

## Integrating genetic susceptibility into obesity risk prediction: Evidence from Jambi Malays with low-to- moderate physical activity

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### Abstract

**Background:** Obesity results from interactions between genetic susceptibility and lifestyle. The association between FTO rs9939609 and obesity phenotype varies across populations, while the added value of genotype information in predictive models remains limited in Southeast Asia. **Objective:** To determine the association between FTO rs9939609 polymorphism and obesity, and to evaluate its contribution to predictive models incorporating demographic and lifestyle variables. **Methods:** A case–control study was conducted among 126 Malay adults (63 obese, 63 non-obese). Anthropometric indices, physical activity, and dietary intake were assessed. Genotyping of FTO rs9939609 was performed using the Tetra-ARMS PCR method. Logistic regression evaluated genotype–phenotype associations, and receiver operating characteristic (ROC) analysis assessed model discrimination. **Results:** Carriers of the AT genotype had higher odds of obesity than AA (adjusted OR = 3.20; 95 % CI 1.25–8.17; p = 0.015), while TT was not significant. Under the dominant model (AT + TT vs AA), T-allele carriers had nearly a three-fold increased risk (adjusted OR = 2.77; 95 % CI 1.13–6.82; p = 0.027). Incorporating genotype data improved prediction (AUC = 0.716 vs 0.655). **Conclusion:** The FTO rs9939609 variant contributes independently to obesity risk among Malay adults in Jambi and modestly enhances prediction accuracy when combined with lifestyle variables. Integrating genetic information may improve precision-based obesity-prevention strategies in Indonesian populations.

**Keywords:** FTO rs9939609; obesity; genetic susceptibility; prediction model; malay population; Indonesia.

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### Editor

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## Article info

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## INTRODUCTION

The prevalence of obesity continues to increase globally and represents one of the most pressing public health challenges of the twenty-first century. According to the World Health Organization, the worldwide prevalence of obesity has nearly tripled since 1975, with more than 650 million adults currently affected [1]. In Indonesia, the most recent national health survey reported a significant rise in adult obesity, from 14.8% in 2013 to 23.1% in 2018, reflecting rapid urbanization, dietary transition, and increasingly sedentary lifestyles [2]. Obesity is a major contributor to metabolic and cardiovascular diseases, including type 2 diabetes, hypertension, and chronic kidney disease, which together account for a growing proportion of noncommunicable disease–related mortality in Southeast Asia [3,4].

Although lifestyle and environmental factors play central roles in the pathogenesis of obesity, interindividual variation in body weight and fat distribution cannot be fully explained by life style determinants alone. Evidence from genome-wide association studies (GWAS) has established that obesity has a substantial heritable component, with common genetic variants accounting for approximately 20–40% of interindividual differences in body mass index (BMI) [5]. Among the identified loci, the fat mass and obesity-associated (FTO) gene remain one of the most consistently replicated and biologically plausible contributors to adiposity [6,7]. The FTO rs9939609 single-nucleotide polymorphism (SNP) has been strongly associated with obesity risk across multiple ethnic groups, though the magnitude of its effect varies by ancestry and environmental context [8,9].

Functional studies suggest that FTO influences energy balance through hypothalamic regulation of appetite, food preference, and satiety. Carriers of the risk allele tend to exhibit higher caloric intake and preference for fat- and sugar-dense foods, resulting in greater long-term adiposity [10,11]. Notably, the genetic effect of FTO appears to interact with lifestyle: regular physical activity and balanced diet can mitigate, whereas low activity and excessive energy intake can amplify, the obesogenic effect of risk alleles [12,13]. These gene–environment interactions highlight the importance of considering both genetic and life style factors when assessing obesity susceptibility.

The Malay population in Jambi Province represents an ethnically distinct group within Indonesia, characterized by shared cultural dietary patterns and predominantly low-to-moderate physical activity levels [14]. However, to date, no study has examined FTO rs9939609 variation and its association with obesity in this population. Exploring genetic contributions among Malays in Jambi is crucial, as allele frequencies and effect estimates observed in other Asian or European cohorts may not generalize to local populations due to genetic heterogeneity and unique lifestyle exposures. Understanding these patterns can inform population-specific risk models and precision public health strategies. Therefore, this study aimed to determine the association between FTO rs9939609 polymorphism and obesity among Malay adults in Jambi and to evaluate the incremental predictive value of incorporating genotype data into obesity-risk models based on demographic and life style factors.

## METHODS

### *Study design and setting*

This was a community-based case–control study conducted between June and October 2025 in Jambi City and Muaro Jambi District, Indonesia. Participants were recruited through local community health posts and public health campaigns. Eligibility criteria included self-reported Malay ethnicity for at least two generations, age between 20 and 56 years, residence in Jambi for  $\geq 5$  years, and engagement in low-to-moderate physical activity levels as determined by the International Physical Activity Questionnaire (IPAQ) short form. Individuals who were pregnant, had endocrine disorders, chronic kidney disease, or malignancy were excluded. A total of 126 participants were included, comprising 63 individuals classified as obese and 63 as non-obese. Obesity was defined based on the criteria of the Indonesian Ministry of Health (Body Mass Index [BMI]  $\geq 27$  kg/m<sup>2</sup>), while non-obesity referred to BMI  $< 27$  kg/m<sup>2</sup> [15]. Written informed consent was collected from all participants before data collection.

### *Data collection and measurements*

Sociodemographic characteristics, medical history, and lifestyle factors were obtained through interviewer-administered questionnaires. Anthropometric measurements included body weight and height, measured to the nearest 0.1 kg and 0.1 cm, respectively, using calibrated instruments with participants wearing light clothing and no footwear. BMI was calculated as weight (kg) divided by height squared (m<sup>2</sup>). Physical activity was assessed using the validated Indonesian version of the IPAQ-short form, and participants were categorized into low, moderate, or high activity levels following WHO guidelines [16]. Dietary intake was recorded using three nonconsecutive 24-hour dietary recalls (two weekdays and one weekend day). Nutrient analysis was performed using Nutrisurvey 2007 software, and energy and macronutrient intakes were expressed as percentages of the Indonesian Recommended Dietary Allowance (%RDA) [17].

### *DNA extraction and genotyping*

Venous blood (3 mL) was collected in EDTA tubes and stored at  $-20^{\circ}\text{C}$  prior to analysis. Genomic DNA was extracted using a commercial DNA isolation kit (Geneaid®, Taiwan) according to the manufacturer's protocol. Genotyping of FTO rs9939609 (A>T) was performed using the Tetra-primer Amplification Refractory Mutation System Polymerase Chain Reaction (Tetra-ARMS PCR) method, as validated by Maharani and Puspasari (2025) [18]. Primer sequences were designed using Primer1 software, and PCR reactions were performed in a 25  $\mu\text{L}$  reaction volume containing genomic DNA, primers, and master mix (GoTaq® Green, Promega). The PCR conditions included initial denaturation at  $95^{\circ}\text{C}$  for 5 min, followed by 35 cycles of  $95^{\circ}\text{C}$  for 30 s,  $58^{\circ}\text{C}$  for 30 s, and  $72^{\circ}\text{C}$  for 30 s, with a final extension at  $72^{\circ}\text{C}$  for 5 min. PCR products were visualized by 2% agarose gel electrophoresis and photographed under UV illumination. Genotypes were classified as AA (wild type), AT (heterozygous), or TT (homozygous mutant) based on specific banding patterns. To ensure reliability, 20% of the samples were randomly selected for repeat genotyping, showing 100% concordance between runs.

### *Statistical analysis*

Data were analyzed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean  $\pm$  standard deviation (SD) and

categorical variables as frequencies and percentages. Differences between obese and non-obese groups were assessed using independent-samples t-tests or Chi-square tests, as appropriate. Allele and genotype frequencies were calculated, and Hardy–Weinberg equilibrium (HWE) was evaluated using Chi-square tests in both case and control groups. Logistic regression analysis was performed to estimate crude and adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between FTO rs9939609 genotypes and obesity, under codominant and dominant genetic models. Adjustment variables included age, sex, physical activity, and dietary intake. Receiver operating characteristic (ROC) curve analysis was used to assess the predictive accuracy of three models: (1) non-genetic model (demographic and lifestyle variables), (2) genetic codominant model, and (3) genetic dominant model. Model discrimination was quantified using the area under the curve (AUC), and optimal cut-off points were determined using Youden's Index. Statistical significance was defined as  $p < 0.05$  (two-tailed).

### **Ethical considerations**

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Faculty of Medicine, Universitas Jambi (Ethical Clearance No. 2083/UN21.8/PT.01.04/2025).

## **RESULTS**

### **Subject characteristics**

A total of 126 subjects were participated in this study which grouped as obesity ( $n = 63$ ) and non-obesity ( $n = 63$ ). The mean age in the obesity group was slightly higher than in the non-obesity group ( $37.70 \pm 8.00$  vs.  $34.27 \pm 11.16$  years), a difference that approached statistical significance ( $p = 0.050$ ). There were no statistically significant differences between groups based on distribution or in the percent of recommended dietary allowance (%RDA) for energy, protein, fat, and carbohydrate intake (table 1).

**Table 1.** Baseline subject characteristics

<b>Characteristic</b>	<b>Obese (n=63)</b>	<b>Non-Obese (n=63)</b>	<b>p-value</b>
Age, years old	37.70 ± 8.00	34.27v ± 11.16	0.050
Gender			
Female, n	49	14	0.164
Male, n	42	21	
% RDA for energy intake	76.12 (17.69-258.47)	76.64 (30.77-345.05)	0.607
% RDA for protein intake	109.00 (28.31-351.54)	115.54 (52.17-436.17)	0.255
% RDA for fat intake	92.00 (8.29-380.67)	90.14 (13.60-494.46)	0.803
% RDA for carbohydrate intake	61.93 (7.59-202.79)	63.98 (18.12-420.32)	0.378

Remarks: RDA= Indonesian recommended daily allowance 2019

### **Genotype distribution and allelic frequency**

All three FTO rs9939609 genotypes (AA, AT, TT) were detected in this Malay cohort. The A allele was the major (wild-type) allele, and T the minor allele. The genotype distribution in the non-obesity group was in Hardy–Weinberg equilibrium ( $\chi^2 = 0.126$ ;  $p = 0.723$ ; minor allele frequency  $\approx 0.405$ ), whereas the obesity group deviated from equilibrium ( $\chi^2 = 11.886$ ;  $p = 0.0007$ ; minor allele frequency  $\approx 0.468$ ). A random recall

of 20% of samples showed 100% concordance between repeated genotyping results, confirming the reliability of the assay (Table 2).

**Table 2.** Hardy Weinberg Equilibrium Estimation

Genotype	Obese					Non-Obese				
	Observed value	Expected value	Chi-square	p-value	MAF	Observed value	Expected value	Chi-square	p-value	MAF
AA	11	18				23	22			
TA	45	31	11.886	0.0007	0.468	29	31	0.126	0.723	0.405
TT	7	14				11	10			

MAF= minor allele frequency; p-value calculated with degree of freedom= 1

### **Association between genotype and obesity**

In the bivariate analysis, individuals carrying the heterozygous AT genotype had significantly higher odds of obesity compared with those carrying the AA genotype (OR = 3.24; 95% CI 1.38–7.64; p = 0.006). This association remained significant after adjustment for age, sex, physical activity, and dietary intake (adjusted OR = 3.20; 95% CI 1.25–8.17; p = 0.015). The homozygous TT genotype did not show a significant association with obesity in either unadjusted or adjusted models (adjusted OR = 1.03; 95% CI 0.26–4.11; p = 0.986). Under the dominant genetic model (AT + TT vs. AA), carriers of the T allele demonstrated an increased likelihood of obesity (adjusted OR = 2.77; 95% CI 1.13–6.82; p = 0.027), indicating that the presence of a single T allele confers substantial risk (Table 3).

**Table 3.** Association of genetic and obesity in bivariate and multivariate analysis.

Genotype	Obese (n=63)	Non-Obese (n=63)	p-value	OR (95% CI)	Adjusted p-value	Adjusted OR (95% CI)
AA	11	23	ref	ref		
TA	45	29	0.006	3.24 (1.38-7.64)	0.015	3.20 (1.25-8.17)
TT	7	11	0.637	1.33 (0.40-4.37)	0.986	1.03 (0.26-4.11)
TATT	52	40	0.016	2.72 (1.19-6.22)	0.027	2.77 (1.13-6.82)

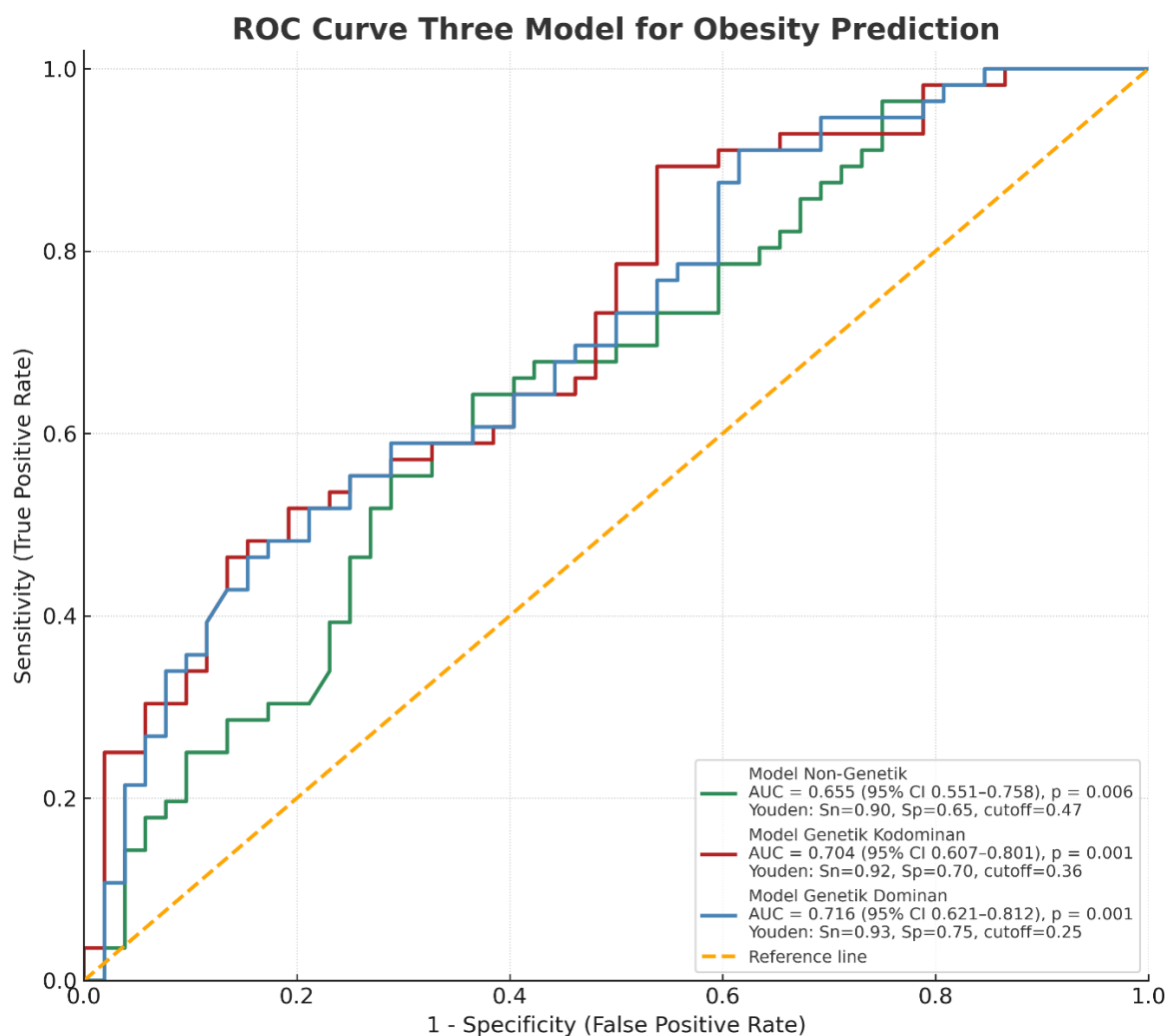
### **Predictive model performance**

ROC analysis was performed to evaluate the discriminative ability of three predictive models (Table 4; Figure 1). The non-genetic model, comprising demographic and lifestyle factors, yielded an AUC = 0.655 (95% CI 0.551–0.758; p = 0.006) with sensitivity = 0.90 and specificity = 0.65 at a cut-off = 0.47. When the FTO genotype was incorporated into the codominant model, the predictive performance improved (AUC = 0.704; 95% CI 0.607–0.801; p < 0.001), with sensitivity = 0.92 and specificity = 0.70 at a cut-off = 0.36. The dominant genetic model provided the best discriminative capacity, yielding AUC = 0.716 (95% CI 0.621–0.812; p < 0.001), sensitivity = 0.93, and specificity = 0.75 at a cut-off = 0.25.

**Table 4.** Comparison for 3 model for prediction of obesity

Model	AUC	95% CI	p-value	Sensitivity (Sn)	Specificity (Sp)	Cutoff
Age+gender+physical activities+dietary intake (no genetic insertion)	0.655	0.551–0.758	0.006	0.90	0.65	0.47
Age+gender+physical activities+dietary intake+codominant genetic susceptibility	0.704	0.607–0.801	<0.001	0.92	0.70	0.36
Age+gender+physical activities+dietary intake+dominant genetic susceptibility	0.716	0.621–0.812	<0.001	0.93	0.75	0.25

**Remarks:** AUC= area under curve



**Figure 1.** ROC curve for obesity prediction model

**DISCUSSION**

The present findings indicate that demographic and dietary profiles were generally comparable between obese and non-obese participants, suggesting that differences in obesity risk were unlikely to be explained solely by lifestyle factors. Instead, these

variations may reflect underlying genetic influences [19]. The deviation from Hardy–Weinberg equilibrium (HWE) observed among obese participants is unlikely to result from genotyping error. Rather, it may represent a genuine association between genotype and obesity status, sampling fluctuation, or subtle population substructure. Similar deviations restricted to case groups have been reported in other gene–disease association studies and are often interpreted as indicators of genotype–phenotype linkage [20,21].

The association between the FTO rs9939609 polymorphism and obesity identified in this study is consistent with findings from diverse populations. Multiple studies have demonstrated that the A allele of rs9939609 is associated with increased body mass index (BMI), adiposity, and overall obesity risk in European, East Asian, and other Southeast Asian populations [22,23]. The risk allele has been suggested to influence energy balance through its regulatory effects on hypothalamic pathways involved in appetite control, energy expenditure, and satiety signaling. Functional studies indicate that FTO variants may alter expression of genes such as IRX3 and IRX5, which are implicated in adipocyte differentiation and lipid storage, thereby promoting a shift toward energy-conserving white adipose tissue rather than thermogenic brown adipose tissue. These molecular mechanisms provide biological plausibility for the observed association between FTO variation and obesity susceptibility.

The inclusion of FTO rs9939609 genotype data in predictive models modestly improved the discrimination between obese and non-obese individuals beyond demographic and lifestyle variables alone. Although the magnitude of improvement was moderate, this trend aligns with prior research demonstrating that single genetic variants contribute incremental predictive value when integrated into multifactorial models [24,25]. This suggests that obesity is a complex polygenic trait, where cumulative effects of multiple genes, combined with behavioral and environmental factors, determine overall risk. Future studies employing polygenic risk scores (PRS) incorporating multiple loci could substantially enhance predictive accuracy compared with single-variant approaches.

Several factors should be considered when interpreting these findings. The relatively small sample size, particularly the limited number of TT homozygotes, may have reduced statistical power and the ability to detect more subtle genetic effects. The cross-sectional design restricts causal inference, and reliance on self-reported dietary intake introduces potential recall bias. Furthermore, as participants were exclusively Malay adults from Jambi, extrapolation to other ethnic or regional populations should be made with caution, given that allele frequencies and gene–environment interactions may vary across ethnicities.

Despite these limitations, this study provides meaningful contributions as one of the first to examine FTO rs9939609 polymorphism in an Indonesian Malay cohort. The integration of genetic, demographic, and behavioral data allowed a more comprehensive evaluation of obesity determinants in this understudied population. Moreover, the application of a validated, cost-effective Tetra-ARMS PCR method underscores the feasibility of implementing genetic association studies in resource-limited laboratory settings [18].

Importantly, these findings have implications for the development of precision-based obesity prevention strategies in Indonesia. The modest but consistent improvement in predictive performance suggests that genetic information can complement traditional risk assessments and could be incorporated into early

screening tools to identify individuals at higher genetic risk. As Indonesia and other Southeast Asian countries face rising obesity prevalence, integrating genetic susceptibility markers such as FTO into community health programs may facilitate targeted interventions, promote personalized dietary counseling, and support more efficient resource allocation [26–28].

## CONCLUSIONS

This study demonstrates that the FTO rs9939609 polymorphism is significantly associated with increased odds of obesity among Malay adults in Jambi, Indonesia. Carriers of the T allele exhibited nearly a threefold higher risk of obesity, independent of demographic, dietary, and physical activity factors. Incorporating this genotype into multivariable models modestly improved discrimination, indicating that genetic susceptibility provides complementary predictive value alongside life style determinants. These findings underscore the importance of integrating genetic information into obesity risk assessment frameworks, particularly within ethnically specific populations undergoing lifestyle transitions. Future studies with larger, multiethnic cohorts and multi-locus analyses are warranted to validate these results and to develop cost-effective, population-tailored genetic screening strategies for obesity prevention in Indonesia.

## CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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