

Original Article



Minor alleles in the *FTO* SNPs contributed to the increased risk of obesity among Korean adults: meta-analysis from nationwide big data-based studies

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Corresponding Author:

Myoungsook Lee

Department of Food & Nutrition, School of Bio-Health Convergence, Health & Wellness College, Sungshin Women's University, 2 Bomun-ro 34da-gil, Seongbuk-gu, Seoul 02844, Korea.

Tel. +82-2-920-7211

Fax. +82-2-920-2076

Email. mlee@sungshin.ac.kr


*Oh Yoen Kim and Jihyun Park contributed equally to this work.

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ORCID iDs

Oh Yoen Kim 


<https://orcid.org/0000-0001-9262-3309>

Jihyun Park 

<https://orcid.org/0000-0003-1038-2586>

Jounghee Lee 

<https://orcid.org/0000-0001-8240-7602>

Cheongmin Sohn 

<https://orcid.org/0000-0003-0529-7037>

Oh Yoen Kim ^{1,2*}, Jihyun Park ^{2*}, Jounghee Lee ³, Cheongmin Sohn ⁴,
Mi Ock Yoon ⁵, and Myoungsook Lee ^{6§§}

¹Department of Food Science & Nutrition, Dong-A University, Busan 49315, Korea

²Department of Health Science, Graduates School of Dong-A University, Busan 49315, Korea

³Department of Food and Nutrition, Kunsan National University, Gunsan 54150, Korea

⁴Department of Food and Nutrition, Wonkwang University, Iksan 54538, Korea

⁵Nutrition Information Center, Korean Nutrition Society, Seoul 04376, Korea

⁶Department of Food & Nutrition, School of Bio-Health Convergence, Health & Wellness College, Sungshin Women's University, Seoul 01133, Korea

ABSTRACT


BACKGROUND/OBJECTIVES: Many studies have revealed an association between fat mass and the obesity-related gene (*FTO*) and obesity. On the other hand, no meta-analysis was conducted with data from only Koreans. Therefore, this study performed a meta-analysis using Korean data to provide evidence for the association between *FTO* single nucleotide polymorphisms (SNPs) and the risk of obesity among Korean adults.

SUBJECT/METHODS: Meta-analysis was finally conducted with data extracted from seven datasets of four studies performed on Korean adults after the screening passed. Five kinds of *FTO* SNPs (rs9939609, rs7193144, rs9940128, rs8050136, and rs9926289) were included, and the relationship between *FTO* SNPs and body mass index (BMI) was investigated using linear regression with an additive model adjusted for covariants, such as age, sex, and area.

RESULTS: The minor alleles of *FTO* SNPs were associated with increased BMI (odds ratio [OR], 1.31; 95% confidence interval [CI], 1.21–1.42). In sub-group analysis, *FTO* rs9939609 T>A was significantly associated with BMI (OR, 1.23; 95% CI, 1.06–1.42). The other *FTO* SNPs together were significantly associated with BMI (OR, 1.37; 95% CI, 1.25–1.49). The publication bias was not observed based on Egger's test.

CONCLUSIONS: This meta-analysis showed that minor alleles in the *FTO* SNPs were significantly associated with an increased BMI among Korean adults. This meta-analysis is the first to demonstrate that minor alleles in the *FTO* SNPs contribute significantly to the increased risk of obesity among Korean adults using data from a Korean population.

Keywords: Obesity; genes; polymorphism, single nucleotide; adult; meta-analysis

Mi Ock Yoon 

<https://orcid.org/0000-0003-1404-9158>

Myoungsook Lee 

<https://orcid.org/0000-0003-1344-6979>

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Conflict of Interest

The authors declare no potential conflicts of interests.

Author Contributions

Conceptualization: Lee M; Data curation: Kim OY, Park J, Lee J, Sohn C, Yoon MO; Formal analysis: Kim OY, Park J; Investigation: Lee J, Sohn C, Yoon MO, Lee M; Writing - original draft: Kim OY, Park J; Writing - review & editing: Lee M.

INTRODUCTION

The prevalence of obesity has been increasing gradually worldwide over the past few decades [1]. Obesity has also been increasing in Korea for more than ten years, and 38.8% of Koreans were reported to be obese in 2020 [2,3]. Obesity is a public health problem as the main cause of developing non-communicable diseases, such as metabolic syndrome, type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, and cardiovascular disease (CVD) [1,4,5]. Hence, many endeavors have been made to prevent and manage obesity, e.g., by modifying energy intake, physical activity, eating habits, and lifestyle and suggesting optimal nutrition therapy according to genetic properties [6-9].

In 2007, a genome-wide association study identified a single nucleotide polymorphism (SNP) at the intron 1 of the fat mass and obesity-related gene (*FTO*) located on chromosome 16q12.2 as the first obesity-susceptibility locus [10,11]. *FTO* is associated with the body composition, such as body mass index (BMI), body weight, waist circumference, hip circumference, subcutaneous mass, and energy intake [10-12]. In particular, individuals carrying the minor A allele homozygotes in the *FTO* SNP rs9939609 had a relatively high risk of being overweight and obese compared to those carrying the major T allele homozygotes [10]. Since then, many studies have reported that genetic variants at several SNPs in the *FTO* were linked to an obesity-related trait in diverse ethnicities [13-18]. Meta-analyses were also conducted to elucidate the relationship between *FTO* and obesity [19-21].

A replication study from Korean cohorts also reported that the *FTO* was significantly related to an increased BMI [22]. Currently, the *FTO* is being provided as an obesity-related gene by the direct-to-customer (DTC) gene test, which was approved by the Ministry of Health and Welfare in Korea in June 2016 (notice No. 2016-97) [23]. On the other hand, no meta-analysis has been conducted using data from only Koreans that can provide conclusive evidence for the association between *FTO* and obesity. Therefore, this study performed a meta-analysis using the data from Koreans to provide evidence for the association between *FTO* SNPs and the risk of obesity among Korean adults.

SUBJECTS AND METHODS

Search strategy and inclusion criteria

Comprehensive literature research was conducted in a database (DB) to identify the studies investigating the association between *FTO* SNPs and obesity risk in Koreans (up to September 22, 2022). The database consisted of PubMed, Web of Science, and Korean databases, such as Research Information Sharing Service (RISS) and KoreaMed. The following keywords were used for the search: “*FTO*”, “Obesity”, “fat mass”, “waist”, “BMI”, “body weight,” and “Korean”. “Asian” along with “*FTO*” and “obesity” was also searched in PubMed and Web of Science to prevent the omission of the Korean data. A similar search was performed using the Korean language terms in the Korean database (RISS and KoreaMed). The studies included in the meta-analysis should satisfy the following inclusion criteria: 1) The contents can evaluate the association between *FTO* SNPs and obesity-related parameters; 2) Subjects should be Korean adults; and 3) Full-text articles are available in English or Korean. Two researchers, Kim & Park, determined the quality of each article and the consensus reached on the scores calculated by the risk of bias (RoB) through discussion. A third reviewer (Lee M) resolved the disagreement about the RoB. **Fig. 1** presents the flow diagram for the search strategy of the

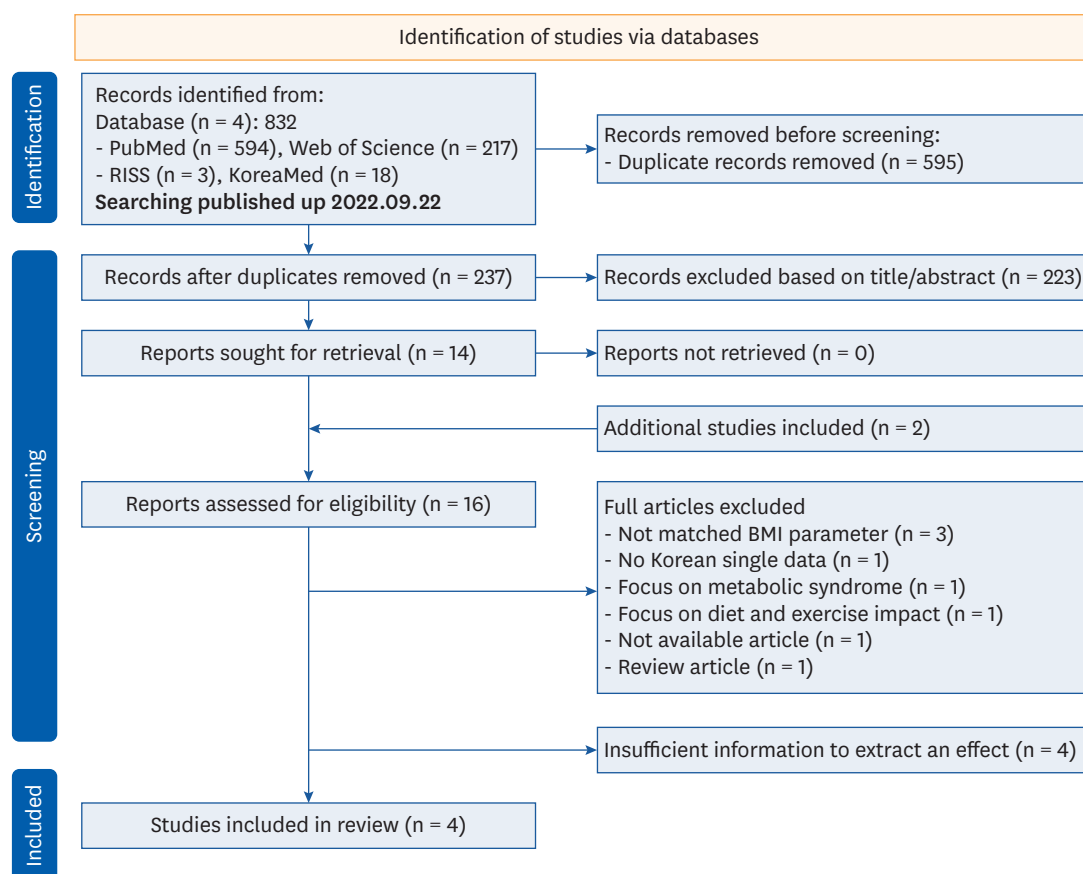


Fig. 1. PRISMA flow diagram of studies in the meta-analysis.

PRISMA, Preferred Reporting Items for Systematic review and Meta-Analysis; RISS, Research Information Sharing Service; BMI, body mass index.

literature in the meta-analysis. The analysis was conducted based on the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) protocol 2020 [24].

Data extraction

Data extraction was conducted preliminarily by one researcher. The following information was extracted: 1) first study author; 2) publication year; 3) cohort information in the study; 4) study design and sample size; 5) *FTO* SNPs with the rs number and minor allele frequency (MAF); 6) subject and sex distribution; 7) age (yrs) and BMI (kg/m^2); 8) BMI as an obesity parameter being indicated to the effect size under an additive model; and 9) adjustment for covariants. The BMI was used as a parameter of obesity in the analysis because there is a lack of evidence of Korean using other obesity indicators. The other researcher confirmed the extracted data. The information that needed to be confirmed while extracting the data was discussed by the 2 researchers.

RoB assessment

The RoB was assessed by Strengthening the Reporting of Observational Studies in the Epidemiology (STROBE) checklist [25]. The checklist was used for cross-sectional studies in the STROBE tool. This tool consisted of 22 items, based on “title and abstract”, “introduction”, “method”, “results”, “discussion”, and “other information”. Overall, RoB in each article was calculated based on the STROBE checklist criteria. The reporting bias was assessed by judging the consistency between results in the method section of the publication and the protocol.

Statistical analysis

In all studies, the association between *FTO* SNPs and BMI was estimated by $\beta \pm SE$ under an additive model adjusted for the covariant. Therefore, the odds ratio (OR) and 95% confidence intervals (CIs) were conducted by generic inverse variance methods. The heterogeneity among the studies was investigated using an I^2 test. A random effects model was used because the value was more than 50%, and the number of studies included in the analysis was small. Sub-analyses were conducted according to the following SNPs: the *FTO* rs9939609 T>A and the other SNPs, respectively. The funnel plot of publication bias was assessed using an Egger's test. The overall effect and subgroup analysis between the *FTO* SNPs and BMI increment under an additive model was indicated through a forest plot. Data analysis was performed using R software version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria). The RoB assessment was performed using Review Manager 5.4 with the STROBE checklist (The Nordic Cochrane Centre, Copenhagen, Denmark).

RESULTS

Results of the literature search

Based on the search strategy, 832 articles were identified in the four databases (594 from PubMed, 217 from Web of Science, three from RISS, and 18 from KoreaMed with duplicates of 595 articles). After removing duplicates, 237 articles were screened based on the title and abstract. Fourteen articles that passed the screening were included for screening the full-text article together with an additional two articles that were cited as references. Among the 16 articles, eight articles were excluded for the following reasons: unmatched BMI parameters (unavailable for the relationship between the *FTO* SNPs and obesity-related parameters to be expressed as OR or β effect size) ($n = 3$), no single data from Koreans with obesity-related parameters ($n = 1$), data focusing on metabolic syndrome ($n = 1$) or the effect of diet and exercise ($n = 1$), full-text unavailable ($n = 1$), and review article ($n = 1$). Among the eight articles corresponding to the inclusion criteria, four were also excluded because they had not satisfied the criteria for calculating the effect size for meta-analysis. Finally, the remaining four articles were eligible and included in the meta-analysis (**Fig. 1**).

Characteristics of included studies

Table 1 lists the characteristics of the data among the four articles. All the studies were population-based cross-sectional studies performed on Koreans. As the Korea Association REsource (KARE) cohort was used in all four studies, the most recent data were only included in the analysis if the same cohort and *FTO* SNPs were included. On the other hand, the cases examined by different SNPs in the *FTO*, even from the same cohort, were included in the analysis. The cohort data included in the analysis are marked in bold in **Table 1**. Therefore, a meta-analysis was performed by extracting seven data from four articles. The sample size ranged from 2,281 to 8,840, and the age ranged from 30 to 69 showing similar patterns among the studies. In addition, the average BMI was 23.4–24.7 kg/m². Five kinds of *FTO* SNPs (rs9939609 T>A, rs7193144 T>C, rs9940128 G>A, rs8050136 C>A, and rs9926289 G>A) were investigated among the four studies. Except for *FTO* SNPs, rs7193144 T>C and rs9940128 G>A, the MAF of rs9939609 T>A, rs8050136 C>A, and rs9926289 G>A for Korean were 12.5–18% with similarity. All studies indicated the relationship between the *FTO* SNPs and BMI by effect size (β) \pm SE. The *P*-values were also calculated by linear regression under an additive model adjusted for covariants, such as age, sex, and area. **Fig. 2** gives a summary of the RoB assessment (STROBE). All 4 articles categorized as “low” risk of bias were finally included in the meta-analysis.

Contribution of *FTO* SNPs to the obesity risk among Korean adults

Table 1. Characteristics of the studies included in the meta-analysis

| Study (Author) | Year | Cohort* | Study design | Sample size | <i>FTO</i> SNP | MAF | Age (yrs) | Sex (M/F) | BMI (kg/m ²) | Effect size | SE | <i>P</i> -value† | Adjustment |
|--------------------|------|-------------------------|----------------------------------|-------------|----------------------------|----------------|--------------------------|-------------|--------------------------|-------------|-------|-----------------------|----------------|
| | | | | | | | Mean ± SD (range) | | Mean ± SD | (β) | | | |
| Cho <i>et al.</i> | 2009 | KARE, Health2 | Population-based | 7,861 | rs9939609 T>A | 0.18 (Total) | 56.58 ± 7.85 (40–69 yrs) | 3,214/4,647 | 24.49±3.18 | 0.123 | 0.054 | 2.2E-02 | Age, sex, area |
| Cho <i>et al.</i> | 2020 | KARE | Population-based | 8,840 | rs9939609 T>A | 0.1262 (Total) | 52.22 ± 8.91 (40–69 yrs) | 4,182/4,658 | 24.58±3.13 | 0.334 | 0.07 | 1.76*10 ⁻⁶ | Age, sex, area |
| | | | | 8,840 | rs7193144 T>C | NA | 52.22 ± 8.91 (40–69 yrs) | 4,182/4,658 | 24.58±3.13 | 0.328 | 0.07 | 2.80*10 ⁻⁶ | Age, sex, area |
| | | | | 8,840 | rs9940128 G>A | NA | 52.22 ± 8.91 (40–69 yrs) | 4,182/4,658 | 24.58±3.13 | 0.205 | 0.063 | 1.12*10 ⁻³ | Age, sex, area |
| Lee <i>et al.</i> | 2011 | KARE, Health2 | Population-based | 6,742 | rs8050136 C>A | 0.125 (Total) | 48.3 ± 6.06 (40–60 yrs) | 3,275/3,467 | 24.7±3.07 | 0.379 | 0.078 | 1.37E-06 | Age, sex, area |
| | | | | 6,742 | rs9926289 G>A [‡] | 0.126 (Total) | 48.3 ± 6.06 (40–60 yrs) | 3,275/3,467 | 24.7±3.07 | 0.373 | 0.079 | 2.07E-06 | Age, sex, area |
| Sull <i>et al.</i> | 2013 | Bundang-gu, KARE | Population-based & Meta-analysis | 2,281 | rs9939609 T>A | 0.127 (Total) | 42.9 ± 7.8 (30–59 yrs) | 1,256/1,025 | 23.4±3.0 | 0.15 | 0.12 | 0.223 | Age, sex |

FTO, fat mass and obesity-related gene; SNP, single nucleotide polymorphism; MAF, minor allele frequency; BMI, body mass index; NA, no available.

*Studies included in the current meta-analysis are shown in bold. †Main results under an additive model. ‡Original article, *FTO* polymorphism data was rs9926289 C>T.

| | Title and abstract | Background | Objectives | Study design | Setting | Participants | Variables | Data sources/measurement | Bias | Study size | Quantitative variables | Statistical methods | Participants | Descriptive data | Outcome data | Main results | Other analyses | Key results | Limitations | Interpretation | Generalisability | Funding | |
|---------------------------|--------------------|------------|------------|--------------|---------|--------------|-----------|--------------------------|------|------------|------------------------|---------------------|--------------|------------------|--------------|--------------|----------------|-------------|-------------|----------------|------------------|---------|---|
| Cho <i>et al.</i> (2009) | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Cho <i>et al.</i> (2020) | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lee <i>et al.</i> (2011) | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Sull <i>et al.</i> (2013) | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

Fig. 2. Summary for the risk of bias assessment (STROBE).

STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

Outcomes of meta-analysis

Fig. 3 shows the Forest plot for the overall effect of *FTO* SNPs on BMI. From the seven datasets, the minor alleles of *FTO* SNPs were significantly associated with the increased BMI under an additive model adjusted for covariants (OR, 1.31; 95% CIs, 1.21–1.42). Moderate-substantial heterogeneity was noted ($I^2 = 59\%$; $P = 0.02$). Publication bias was evaluated using funnel plots (**Fig. 4**). Dissymmetry was not observed in the funnel plot according to the Egger's test ($P = 0.4019$). That is, there was no publication bias in this meta-analysis that examined the effects of minor alleles in *FTO* SNPs on the risk of obesity.

In addition, sub-group analysis was performed according to *FTO* SNPs (rs9939609) and the other SNPs. **Fig. 5** presents a forest plot by sub-group analysis. Precisely, *FTO* rs9939609 T>A was analyzed in the data from the three articles and found to be significantly associated with the BMI under an additive model adjusted for covariant (OR, 1.23; 95% CI, 1.06–1.42). The other *FTO* SNPs were also analyzed in the data from the two articles and showed a significant association with the BMI under an additive model adjusted for covariant (OR, 1.37; 95% CI, 1.25–1.49). On the other hand, the heterogeneity for the sub-analysis was different between the *FTO* rs9939609 T>A group ($I^2 = 66\%$; $P = 0.05$) and the other *FTO* SNPs group ($I^2 = 30\%$; $P = 0.23$).

| Study | <i>FTO</i> | β | SE | OR | OR (95% CI) | Weight (%) |
|--|---------------|---------|------|----|------------------|------------|
| Cho et al. (2009) | rs9939609 T>A | 0.12 | 0.05 | | 1.13 (1.02–1.26) | 18.1 |
| Cho et al. (2020) | rs9939609 T>A | 0.33 | 0.07 | | 1.40 (1.22–1.60) | 15.0 |
| Cho et al. (2020) | rs7193144 T>C | 0.33 | 0.07 | | 1.39 (1.21–1.59) | 15.0 |
| Cho et al. (2020) | rs9940128 G>A | 0.20 | 0.06 | | 1.23 (1.08–1.39) | 16.3 |
| Lee et al. (2011) | rs8050136 C>A | 0.38 | 0.08 | | 1.46 (1.25–1.70) | 13.7 |
| Lee et al. (2011) | rs9926289 G>A | 0.37 | 0.08 | | 1.45 (1.24–1.70) | 13.5 |
| Sull et al. (2013) | rs9939609 T>A | 0.15 | 0.12 | | 1.16 (0.92–1.47) | 8.3 |
| Random effects model | | | | | | |
| Heterogeneity: $I^2 = 59\%$, $\tau^2 = 0.0068$, $P = 0.02$ | | | | | | |
| | | | | | 1.31 (1.21–1.42) | 100.0 |

Fig. 3. Association between *FTO* polymorphism and BMI under an additive genetic model adjusted for covariant. Effect size combined using the random-effects meta-analysis. Meta-analysis using generic inverse variance methods. *FTO*, fat mass and obesity-related gene; BMI, body mass index; OR, odds ratio; CI, confidence interval.

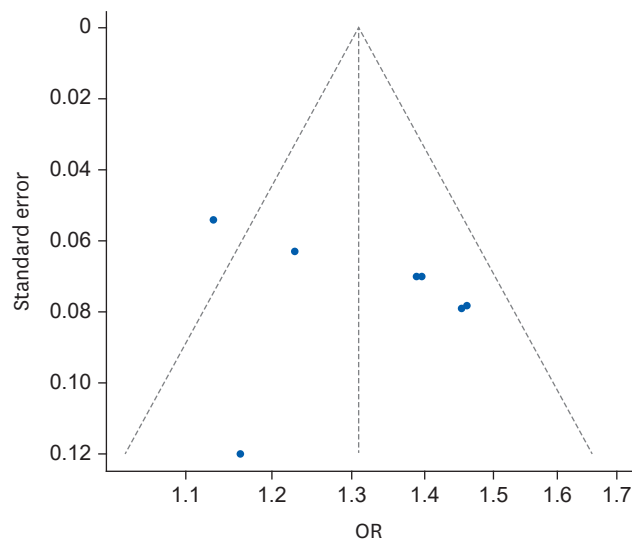


Fig. 4. Egger's funnel plot for publication bias in an additive model. OR, odds ratio.

DISCUSSION

This report is the first meta-analysis to show that minor alleles in the *FTO* SNPs contribute significantly to the increased risk of obesity among Korean adults using data from only the Korean population. Minor alleles in the 5 SNPs at *FTO* (rs9939609 T>A, rs7193144 T>C, rs9940128 G>A, rs8050136 C>A, and rs9926289 G>A) were associated with the increased BMI among Korean adults.

The association between the *FTO* SNPs and increased BMI observed in this study was similar to those observed in the diverse East Asian population [16,17,26-28]. An obesity case-control study performed in the Chinese population showed that the *FTO* SNP was related to the risk of obesity [17,26,27]. The A allele at the rs9939609 in the *FTO* was significantly associated with obesity compared to the major T allele (OR, 1.447; 95% CI, 1.104–1.896) [26]. The A allele at the *FTO* SNP rs9939609 was also associated with increased BMI ($P = 0.0024$) and obesity (OR, 1.43; 95% CI, 1.16–1.75) [17]. Furthermore, a meta-analysis of the Chinese population showed that minor alleles at the *FTO* SNPs, including rs9939609, rs6499640, rs8050136, and rs1558902 were related to the risk of obesity in children, adolescents, and adults. In

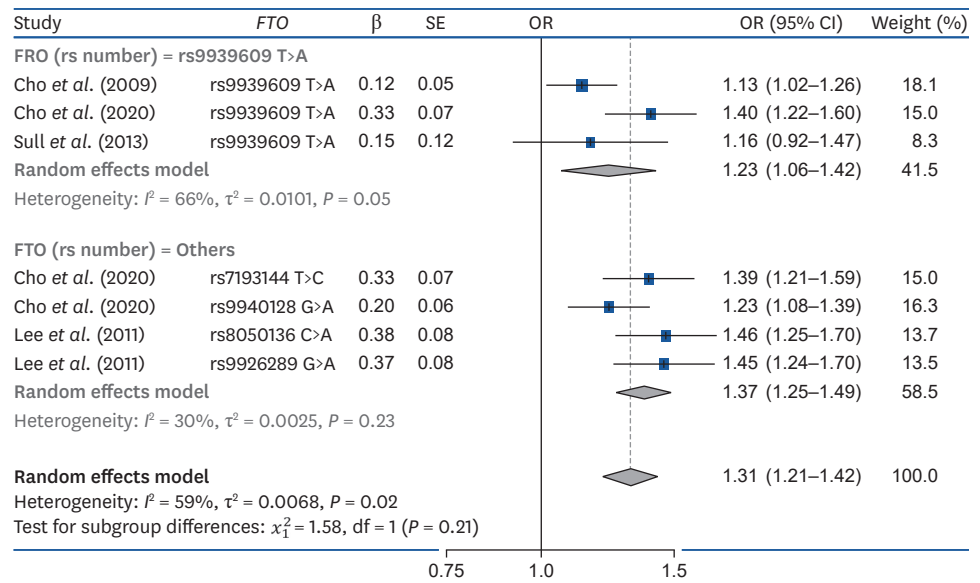


Fig. 5. Sub-group analysis of the association between *FTO* polymorphism (rs number) and BMI under an additive model adjusted for covariant. Effect size combined using random-effects meta-analysis. Meta-analysis using generic inverse variance methods.

FTO, fat mass and obesity-related gene; BMI, body mass index; OR, odds ratio; CI, confidence interval.

particular, the association between *FTO* SNPs (rs9939609 or its proxy) and obesity risk under an additive model observed in the Chinese population (OR, 1.20; 95% CI, 1.03–1.40) was similar to the results in the present study [27]. Japanese population studies also showed a significant association between *FTO* SNP and obesity [16,28]. The case-control association study showed that the AA genotype in the *FTO* SNP rs9939609 was significantly associated with obesity (OR, 1.53; 95% CI, 1.04–2.24) [16]. Similarly, another *FTO* SNP rs11558902 was significantly related to obesity under an additive model adjusted for age and gender (OR, 1.41; 95% CI, 1.22–1.62) [28].

The size of the MAFs in *FTO* SNPs supposed to be contributing to the increased BMI was reported to be much higher in Europeans (up to 42%) than in East Asia (12–20%) [29]. In this study, MAFs of rs9939609 T>A, rs8050136 C>A, and rs9926289 G>A for Korean were 12.5–18%, which were similar to the others. East Asians had a lower MAF of BMI-associated alleles at the SNPs in the *FTO* than Europeans but showed a similar pattern on the risk of obesity (OR per allele) shown in both ethnics (European, 1.20; East Asian, 1.27) [29]. This result may be related to the difference in the BMI cut-off point defining obesity between Western and Asian populations [30,31]. WHO defined BMI ≥ 30 kg/m² as obesity and 25 kg/m² \leq BMI < 30 kg/m² as overweight [30]. On the other hand, East Asians, including Koreans, used the Asia-Pacific criteria of the WHO guideline defining obesity as BMI ≥ 25 kg/m² [30]. The difference in criteria for obesity is supported by the evidence that compared with the Western and Asian populations are more likely to be exposed to the risk of comorbidities, such as CVD and T2DM, even though they are below 25 kg/m² of BMI, which may be related to the differences in the endocrine metabolism between populations [31]. According to the pattern analysis of linkage disequilibrium (LD) from HapMap DB, *FTO* SNPs rs9939609 and rs8050136 were strongly associated with Caucasian, Asian (Chinese and Japanese), and South American, but *FTO* SNPs rs8050136 did not affect the risk of obesity in Asian [32]. These results might be due to the differences in LD patterns or MAF across different ethnic populations. Therefore, further studies will be needed to suggest the appropriate evidence

for the association between *FTO* SNPs and obesity risk according to racial characteristics. In this aspect, this meta-analysis study provides additional evidence to identify the effect of *FTO* SNPs on the risk of obesity among Koreans.

Several studies performed in the Western population reported that *FTO* SNPs and environmental parameters might affect the BMI changes interactively [33-38]. For example, the minor allele effect of the *FTO* SNPs on the increased BMI was highly observed in the subjects consuming the high-fat diet or those with low physical activity [33,34]. In addition, increased physical activity weakened the effects of *FTO* SNPs on obesity by reducing the genetic susceptibility [37,38]. On the other hand, some studies did not find an interaction effect of *FTO* SNPs and physical activity on obesity [39,40]. This result may be due to the differences in physical activity intensity, participant characteristics, study design, and study period. *FTO* SNPs were also reported to affect the metabolic status, such as insulin metabolism and circulating high-density lipoprotein cholesterol levels, and are involved in diminished satiety and its genetic susceptibility to obesity by macronutrient composition in the diet consumed [41-46]. On the other hand, environmental parameters, such as physical activity and dietary nutrient composition, could not be considered in the meta-analysis because the number of publications on the association between *FTO* SNPs and obesity among Korean adults was very small and did not have sufficient information on the environmental parameters mentioned above. Therefore, further studies investigating the interaction between *FTO* SNPs and environmental parameters affecting obesity and the related metabolic status among Koreans are needed.

This meta-analysis study had several limitations. First, the association between the *FTO* SNPs and obesity-related traits was confirmed in Koreans. On the other hand, it was difficult to compare them due to the small number of papers and the differences in the study characteristics. Second, most studies used the big data of the KARE cohort. Therefore, extracted data overlapped among studies. Moreover, the causality between *FTO* SNPs and obesity risk could not be suggested because of all studies with cross-sectional design. Hence, many kinds of gene-based research must be performed by the life cycle (adults, children, elderly, and patients). Third, this meta-analysis could not analyze a single *FTO* SNP due to the limited literature. *FTO* SNP rs9939609 focused on obesity risk due to much evidence without racial differences because LD pattern analysis of five *FTO* SNPs on Korean was unavailable.

Despite some limitations, this study is the first meta-analysis study identifying that minor alleles in the *FTO* SNPs are associated with the increased risk of obesity among Korean adults using the data from only a Korean population. These results provide evidence that *FTO* is suitable for the DTC genetic test predicting the risk of obesity in Koreans. The prospective or retrospective studies examining whether the prevalence of obesity or BMI increase for a certain period (i.e., for 10 years) is associated with *FTO* SNPs should be performed to elucidate the relationship.

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