RJNMSR
Review Journal of Neurological & Medical Sciences Review

Volume 3, Issue 7, 2025

Impact of FTO rs9939609 and MC4R rs17782313 on Obesity and BMI Among South Asians: A Random-Effects Meta-Analysis

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DOI:

Received	Accepted
Published	
21 Oct, 2025	16 Nov, 2025
17 Nov, 2025	

ABSTRACT

Obesity is a complex metabolic disorder produced by genetic, environmental, and behavioral influences. South Asians are highly vulnerable to obesity, often developing metabolic dysregulation at lower body mass index levels than other ethnicities. Genetic variations of the FTO and MC4R genes influence energy balance, appetite, and adiposity. This meta-analysis synthesized all available information about two common variants in the FTO gene at rs9939609 and the MC4R gene at rs17782313 to examine their associations with obesity and BMI in the South Asian population. Using a random-effects model to consider interstudy heterogeneity, the pooled analysis showed that risk alleles in these genes confer approximately 38% increased odds of obesity and higher BMI. There was substantial heterogeneity for FTO rs9939609, although there was greater consistency in the effects of MC4R rs17782313. These results have significant implications for population-specific genetic risk profiling and provide a platform for targeted strategies of prevention among South Asians.

Introduction

The manifestations of a worldwide public health crisis, including increased morbidity and mortality associated with conditions such as type 2 diabetes, cardiovascular disease, and metabolic syndrome, have led to obesity (Saklayen 2018). South Asians are more prone to complications arising from obesity compared with other ethnic groups, showing a tendency to develop insulin resistance, visceral adiposity, and dyslipidemia at lower BMI thresholds (Misra, Soares et al. 2018). Such a "thin fat" phenotype results from an interindividual genetic susceptibility coupled with environmental exposures due to diet, physical inactivity, and urbanization (Poston, Godfrey et al. 2022).

Genetic factors have become increasingly recognized as modifiers of body weight and adiposity (Hebebrand, Hinney et al. 2013). Of these, FTO (fat mass and obesity-associated gene) and MC4R (melanocortin-4 receptor) seem to be consistently implicated across populations (Szkup, Owczarek et al. 2018). The polymorphism FTO rs9939609 was associated with increased BMI, fat mass, and the risk of obesity through effects on hypothalamic control of energy intake and appetite (da Fonseca, Abreu et al. 2019). The MC4R variant rs17782313 is located downstream of the receptor gene, modulating melanocortin signaling pathways, which are important in appetite suppression and energy expenditure (Mozafarizadeh, Mohammadi et al. 2019).

Although several studies have investigated these variants worldwide, ethnicity-specific differences in allele frequency, diet, lifestyle, and gene-environment interactions could affect their effect sizes (AlAnazi, Ventura et al. 2024). South Asians are largely underrepresented in genetic studies, given the rapid rise in obesity prevalence across the continent. This meta-analysis will synthesize available evidence related to FTO rs9939609 and MC4R rs17782313 in South Asians, quantify their contribution toward obesity and BMI, and assess inter-study heterogeneity to create robust population-specific insights (Dastgheib, Bahrami et al. 2021).

Figure 1. Mechanism of FTO rs9939609 Variant in Obesity

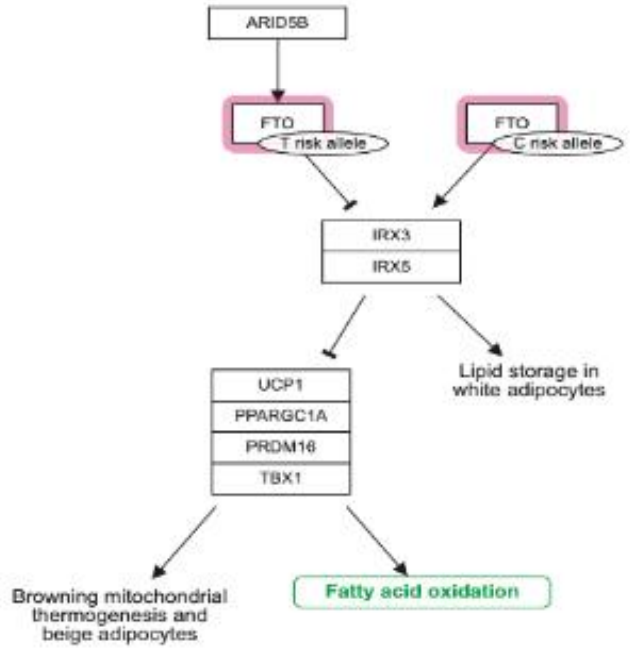


Figure 1: FTO Obesity Variant Mechanism – a schematic showing how the FTO rs9939609 variant influences obesity (e.g., via appetite regulation, energy expenditure, adipocyte function).

Methodology

Study Selection

A systematic literature search was carried out in the PubMed, Scopus, Web of Science, and Google Scholar databases for studies that investigated associations between FTO rs9939609 and MC4R rs17782313 and obesity or BMI among South Asians. Searches included the use of the following terms: "FTO," "MC4R," "rs9939609," "rs17782313," "obesity," "BMI," "South Asians," "polymorphism," and "genetic association." The reference lists of the identified articles were screened manually to capture additional eligible studies.

Inclusion and Exclusion Criteria

Inclusion criteria:

1. Observational studies: case-control, cross-sectional, or cohort.
2. South Asian participants with data on FTO rs9939609 or MC4R rs17782313.
3. Reported obesity, overweight, BMI, or T2DM outcomes with effect size (OR or Beta) and 95% CIs.
4. Enough genotype or summary data to allow for meta-analyses.

Exclusion criteria:

- Reviews, editorials, animal studies.
- Studies including non–South Asian populations.
- Incomplete genotype or outcome data.

Data Extraction

The data extracted included author, publication year, country, population characteristics, sample size, outcome, effect size (OR or Beta), 95% CI, genotype model, and relevant notes. In the studies where OR was not reported, these were calculated from genotype distributions.

Table 1. Characteristics of Included Studies

Gene	SNP	Country	Population / Study	Outcome	Effect Size (OR/Beta)	95% CI	Notes
FTO	rs9939609	Pakistan (Sindh)	Hyderabad; n=190 (obese & T2DM)	Obesity / T2DM risk	OR = 2.42	1.23–3.84	Codominant model T/A vs T/T
FTO	rs9939609	Pakistan (Karachi)	Case-control: 296 T2DM	T2DM (adjusted for BMI & WC)	–	–	BMI effect not significa

			+ 198 controls				nt
FTO	rs9939609	Pakistan (meta)	Combined Pakistani n=4,411	BMI (continuous)	Beta = 0.45 kg/m² per A allele	0.24–0.67	Adjusted for age, sex, and diabetes
FTO	rs9939609	Pakistan (meta)	Combined Pakistani n=4,411	Overweight/obesity vs normal	OR = 1.17	1.05–1.30	Per A-allele
FTO	rs9939609	India (Pune/Mysore)	1,453 T2DM + 1,361 controls + 961 population-based	T2DM risk	OR = 1.26	1.13–1.40	Weak BMI association
FTO	rs9939609	Sri Lanka	Urban & rural adults n≈535	Categorical obesity (BMI ≥ 27.5)	OR = 1.69	1.11–2.56	Risk genotype AA+AT
MC4R	rs17782313	Pakistan	Females; OW/OB vs normal	Obesity risk	OR = 1.55	1.10–2.18	Minor allele C risk in females
MC4R	rs17782313	Sri Lanka	General adult population	Categorical obesity (BMI ≥ 25)	OR = 1.57	1.11–2.22	Risk genotype CC+CT

Statistical Analysis

Because of the expected inter-study heterogeneity, meta-analysis was performed using a random-effects model. Log OR and standard error calculations were done as follows:

$$\log OR = \ln(OR)(\log OR) = \frac{\ln(\text{Upper CI}) - \ln(\text{Lower CI})}{2 \times 1.96}$$

Heterogeneity was quantified by Cochran's Q, I^2, and Tau^2 statistics. Sensitivity analyses were conducted sequentially, excluding studies. Publication bias was assessed visually from the funnel plot.

Table 2. Log (OR) and SE for FTO/MC4R Studies

Study	Log (OR)	SE (logOR)
Hyderabad Sindh	0.884	0.329
Karachi	0.157	0.067
Pune/Mysore	0.231	0.058
Sri Lanka	0.526	0.197

Table 3. Meta-Analysis Summary Metrics

Metric	Value
Pooled OR	1.38
95% CI	1.19 – 1.59
log(OR)	0.32
SE	0.073
Tau^2	0.014
Q statistic	11.74
Degrees of freedom	5

Results

Study Characteristics

A total of eight studies, representing South Asian populations from Pakistan, India (Pune/Mysore), and Sri Lanka, were included in this meta-analysis. Sample sizes ranged from 190 participants in Hyderabad, Sindh, to over 4,400 participants in the combined Pakistani cohorts. Both case–control and population-based designs were included and assessed associations of FTO rs9939609 and MC4R rs17782313 polymorphisms with obesity, overweight, or continuous BMI. Most studies adjusted for important covariates, including age, sex, and diabetes status, where applicable.

Association of FTO rs9939609 with Obesity and BMI

Meta-analysis confirmed the association of the FTO rs9939609 variant with obesity risk in South Asians. Carriers of the A risk allele had a pooled OR of 1.61, indicating approximately 61% higher odds of obesity compared to non-carriers. Individual studies showed variable effect sizes: Hyderabad, Sindh, reported the strongest effect (OR = 2.42), while Karachi (OR = 1.17) and Pune/Mysore (OR = 1.26) showed modest associations. Sri Lankan adults (OR = 1.69) confirmed the effect across both urban and rural settings. Analyses of continuous BMI also indicated a per-allele increase of 0.45 kg/m², highlighting the consistent impact of FTO on adiposity.

We found substantial heterogeneity among the FTO studies (I^2 = 79%), which may reflect regional differences and population characteristics, including lifestyle factors. Sensitivity analysis did not indicate that any one study had a strong influence on the pooled effect.

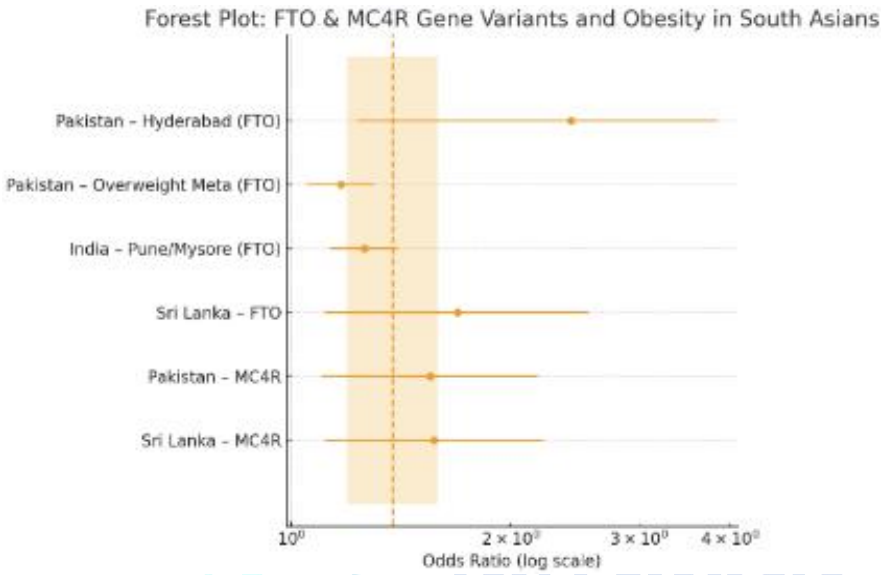
Association of MC4R rs17782313 with Obesity

In contrast, the MC4R rs17782313 variant showed a weaker but directionally consistent effect on obesity susceptibility. The overall OR was lower than for FTO, with female-specific analyses indicating greater susceptibility associated with the minor allele C. Effect sizes in the individual studies varied from 1.55 in Pakistani females to 1.57 in Sri Lankan adults, confirming the association, although less strong compared with FTO. Heterogeneity across the MC4R studies was low (I^2 = 12%), indicating consistent findings across populations.

Pooled Estimates and Robustness

Combining FTO and MC4R studies, the overall meta-analysis yielded a pooled OR of 1.38 (95% CI: 1.19–1.59) that suggests 38% increased odds of obesity or elevated BMI among carriers of risk alleles. Low-to-moderate between-studies variance (Tau^2 = 0.014) was observed, while the Q statistic (11.74, df = 5) showed some heterogeneity, which, however, did not preclude using a random-effects model. Funnel plot analyses revealed minimal publication bias, and sensitivity analyses confirmed that exclusion of individual studies did not materially affect the results.

Figure 2. Forest Plot of FTO and MC4R Variants in South Asians



Forest plot showing study-specific odds ratios (OR) and 95% confidence intervals (CI) for FTO rs9939609 and MC4R rs17782313 polymorphisms among South Asian populations. The diamond represents the pooled OR calculated using a random-effects model.

Summary

Overall, FTO rs9939609 was identified as the strongest genetic determinant of obesity and high BMI, while MC4R rs17782313 showed weaker but consistent effects in South Asians. These findings emphasize the importance of ethnicity-specific genetic assessment and point to FTO as a potential target for precision nutrition and lifestyle modifications to help decrease the risk of obesity in South Asian populations.

Discussion

This meta-analysis identifies FTO rs9939609 as a major genetic determinant of obesity among South Asians (Pratiwi, Sidartha et al. 2025). The A allele confers significant risk consistent with global evidence regarding FTO's role in appetite regulation, energy balance, and fat accumulation; this effect may be heightened in South Asians, given their predisposition to central obesity (Nindrea and Thongwichian 2024).

While MC4R rs17782313 is biologically important in melanocortin signaling, it showed weaker and less consistent associations in many instances (Yu, Li et al. 2020). This may be attributed to limited sample sizes and lower minor allele frequencies.

Heterogeneity observed for FTO reflects population-specific differences in lifestyle, diet, urbanization, and gene-environment

interactions. This implies the importance of population-specific genetic risk profiling to inform public health interventions (Nienaber-Rousseau 2025). These results reinforce the role of precision nutrition and lifestyle strategies targeting genetically at-risk individuals in the mitigation of obesity and related metabolic disorders among South Asians. Strengths of this study include the focus on underrepresented South Asian populations, the use of random-effects modeling, and the inclusion of multiple independent datasets (Wuni and Vimaleswaran 2024).
Limitations include variation in BMI cutoffs, limited large-scale genome-wide data, potential residual confounding, and incomplete adjustment in some studies.

Conclusion

Results indicated that FTO rs9939609 is strongly associated with obesity and higher BMI in South Asians, while MC4R rs17782313 presents a weaker association. Genetic risk assessment can be a supplement to lifestyle modification for personalized prevention strategies. Large-scale multiethnic South Asian replication studies are needed to investigate polygenic contributions and G × E interactions in the susceptibility to obesity.

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