, Ibba A, Moi L, Guzzetti C, Casini MR, Loche S. rs9939609 in the FTO gene is associated with obesity but not with several biochemical parameters in Sardinian obese children. Ann Hum Genet 2011; 75: 648-654.

16) 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.

17) Jacobsson JA, Danielsson P, Svensson V, Klovins J, Gyllensten U, Marcus C, Schiöth HB, Fredriksson R. Major gender difference in association of FTO gene variant among severely obese children with obesity and obesity related phenotypes. Biochem Biophys Res Commun 2008; 368: 476-482.

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) Pyrzak B, Wisniewska A, Majcher A, Tysarowski A, Demkow U. Relation of fat-mass and obesity-associated gene polymorphism to fat mass content and body mass index in obese children. In: Respiratory Regulation-The Molecular Approach. Springer, 2013; pp. 255-262.

20) Olza J, Ruperez AI, Gil-Campos M, Leis R, Fernandez-Orth D, Tojo R, Cañete R, Gil A, Aguilera CM. Influence of FTO variants on obesity, inflammation and cardiovascular disease risk biomarkers in Spanish children: a case—control multicentre study. BMC Med Genet 2013; 14: 123.

21) Riffo B, Asenjo S, Sáez K, Aguayo C, Muñoz I, Bustos P, Celis Morales C, Lagos J, Sapunar J, Ulloa N. FTO gene is related to obesity in Chilean Amerindian children and impairs HOMA-IR in prepubertal girls. Pediatr Diabetes 2012; 13: 384-391.

22) Mangge H, Renner W, Almer G, Weghuber D, Möller R, Horejsi R. Rs9939609 variant of the fat mass and obesity-associated gene and trunk obesity in adolescents. J Obes 2011; 2011: 186368.

23) Luczynski W, Zalewski G, Bossowski A. The association of the FTO rs9939609 polymorphism with obesity and metabolic risk factors for cardiovascular diseases in Polish children. J Physiol Pharmacol 2012; 63: 241.

24) González JR, González-Carpio M, Hernández-Sáez R, Vargas VS, Hidalgo GT, Rubio-Rodrigo M, García-Nogales A, Estévez MN, Pérez LML, Rodríguez-López R. FTO risk haplotype among early onset and severe obesity cases in a population of western Spain. Obesity 2012; 20: 909-915.

25) Ibba A, Pilia S, Zavattari P, Loche A, Guzzetti C, Casini MR, Minerba L, Loche S. The role of FTO genotype on eating behavior in obese Sardinian children and adolescents. J Pediatr Endocrinol Metab 2013; 26: 539-544.

26) 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.

27) Li H, Kilpeläinen T, Liu C, Zhu J, Liu Y, Hu C, Yang Z, Zhang W, Bao W, Cha S. Association of genetic variation in FTO with risk of obesity and type 2 diabetes with data from 96,551 East and South Asians. Diabetologia 2012; 55: 981-995.

28) Liu Y, Liu Z, Song Y, Zhou D, Zhang D, Zhao T, Chen Z, Yu L, Yang Y, Feng G. Meta-analysis added power to identify variants in FTO associated with type 2 diabetes and obesity in the asian population. Obesity 2010; 18: 1619-1624.

29) Qi L, Cho Y. Gene-environment interaction and obesity. Nutr Rev 2008; 66: 684-694.

30) Rankinen T, Zuberi A, Chagnon YC, Weisnagel SJ, Argyropoulos G, Walts B, Pérusse L, Bouchard C. The human obesity gene map: the 2005 update. Obesity 2006; 14: 529-644.

31) Peeters A, Beckers S, Verrijken A, Roevens P, Peeters P, Van Gaal L, Van Hul W. Variants in the (FTO) gene are associated with common obesity in the Belgian population. Mol Genet Metab 2008; 93: 481-484.

32) Almén MS, Rask-Andersen M, Jacobsson JA, Ameur A, Kalnina I, Moschonis G, Juhlin S, Bringeland N, Hedberg LA, Ignatovica V. Determination of the obesity-associated gene variants within the entire FTO gene by ultra-deep targeted sequencing in obese and lean children. Int J Obes 2012; 37: 424-431.

33) Ntalla I, Panoutsopoulou K, Vlachou P, Southam L, William Rayner N, Zeggini E, Dedoussis GV. Replication of established common genetic variants for adult BMI and childhood obesity in Greek adolescents: the TEENAGE study. Ann Hum Genet 2013; 77: 268-274.

34) Li H, Wu Y, Loos RJ, Hu FB, Liu Y, Wang J, Yu Z, Lin X. Variants in the fat mass–and obesity-associated (FTO) gene are not associated with obesity in a Chinese Han population. Diabetes 2008; 57: 264-268.

35) Horikoshi M, Hara K, Ito C, Shojima N, Nagai R, Ueki K, Froguel P, Kadowaki T. Variations in the HHEX gene are associated with increased risk of type 2 diabetes in the Japanese population. Diabetologia 2007; 50: 2461-2466.

36) Ohashi J, Naka I, Kimura R, Natsuhara K, Yamauchi T, Furusawa T, Nakazawa M, Ataka Y, Patarapotikul J, Nuchnoi P. FTO polymorphisms in oceanic populations. J Hum Genet 2007; 52: 1031-1035.

37) 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.

38) Tschritter O, Preissl H, Yokoyama Y, Machicao F, Häring H-U, Fritsche A. Variation in the FTO gene locus is associated with cerebrocortical insulin resistance in humans. Diabetologia 2007; 50: 2602-2603.

39) Wåhlén K, Sjölin E, Hoffstedt J. The common rs9939609 gene variant of the fat mass-and obesity-associated gene FTO is related to fat cell lipolysis. J Lipid Res 2008; 49: 607-611.