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Review

Association of single nucleotide polymorphisms in the first intron of the Fat mass and obesity associated (FTO) gene with obesity risk in Asians: a meta-analysis

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Summary. *Objective:* This meta-analysis was performed to examine the association between the fat mass and obesity associated (FTO) gene polymorphisms and the risk of obesity in Asian populations. *Methods*: We conducted a meta-analysis based on searches of PubMed and Scopus up to October 19th, 2015 to identify relevant studies. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using random- or fixed-effect models. *Results:* Fourteen studies for rs9939609 (8810 cases and 17031 controls) and eight studies for rs8050136 (3305 cases and 6841 controls) were finally included. There was a significant association between both polymorphisms and the risk of obesity under all models. For rs9939609, allele model (A allele vs. T allele): OR=1.29, 95%CI 1.20–1.39; recessive model (AA vs. TT+TA): 1.45, 95%CI 1.26-1.65; dominant model (AA+TA vs. TT): OR=1.31, 95 %CI 1.19-1.44; and the homozygous model (AA vs. TT): OR=1.63, 95%CI 1.39–1.87. For rs8050136, allele model (A allele vs. T allele): OR=1.32, 95%CI 1.16–1.48; recessive model (AA vs. TT+TA): 1.36, 95%CI 1.09-1.62; dominant model (AA+TA vs. TT): OR=1.36, 95%CI 1.16-1.56; and the homozygous model (AA vs. TT): OR=1.51, 95%CI 1.20–1.82. *Conclusions*: This meta-analysis indicated a significant positive association between the single nucleotide polymorphisms near to FTO (rs9939609 and rs8050136) and obesity risk among Asians.

Key words: FTO, rs9939609, rs8050136, polymorphism, obesity, meta-analysis, Asian

Contributors
JRS designed the study. HM, AS and FK contributed to the literature searches, data extraction, and independent reviewing. HM performed the statistical analyses and wrote a first draft of the manuscript. S.S-b and KD prepared final draft.

Introduction

Obesity has become a global problem and a major independent risk factor for chronic non-communicable diseases, such as hypertension, type 2 diabetes, cardiovascular disease, and non-alcoholic fatty liver disease, with additional consequences for quality of life (1). Obesity is underpinned by both genetic and environmental factors (2). The Fat mass and obesity associated (FTO) gene was the first gene identified where nearly common variants (single nucleotide polymorphisms) were linked to obesity via genome wide association studies (GWAS) (3, 4). Subsequently, association of the FTO gene polymorphisms with obesity has been established by several case control studies. (4-6). Moreover, the association of FTO gene polymorphisms with

risk of overweight and obesity has been investigated in different ethnic populations. A previous meta-analysis by Peng et al (7) indicated a significant but modest association between FTO gene polymorphisms and the risk of obesity. However, subgroup analysis revealed no significant association between the SNP rs8050136 and obesity risk in individuals of Asian and African ethnicity, while in Caucasians it is highly significant. This difference between ethnicities may be because of the limited number of studies included into the analysis and the paucity of samples of Asian and African ethnicity when compared to Caucasians. Controversial results in Asian ethnicity generated a need to perform large-scale studies with large sample size to clarify the association of FTO gene polymorphisms with the risk of obesity in Asian population.

Despite studies carried out in Japan, China, and Pakistan which showed significant associations between FTO gene polymorphisms with obesity risk (8-10), cohort studies conducted in China cast doubt on such results (11). Hence, in the current study, a meta-analysis was carried out to examine the association between FTO gene polymorphisms (rs9939609 and rs8050136) and the risk of obesity in individuals of Asian ancestry.

Methods

We conducted a meta-analysis based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (12). This systematic review and meta-analysis protocol was registered in the PROSPERO (International prospective register of systemic reviews, http://www.crd.york.ac.uk/prospero; CRD42016032680).

Literature and search strategy

An in-depth search to identify related English language published literature via MEDLINE and EMBASE databases was performed up to October 19th, 2015. The search strategy involved the use of the following keywords: ("fat mass and obesity associated gene" OR FTO) and (polymorphism OR variant OR genotype) and (obesity OR overweight OR "body mass index" OR BMI).

Study selection

Titles and abstracts of all articles retrieved in the initial search were evaluated independently by 2 reviewers (HM and FK). Articles not meeting the eligibility criteria were excluded by using a screen form with a hierarchical approach based on study design, population or exposure and outcome. The reference lists of relevant review articles identified during this process were also examined to discover additional studies. Full-text articles were retrieved if the citation was considered eligible, and subjected to a second evaluation for relevance by the same reviewers. Any disagreements were discussed and resolved by consensus.

Inclusion and exclusion criteria

Relevant articles that were obtained were included in this review if they: (1) examined the relationship between FTO gene polymorphisms (rs 9939609 and rs8050136) and the risk of obesity in Asian population(s); (2) applied a case-control design; (3) the cases were obese and the controls were lean; and (4) provided an odds ratio (OR) with 95% confidence interval (CI), or sufficient raw data for calculation of OR and CI.

Studies were excluded for the following reasons: (1) lack of available genotype frequency data on FTO gene polymorphisms; (2) did not evaluate the association of FTO gene polymorphisms with the risk of obesity; (3) based on individuals who were members of the same family; (4) the genotype distributions of control population were inconsistent with Hardy–Weinberg equilibrium (HWE); (5) duplicate studies; and (6) reviews, letters, editorial articles, or case reports.

When multiple publications reported same or overlapping data, we used the most recent or largest population.

Data Extraction

The following information was extracted from each study: the first author, year of publication, country of origin, ethnicity, sample size, mean age and BMI of subjects, characteristics of subjects, studied SNPs, genotype, and allele frequencies and *P*-value for HWE test in controls.

Statistical analysis

We calculated pooled odds ratios (ORs) and 95% confidence intervals (CIs) under four genetic models:

the allele model (mutant [M] allele versus wild [W] allele), the dominant model (WM + MM versus WW), the recessive model (MM versus WW + WM), and the homozygous model (MM versus WW). Data was pooled by the generic inverse variance method by the user written "*metan*" command in Stata (version 11) software (13). The Z-test was used to assess the significance of the pooled ORs and P < 0.05 was considered as statistically significant. The degree of heterogeneity between studies was assessed by the Q-test and I^2 statistics. If P_Q>0.1 and I^2< 50% (14), in cases with heterogeneity, random-effects model (DerSimonian–Laird) was used. In order to explore reasons for heterogeneity, subgroup analysis was performed according to age (13). For the subgroup analysis by age, the study population was divided into two groups: adults (>18 years of age), children and adolescents (<18 years of age). To assess whether the results could have been affected distinctly by a single study, an influence analysis (15) was carried out. The HWE was determined in the control groups by chi-square (χ2) test. We also did tests for funnel plot asymmetry with the user written "metabias" command in Stata (version 11) software (16). Possible publication bias was performed by p < 0.1 in Egger's test. Statistical analysis was performed using STATA 11 software (StataCorp, College Station, Texas, USA).

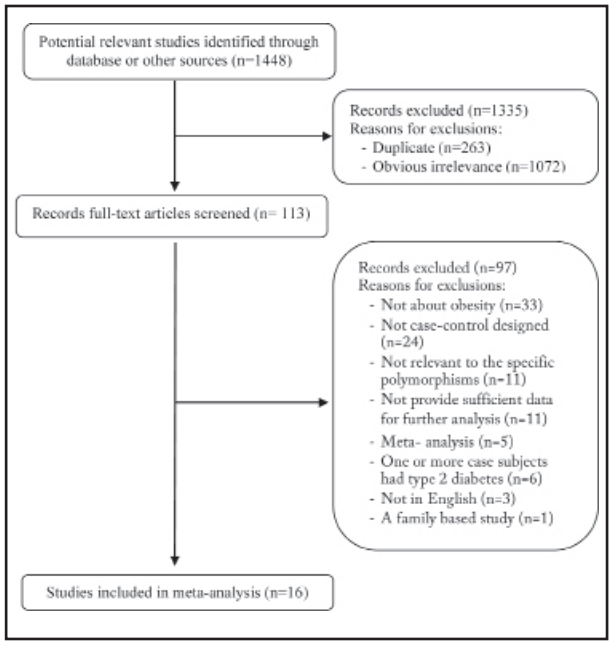

Figure 1 : Flow diagram of the study selection process

Results

Study characteristics

Based on the search strategy, 1448 articles were identified from PubMed and EMBASE. Of them, 1335 papers were excluded because of duplication and obvious irrelevance; then 113 articles were examined and 97 of them were excluded due to being inconsistent with the inclusion criteria. Finally, 16 publications (8, 10, 17-30), including 22 studies, were included into this meta-analysis. The study identification and selection process are illustrated in Figure1.

The characteristics of all eligible studies were summarized in Table 1. Fourteen studies were performed on the relation of the rs9939609 polymorphism with risk of obesity, including 8810 cases and 17031 controls. In addition, 8 studies were conducted on the association of rs8050136 and risk of obesity, including 3305 cases and 6841 controls. In all studies, the genotype frequencies of the controls were in HWE (Table 2).

Association between rs9939609 polymorphism and obesity risk

The results of the assessment of an association between the rs9939609 polymorphism and the risk of obesity are summarized in Table 3. A single study (29) was omitted from the analysis in the recessive and homozygous models due to lack of sufficient weight and wide confidence interval resulting from low events. The results of the overall meta-analysis identified a significant association between the rs9939609 polymorphism and the risk of obesity under all of the four models: allele model (A allele vs. T allele): OR=1.29,95%CI: 1.20–1.39; recessive model (AA vs. TT+TA): 1.45, 95%CI: 1.26-1.65; dominant model (AA+TA vs. TT): OR=1.31, 95 %CI: 1.19-1.44; and the homozygous model (AA vs. TT): OR=1.63, 95%CI: 1.39–1.87 (**Figure 2 and Figure3**). Similarly, in a further subgroup analysis by age, significant associations were observed in all of the genetic models for both ages. In the overall comparison and subgroup analysis, we observed significant heterogeneity under allele and dominant model. The sensitivity analysis indicated that the result was not excessively influenced by any one study. The results of Egger's test are shown in **Table 3.** These results did not show any evidence of publication bias in all genetic models.

Table1. Characteristics of included studies in the meta-analysis

Study	Publication year	Country	Ethnicity	Participants	Diagnosis criteria	Case		Control	
						Age (year)	BMI (kg/m²)	Age (year)	BMI (kg/m²)
						Mean(SD)	Mean(SD)	Mean (SD)	Mean(SD)
Chang Y	2008	China	Chinese	Adult	BMI > 30	37.0(0.5)	38.86(8.2)	61.1(0.3)	24.1(2.9)
Hotta K	2008	Japan	Japanese	Adult	BMI > 30	49.1(14.2)	34.5(5.4)	48.2(16.5)	21.6 (2.1)
Song Y	2008	Asia	Asian	Adult	BMI > 30	NA	NA	NA	NA
Tabara Y	2009	Japan	Japanese	Adult	BMI > 25	NA	NA	61.0(14.0)	23.4(3.2)
Cheung C	2010	China	Chinese	Adult	BMI > 27.5	46.3(11.9)	32.2(4.9)	45.0(12.5)	21.2(1.2)
Karasawa S	2010	Japan	Japanese	Adult	BMI > 25	NA	NA	63.0 (1.2)	23.5 (3.2)
Liu Y	2010	China	Chinese	Adult	BMI > 28	NA	NA	58.0 (9.0)	24.5 (3.2)
Sun Y	2010	China	Chinese	Adult	BMI > 28	NA	NA	NA	NA
Xi Bo	2010	China	Chinese	Children and adolescents	BMI SD values	11.8(2.9)	26.5(3.7)	12.7(3.1)	19.4(3.5)
Ramya K	2011	India	Indian	Adult	BMI > 25	NA	NA	NA	NA
Apalasamy Y	2012	Malaysia	Malay	Adult	BMI > 30	48.6(9.0)	33.8(3.2)	48.2(10.2)	24.9 (3.1)
Dwivedi O	2012	India	Indian	Children and adolescents	the age- and sex-specific BMI by IOTF	13.4(1.9)	26.3(3.4)	13.5(1.8)	17.9(2.5)
Chey W	2013	Malaysia	Mix[a]	Adult	BMI > 27	NA	NA	NA	NA
Meng X	2014	China	Chinese	Children and adolescents	BMI > 95th percentile	12.8(1.9)	25.8(3.4)	13.3(1.6)	19.3(2.1)
Wu J	2014	China	Chinese	Adolescents	BMI cutoffs provided by Working Group of Obesity in China (WGOC)	16.2(1.7)	16.3(1.5)	25.1(1.6)	19.6(1.5)
Yang M	2014	China	Chinese	Children and adolescents	BMI > 95th percentile	11.0(2.6)	11.6(2.4)	27.2(4.0)	17.0(2.3)

[a]: Chinese, Malay, Indian; NA: not available

Association between rs8050136 polymorphism and obesity risk

Results of the association between the rs8050136 polymorphism and obesity risk are summarized in **Table 3**. The same single study (29) was omitted from the analysis in the recessive and homozygous models due to lack of sufficient weight. The meta-analysis showed a significant association between the rs8050136 polymorphism and obesity risk under all of the four models: allele model (A allele vs. T allele): OR=1.32,95%CI: 1.16–1.48; recessive model (AA vs. TT+TA): 1.36, 95%CI: 1.09-1.62; dominant model (AA+TA vs. TT): OR=1.36, 95 %CI: 1.16-1.56; and the homozygous model (AA vs. TT): OR=1.51, 95%CI 1.20–1.82 (Figure.4 and Figure.5). Similarly, in further subgroup analysis by age, significant associations were observed in all of the genetic models in both age groups. In the overall comparison and subgroup analysis, we observed significant heterogeneity under the allele and dominant models. The sensitivity analysis indicated that the result was not excessively influenced by any one study. The results of Egger's test were shown in **Table 3**. These results did not show any evidence of publication bias in all genetic models.

Discussion

In the present study, two SNPs (rs9939609 and rs8050136) found in the first intron of the FTO gene were selected as representative of a cluster of intronic

Table 2. Genotype frequencies of polymorphisms in studies included in the meta-analysis.

Study	Sample size	Genotype case/control			MAF case/control	P_{HWE} [b]
	Total (Case/ Control)	WW[a]	WM	MM		
rs9939609						
Chang Y	2135 (610/1525)	425/1158	167/347	18/20	0.17/0.13	0.29
Hotta K	2423 (919/1504)	534/1005	334/443	51/56	0.24/0.18	0.41
Song Y	240 (77/163)	50/114	23/43	4/6	0.20/0.17	0.44
Tabara Y	1718 (214/1504)	128/1063	77/408	9/33	0.22/0.16	0.39
Karasawa S	2639 (794/1845)	477/1203	271/566	46/76	0.23/0.20	0.36
Liu Y	1167 (276/891)	201/702	70/181	5/8	0.14/0.11	0.32
Sun Y	1760 (560/1200)	142/450	294/545	124/205	0.48/0.40	0.07
Apalasamy Y	578 (158/429)	78/209	61/179	19/41	0.31/0.30	0.76
Chey W	324 (178/146)	117/85	58/57	3/4	0.18/0.22	0.12
Xi Bo	3503 (1229/2274)	915/1803	288/436	26/35	0.14/0.11	0.14
Dwivedi O	2995 (848/2147)	347/985	377/935	124/227	0.35/0.32	0.81
Wu J	396 (176/220)	131/179	42/40	3/1	0.14/0.10	0.43
Yang M	3924 (1348/2576)	951/2031	356/519	41/26	0.16/0.11	0.25
Meng X	2030 (1423/607)	1053/474	336/126	34/7	0.14/0.12	0.66
rs8050136						
Hotta K	2423 (919/1504)	538/1018	336/450	51/56	0.24/0.18	0.47
Song Y	240 (77/163)	52/111	20/45	5/7	0.20/0.18	0.38
Cheung C	1159 (468/691)	326/535	131/149	11/7	0.16/0.12	0.46
Liu Y	1167 (276/891)	201/716	73/178	4/8	0.15/0.11	0.39
Ramya K	999 (323/676)	225/570	93/100	5/6	0.18/0.09	0.49
Apalasamy Y	587 (158/429)	78/209	61/179	19/41	0.31/0.30	0.76
Dwivedi	3034 (874/2160)	351/980	397/944	126/236	0.37/0.33	0.71
Wu	396 (176/220)	131/179	43/40	3/1	0.14/0.10	0.43

[a]: WW, WM, and MM denote TT, TA, and AA for rs9939609; and CC, CA, and AA for rs8050136; [b]:*P* value for Hardy-Weinberg equilibrium test (HWE) in controls; W: Wild allele; M: Mutant allele; MAF: Minor Allele Frequency

Table3. Summary of pooled effects between FTO polymorphisms and obesity in the Asian population.

Polymorphism	Genetic model	N	Sample size	Tests of association		Tests of heterogeneity		Egger's test
			Total (Case/ Control)	OR (95 % CI)	Model	P value	I^2 (%)	P value
rs9939609	Allelic	14	25841 (8810/17031)	1.29 (1.20, 1.39)	Random	0.018	49.5	0.513
	Dominant	14	25841 (8810/17031)	1.31 (1.19, 1.44)	Random	0.016	50.4	0.324
	Recessive	13	25442 (8634/16811)	1.45 (1.26, 1.65)	Fixed	0.903	0.0	0.359
	homozygous	13	25442 (8634/16811)	1.63 (1.39, 1.87)	Fixed	0.744	0.0	0.816
rs8050136	Allelic	8	10146 (3305/6841)	1.32 (1.16, 1.48)	Random	0.08	44.9	0.491
	Dominant	8	10146 (3305/6841)	1.36 (1.16, 1.56)	Random	0.06	48.2	0.818
	Recessive	7	9745 (3127/6618)	1.36 (1.09, 1.62)	Fixed	0.991	0.0	0.092
	homozygous	7	9745 (3127/6618)	1.51 (1.20, 1.82)	Fixed	0.978	0.0	0.589

N: number of studies

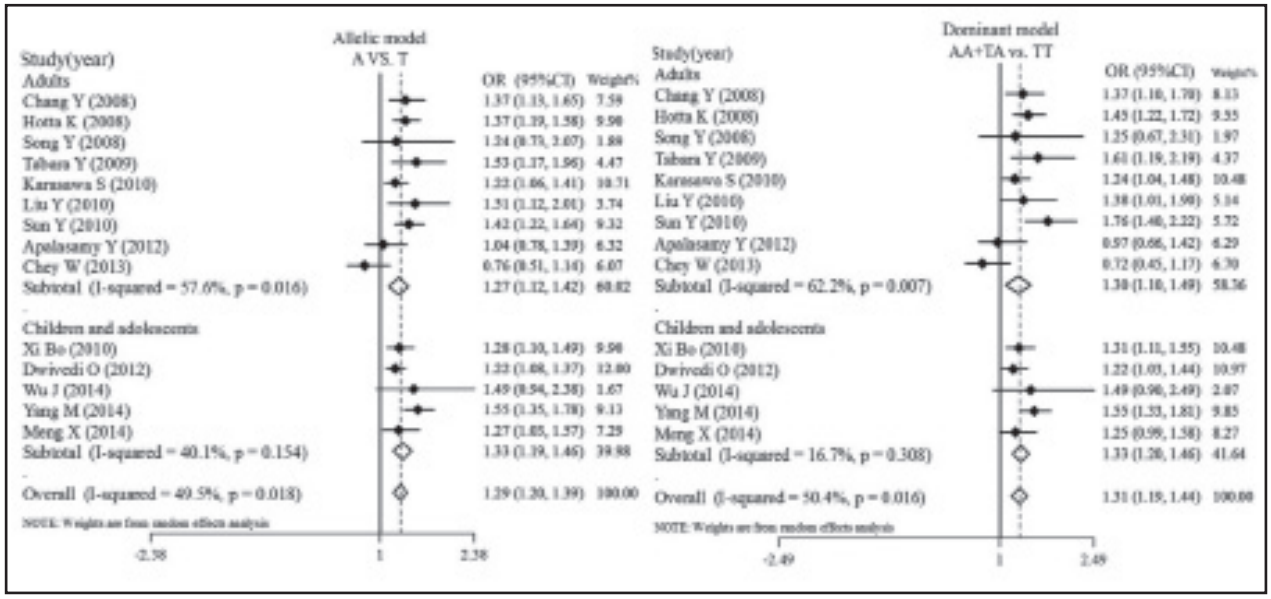

Figure 2: Forest plots for the association between FTO rs9939609 polymorphism and obesity risk under Allelic and Dominant model

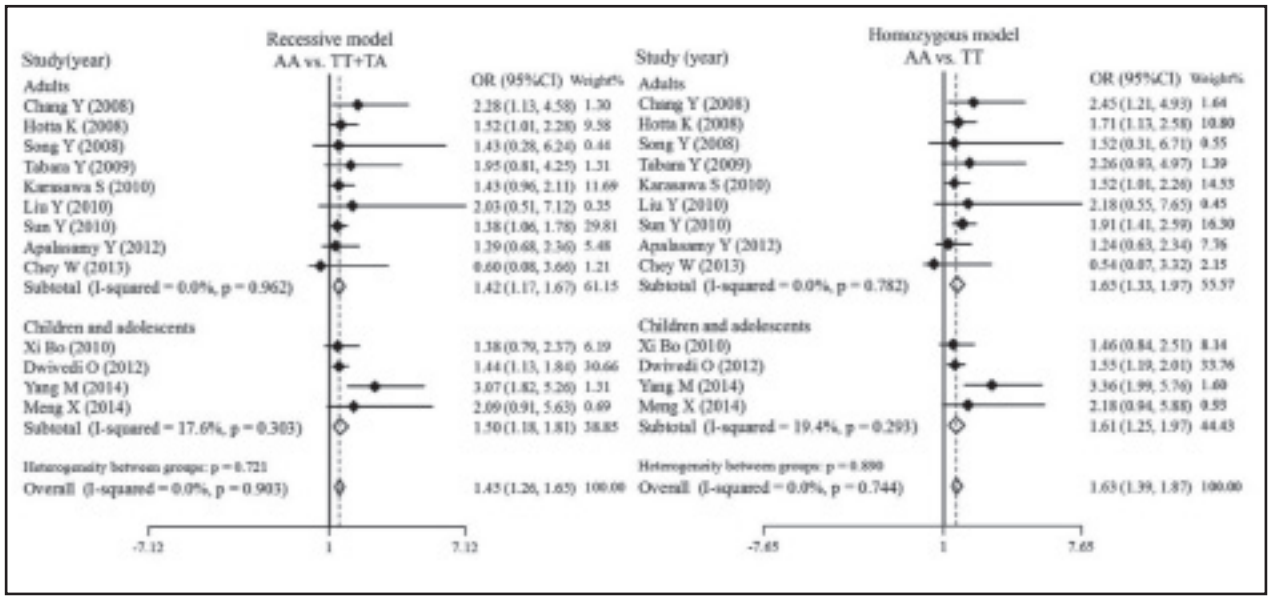

Figure 3: Forest plots for the association between FTO rs9939609 polymorphism and obesity risk under Recessive and Homozygous model

FTO SNPs which have been previously linked to obesity. These SNPs are the most frequently cited SNPs and have an indisputable effect on the BMI phenotype. Previous studies have suggested that while there is a clear association between these polymorphisms and obesity risk in Caucasians, in Asian populations the situation is less clear, possibly because the minor allele frequency (MAF) in such regions is much lower, or due to differences in linkage disequilibrium (LD) patterns (7). In the present study our meta-analysis confirmed that the two variants in the FTO gene (rs9939609, rs8050136) were significantly associated

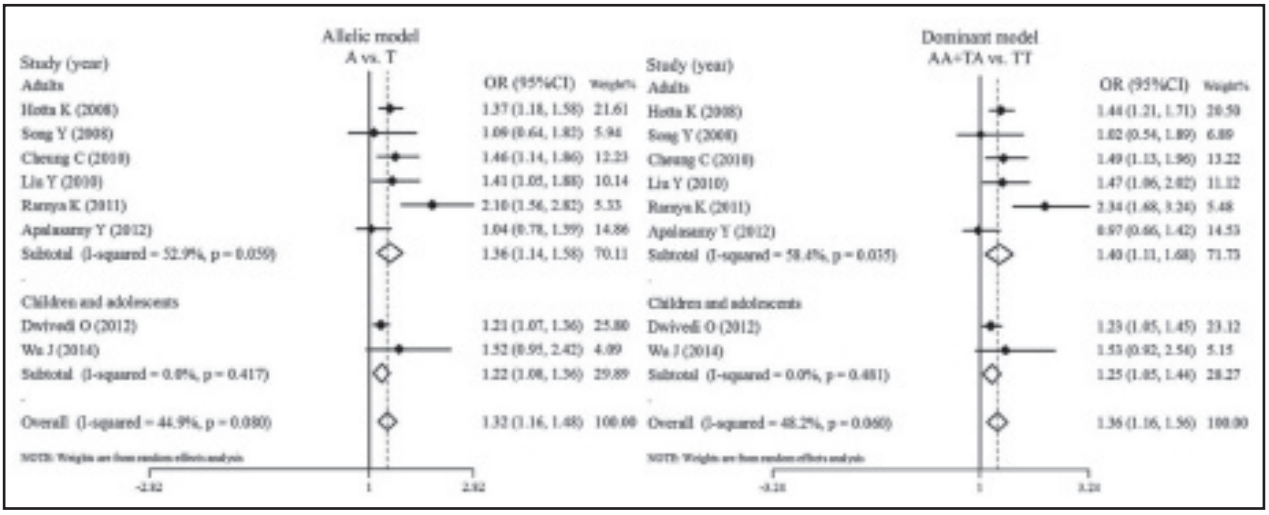

Figure 4: Forest plots for the association between FTO rs8050136 polymorphism and obesity risk under Allelic and Dominant model

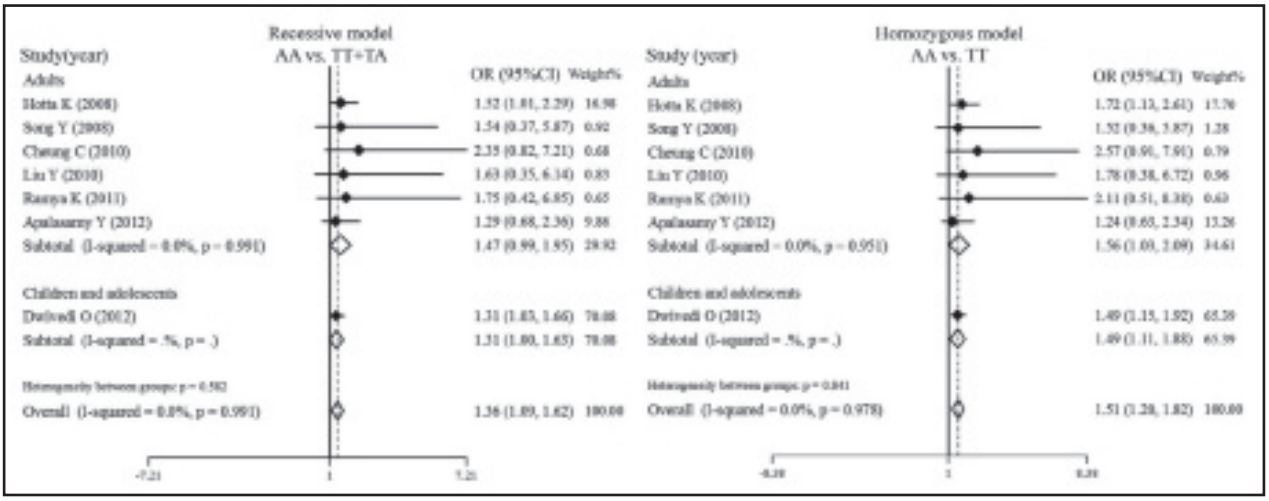

Figure 5: Forest plots for the association between FTO rs8050136 polymorphism and obesity risk under Recessive and Homozygous model

with an increased risk of obesity in Asian population. Moreover, subgroup analysis stratified by age showed similar results among adults and children. Furthermore, positive association was confirmed by the stability of sensitivity analysis and no publication bias.

Results of the association between rs9939609 polymorphism and obesity risk in our study were consistent with previous meta-analyses (7, 21, 31-33). Moreover, the pooled result of rs8050136 was similar to overall result of studies by Peng et al (7) and Liu et al (21). However, in study by Peng et al., in the Asian population a significant association was not found between the rs8050136 and obesity risk, which may be due to the previous small number of included studies (n=4).

Although the initial linkage between the variants near to FTO and obesity was established using BMI as an index of obesity, several studies have since established that the effect of FTO variants on BMI were brought about through fat mass as opposed to skeletal or lean tissue mass (34). The biological mechanism by which FTO variants (including rs9939609 and

rs8050136) augment the risk of obesity is still unclear (35). Some have suggested that the effect of FTO variants on BMI is due to its effect on total calorie intake (36), the frequency of food intake (37), tendency toward fat, or protein preference (38, 39). Nevertheless, there were several studies which did not support these suggestions, probably because of technical limitations in the tools used to evaluate intake (40). As for animal experiments, it has been demonstrated that mice with three or four copies of the FTO gene tend to eat more than mice with only two copies of the gene, and that FTO plays a pivotal role in energy homeostasis, metabolism, and adiposeness (41, 42). Studies concerning mice indicated that whole-body knockout or a dominant mutation in FTO resulted in thinner, smaller mice (41, 42). However more detailed research is needed to explore how FTO mediates its impacts on satiety, hunger signals, and macronutrient selection which can helpful to clarify the mechanisms underlying the association of FTO variants and obesity. Other studies have suggested that these specific SNPs despite being intronic in FTO act via long range effects on other genes such as the Iroquois homeobox 3 gene (IRX3) (43).

Some limitations of the present study should be mentioned. First, because only published studies in English were included in the meta-analysis, and some raw data were not available even after contacting the authors, publication bias may have occurred; even though it was not found by the statistical tests we applied. Second, this meta-analysis was based on unadjusted estimates and CIs, while a more detailed analysis could be conducted by controlling some additional potential confounding factors. Third, obesity is the result of the interaction of multiple genetic and environmental factors and this meta-analysis did not address the gene-gene and gene-environmental interactions. Finally, since the obesity was described by different BMI criteria in different studies, therefore, these results should be interpreted with caution.

In conclusion, this meta-analysis suggests that rs9939609 and rs8050136 polymorphisms near to the FTO gene were significantly correlated with the increased risk of obesity in Asian populations, based on the current published studies. Given the limitations mentioned above, additional studies in Asian population with larger sample sizes, and gene–gene and gene–environmental interactions are required to improve the current results. Further research is needed to clarify the biological mechanisms underlying the observed associations.

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