RESEARCH ARTICLE

Association of *FTO* rs9939609, *MC4R* rs17782313, and *TMEM18* rs6548238 Variants with Body Mass Index and Body Composition in Young Indonesian Adults

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Abstract

BACKGROUND: Obesity is partly driven by genetic variation, including single-nucleotide polymorphisms (SNPs) in the Fat Mass and Obesity-associated (*FTO*), Melanocorti-4 Receptor (*MC4R*), and Transmembran Protein 18 (*TMEM18*) genes. However, only few Indonesian studies have integrated body composition analysis using bioelectrical impedance analysis (BIA) to evaluate the relationship between these genotypes and body mass index (BMI). Therefore, this study was conducted to investigate the association of *FTO* rs9939609, *MC4R* rs17782313, and *TMEM18* rs6548238 with BMI and BIA-derived body composition parameters.

METHODS: A cross-sectional study was conducted involving 111 healthy young adults aged 18–31 years olds. Subjects were examined for their body composition parameters using using the Quadscan 4000 BIA device, and then classified into obese (BMI≥25 kg/m^2) and non-obese (BMI<25 kg/m^2). Buccal rinse samples from each subjects were taken for the DNA extraction. Genotyping for *FTO* rs9939609, *MC4R* rs17782313, and *TMEM18* rs6548238 were then performed using the Kompetitive Allele-Specific Polymerase Chain Reaction (KASP^{TM}) method.

RESULTS: Among 3 SNPs, only the A allele of *FTO* rs9939609 showed a significant association with increased BMI (p=0.0115) and several BIA parameters, including higher fat percentage (p=0.022), greater fat mass (p=0.0071), higher muscle mass (p=0.0334), and lower muscle mass percentage (p=0.022). Mediation analysis indicated that fat mass, fat-free mass index, body fat mass index, and total body water mediated 72.7–94.3% of the *FTO* effect on BMI, with an insignificant direct effect.

CONCLUSION: *FTO* rs9939609 variant is significantly associated with higher BMI in Indonesia young adults, primarily mediated by alterations in fat and muscle mass. In contrast, *MC4R* rs17782313 and *TMEM18* rs6548238 showed no significant associations. These findings underscore the value of integrating genetic profiling with BIA-based body composition measures to refine obesity risk assessment and clarify the regulatory role of the intronic *FTO* variant.

KEYWORDS: *FTO*, *MC4R*, *TMEM18*, obesity, bioelectrical impedance analysis, genetic association, Indonesia

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Introduction

Obesity, characterized by excessive fat accumulation due to an imbalance between energy intake and expenditure, remains a global health issue.(1,2) In Indonesia, data from the Ministry of Health shows an increase in obesity prevalence from 21.8% in 2013 to 23.4% in 2023.(3) This upward trend is alarming, as it increases the risk of diseases such as type 2 diabetes mellitus, cardiovascular disorders,

and fatty liver disease.(4–6) Therefore, early detection of obesity and factors affecting it is crucial to prevent health complications.

Obesity is a multifactorial disease influenced by genetic and lifestyle factors.(7) Genome-wide association studies have identified several obesity-related genes, such as Fat Mass and Obesity-associated (*FTO*), Melanocortin-4 Receptor (*MC4R*), Transmembrane Protein 18 (*TMEM18*), Leptin Receptor (*LEPR*), and Brain-Derived Neutrotrophic Factor (*BNDF*).(8–13) Among them, the SNPs of *FTO* rs9939609, *MC4R* rs17782313, and *TMEM18* rs6548238 are the most frequently replicated obesity-associated loci across different populations. significantly more common in obese individuals than in lean individuals. These variants have been shown to influence body weight regulation through mechanisms related to appetite control, energy metabolism, and adipose tissue development.(13–15) Interestingly, all three SNPs are intronic variants that likely function as regulatory elements rather than coding mutations, potentially affecting gene expression through epigenetic or transcriptional mechanisms rather than protein structure.

Previous studies conducted in children and adults in Indonesia have shown that individuals with the AA/AT genotype of the *FTO* have a higher risk of obesity.(16,17) However, these studies primarily examined the association between *FTO* variants and body mass index (BMI) alone, without evaluating the detailed body composition parameters. However, BMI has limitations as it cannot differentiate between muscle and fat mass, potentially leading to inaccurate results.(18) As an alternative, Bioelectrical Impedance Analysis (BIA) uses electrical currents to measure body composition, providing more accurate results in distinguishing fat and muscle mass.(19) In contrast, the present study integrates BIA to assess how genetic variations, particularly *FTO* rs9939609, influence fat mass, muscle mass, and water compartments, therefore providing more comprehensive understanding on how genetic influences obesity phenotypes. Furthermore, this study includes a comparative analysis of *MC4R* rs17782313 and *TMEM18* rs6548238, which have been reported to have association with obesity in other populations, but whose roles remain underexplored in Indonesian population. (15,20)

Despite increasing evidence linking genetic variants such as *FTO*, *MC4R*, and *TMEM18* to obesity, few studies in Indonesia have examined how these variants relate to detailed body composition parameters rather than BMI alone. This gap is particularly important because several of these loci represent intronic variants, which may exert regulatory rather than direct coding effects, thereby influencing obesity through more complex molecular pathways. The absence of such data limits understanding of how genetic predisposition affects fat and muscle distribution in young Indonesian adults. Therefore, this study was conducted to investigate the association between *FTO* rs9939609, *MC4R* rs17782313, and *TMEM18* rs6548238 gene variants with BMI and body composition measured using BIA. The findings are expected to identify genetic factors that contribute to obesity risk and to determine the most relevant body composition parameters for evaluating genotype–phenotype relationships in the Indonesian population.

Methods

Subjects Recruitment

This cross-sectional study involved 111 young adults aged 18–31 years who were students at Universitas Tarumanagara (Jakarta, Indonesia). Although the sample was drawn from a university students population, yet they represented individuals from both urban and semi-urban areas. Inclusion criteria included apparently healthy individuals with no known chronic diseases. The absence of chronic diseases was confirmed through a self-administered questionnaire, in which subjects reported any previous physician-diagnosed conditions such as diabetes, thyroid disorder, cardiovascular disease and kidney disease. Exclusion criteria included pregnancy, use of medications that could alter body composition (*e.g.*, corticosteroids), and conditions that could interfere with BIA measurements (*e.g.*, pacemaker implantation). All subjects provided written informed consent before data collection. Ethical approval was obtained from the Universitas Tarumanagara Research Ethics Committee (UTREC) under approval number 003-UTHREC/UNTAR/I/2024, with an amendment 011-UTHREC/UNTAR/VII/2025.

Determination of minimum sample size was determined using G*Power 3.1.9.7 software (Heinrich-Heine-University (HHU), Düsseldorf, Germany. The parameters used was F test family for Linear multiple regression: fixed model R2 deviation from zero, with an effect size of 0.15 (medium), α=0.05, and power=0.80 for multiple linear regression with three predictors, the minimum required sample size was 77. However, to adequate stronger statistical power for genotype–phenotype analysis, the final number of subjects includes exceeded the minimal number, which was 111 subjects in total.

Data Collection

Demographic information, including age, sex, and physical activity, was collected using standardized questionnaires to help control for potential confounders. As for data for ethnicity of subjects and their parents, it was obtained using self-reported using an open-ended questionnaire item. Because of the high proportion of mixed ancestry and the modest sample size, ethnicity was summarized descriptively and not included as a covariate in inferential analyses.

BIA

Body composition was assessed using the Quadscan 4000 Bioelectrical Impedance Analysis (BIA) device (Bodystat Ltd., Isle of Man, UK), which measures fat mass (kg), fat-free mass (kg), total body water (TBW, liters), extracellular water (ECW, liters), intracellular water (ICW, liters body cell mass (BCM, kg), phase angle (degrees), basal metabolic rate (BMR, kcal/day), body fat mass index (BFMI), and fat-free mass index (FFMI). Measurements were conducted under standardized conditions: subjects fasted for at least 4 hours, avoided strenuous exercise for 24 hours, and were measured in a supine position after a 10-minute rest to ensure hydration stability.

Measurements were conducted under standardized conditions. All assessments were performed in the morning, with subjects fasting for at least 4 hours, avoiding strenuous exercise for 24 hours, and resting in a supine position for approximately 10 minutes before measurement to ensure hydration stability. Electrodes were placed on the right hand and foot according to the manufacturer's instructions. Each subject was measured once, and the procedure was carried out by trained personnel using the same device and protocol throughout the study. The measurements were conducted in a controlled environment with room temperature maintained between 22–25°C to minimize external variability.

Based on the measurement above, subjects' BMI was calculated and classified into obese and non-obese. Obesity classification was based on the Asia-Pacific BMI criteria, where individuals with BMI≥25 kg/m^2 were categorized as obese, and BMI<25 kg/m^2 as non-obese. Potential sources of selection and measurement bias were considered and are further discussed in the discussion section.

Buccal Genomic DNA Extraction

Genomic DNA was extracted from buccal rinse samples to ensure non-invasive sample collection and subjects comfort. Samples were collected using a standardized protocol: subjects rigorously rinsed their mouths with 10 mL of sterile saline solution for 30 seconds. DNA extraction was performed using the Zymo Research Quick-DNA Miniprep Plus Kit (D4069; Zymo Research, Irvine, CA, USA) following the manufacturer's protocol. The extracted DNA was stored at –20°C until further analysis to prevent degradation.

***FTO*, *MC4R* and *TMEM18* Genotyping**

The genotyping for *FTO* rs9939609, *MC4R* rs17782313, and *TMEM18* rs6548238, were performed using the Kompetitive Allele-Specific PCR Polymerase Chain Reaction (KASP™) method (LGC Biosearch Technologies, Hoddesdon, UK). The KASP assay was conducted using a 0.2 mL PCR tube on the Rotor-Gene Q real-time PCR system (Qiagen, Hilden, Germany). Each reaction contained 10 ng of genomic DNA, KASP master mix, and allele-specific primers designed for each SNP (LGC Biosearch Technologies). The PCR protocol included an initial denaturation at 94°C for 15 minutes, followed by 10 cycles of touchdown PCR (94°C for 20 seconds, 61–55°C decreasing by 0.6°C per cycle for 60 seconds), and 26–35 cycles of amplification (94°C for 20 seconds, 55°C for 60 seconds). The KASP™ method used allele-specific fluorescent labeling to discriminate genotypes, eliminating the need for agarose gel electrophoresis. Fluorescence signals were analyzed using Q-Rex Software (Qiagen) to assign genotypes. Hardy-Weinberg Equilibrium (HWE) was tested for each SNP to verify population representativeness (p≥0.05). An example of genotyping results for the three variants were presented in Figure 1.

Statistical Analysis

Statistical analyses were conducted using R software version 4.3.0 (R Foundation, Vienna, Austria). Descriptive statistics summarized demographic and body composition data, with normality assessed using the Shapiro-Wilk test. Genotype-phenotype associations were evaluated using multiple linear regression, adjusted for age, sex, and physical activity levels to account for potential confounders. The additive genetic model was tested, with each risk allele coded incrementally. Beta coefficients (β), 95% confidence intervals (CI), and p-values were reported. Mediation analysis was performed using the "mediation" package in R to estimate the Average Causal Mediation Effect (ACME), Average Direct Effect (ADE), and proportion mediated for significant genotype-BMI associations, with BIA parameters as mediators. Bootstrapping (1,000 iterations) was used to calculate 95% confidence interval (CI) for mediation effects. Statistical significance was set at p<0.05. To address multiple testing, Bonferroni correction was applied where appropriate.

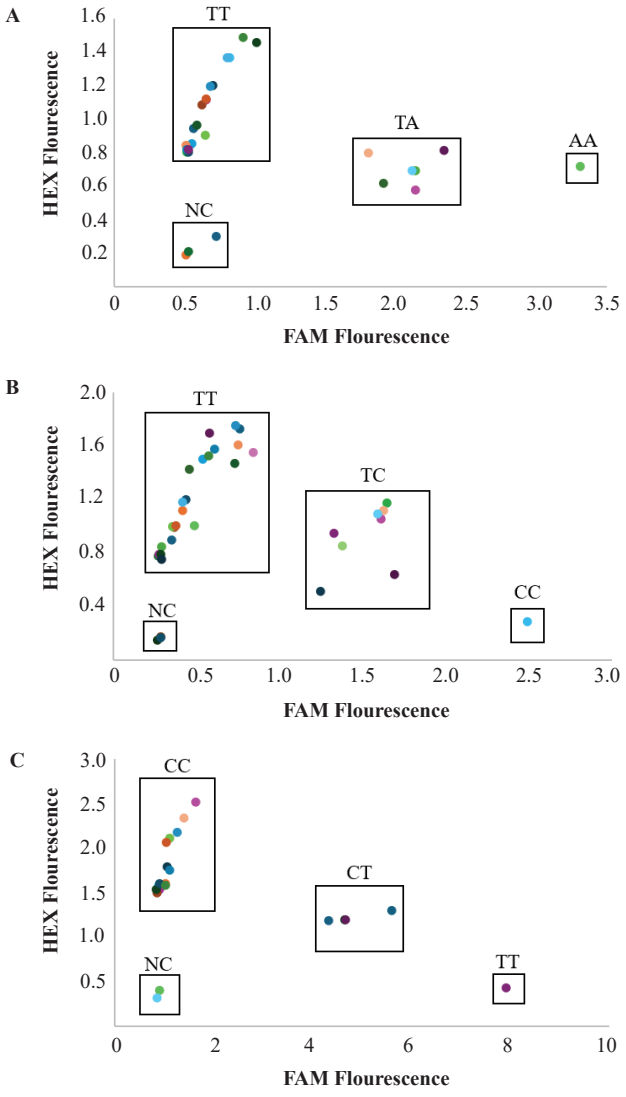

Figure 1. Example of genotyping results using the KASP™ method. Each dot represents an individual sample, plotted according to FAM fluorescence (X-axis) and HEX fluorescence (Y-axis). A: Genotyping results for *FTO* rs9939609, three genotype clusters are visible: AA (FAM-positive, lower Y-axis), TA (dual FAM/HEX fluorescence, central cluster), and TT (HEX-positive, upper Y-axis). B: Genotyping results for *MC4R* rs17782313, three genotype clusters are visible: CC (FAM-positive, lower Y-axis), TC (dual FAM/HEX fluorescence, central cluster), and TT (HEX-positive, upper Y-axis). C: Genotyping results for *TMEM18* rs6548238, three genotype clusters are visible: TT (FAM-positive, lower Y-axis), CT (dual FAM/HEX fluorescence, central cluster), and CC (HEX-positive, upper Y-axis).

Results

Demographic Characteristic of Subjects

As shown in Table 1, the study included a total of 111 subjects, consisting of 64 non-obese and 47 obese subjects aged 18–31 years. The median age of subjects in the obese group was higher than that of the non-obese group, although the difference was not statistically significant (p=0.052), since the age range was 18–28 years old for the non-obese group and 18–31 for the obese group. Regarding sex distribution, males were more prevalent in the obese group (36%) compared to the non-obese group (19%), and this difference reached statistical significance (p=0.050).

BMI was significantly higher in the obese group (median 28.28 kg/m²; IQR: 25.95–32.36) compared to the non-obese group (median 21.74 kg/m²; IQR: 20.11–23.04; p<0.001). Based on BIA results, the obese group demonstrated significantly higher phase angle, fat mass, excess fat percentage, BCM, BMR, and fat-free mass index (FFMI) (all p<0.001).

Conversely, the non-obese group exhibited significantly higher total body water percentage, extracellular water percentage, and lean mass percentage compared with the obese group (all p<0.001). However, dry lean mass (kg) did not differ significantly between the two groups (p=0.500) (Table 1).

In addition, self-reported ethnicity data were collected from all 111 subjects. The majority identified as Chinese (56.8%), followed by Javanese (25.2%), Sundanese (8.1%), Batak (5.4%), and Dayak (3.6%). Smaller proportions reported Minahasan, Bugis, Malay, Palembang, Banjar, Lampung, Balinese, Madurese, Manado, Padang, and other ethnic backgrounds. Mixed ancestry was reported by 17.1% of subjects.

Genotype Distribution and Allele Frequency

The genotype distribution for the *FTO* rs9939609 variant showed that the TT genotype was the most common in both groups (68.8% in the non-obese group and 48.9% in the obese group), followed by the TA and AA genotypes. The heterozygous TA genotype was more frequent in the obese group; however, this difference was not statistically significant (p=0.102). For the *MC4R* rs17782313 variant, the TT genotype was the most frequent, followed by TC and CC, with no significant difference in distribution between groups (p=0.870) (Table 2). Similarly, For the *TMEM18* rs6548238 variant, the CC genotype was predominant, while the TC and TT genotypes were rare (p=0.274).

The frequency of the A allele of the *FTO* gene was higher in the obese group (0.277) than in the non-obese group (0.172). In contrast, the frequency of the C allele for both *MC4R* and *TMEM18* genes were slightly lower among obese participants. All analyzed variants conformed to Hardy–Weinberg Equilibrium (HWE, p≥0.163), indicating that the sample was representative of a genetically stable population (Table 3).

Table 1. Subject's demographic characteristic based on obesity status.

Variable	Non-Obese (n=64)	Obese (n=47)	*p*-value
Age (years), Median (Q1–Q3)	64 20.0 (20.0–21.0)	47 21.0 (20.0–21.0)	0.052
Sex, n (%)			
Male	12 (19%)	17 (36%)	0.050*
Female	52 (81%)	30 (64%)	
BMI (kg/m²), Median (Q1–Q3)	21.74 (20.11–23.04)	28.28 (25.95–32.36)	<0.001*
Phase Angle, Median (Q1–Q3)	5.60 (5.20–6.00)	6.20 (5.50–6.80)	0.001*
Total Body Water (kg), Median (Q1–Q3)	0.53 (0.50–0.56)	0.45 (0.42–0.51)	<0.001*
Dry Lean Mass (kg), Median (Q1–Q3)	0.21 (0.20–0.23)	0.21 (0.18–0.26)	0.500
Excess Fat (kg), Median (Q1–Q3)	0.01 (0.00–0.04)	0.09 (0.04–0.15)	<0.001*
Fat (%), Median (Q1–Q3)	0.27 (0.22–0.29)	0.34 (0.23–0.40)	<0.001*
Fat (kg), Median (Q1–Q3)	13.65 (12.10–16.20)	22.30 (18.50–31.30)	<0.001*
Lean (%), Median (Q1–Q3)	0.73 (0.71–0.79)	0.66 (0.60–0.77)	<0.001*
Lean (kg), Median (Q1–Q3)	38.65 (35.60–43.50)	50.60 (44.70–61.10)	<0.001*
Dry Lean (kg), Median (Q1–Q3)	11.45 (9.75–13.70)	15.70 (14.00–20.60)	<0.001*
Total Weight (kg), Median (Q1–Q3)	54.45 (48.65–59.25)	77.60 (69.00–84.90)	<0.001*
TBW (%), Median (Q1–Q3)	0.53 (0.50–0.56)	0.45 (0.42–0.51)	<0.001*
TBW (L), Median (Q1–Q3)	27.70 (25.95–29.70)	35.30 (30.60–42.10)	<0.001*
ECW (%), Median (Q1–Q3)	0.24 (0.23–0.26)	0.21 (0.20–0.23)	<0.001*
ECW (L), Median (Q1–Q3)	13.05 (12.40–14.25)	16.50 (14.70–17.90)	<0.001*
ICW (%), Median (Q1–Q3)	0.27 (0.26–0.29)	0.26 (0.24–0.30)	0.007*
ICW (L), Median (Q1–Q3)	14.40 (13.15–15.75)	20.40 (17.20–24.20)	<0.001*
3rd Space Water (L), Median (Q1–Q3)	0.20 (-0.10–0.60)	-0.90 (-1.70–-0.30)	<0.001*
BCM (kg), Median (Q1–Q3)	20.60 (18.80–22.55)	29.20 (24.60–34.50)	<0.001*
BMR (kcal), Median (Q1–Q3)	1,362.50 (1,288.50–1,473.00)	1,643.00 (1,504.00–1,882.00)	<0.001*
Estimated Avg Requirement (kcal), Median (Q1–Q3)	2,169.50 (2,051.50–2,342.50)	2,628.00 (2,406.00–3,011.00)	<0.001*
BFMI, Median (Q1–Q3)	5.70 (4.50–6.50)	9.50 (6.60–12.40)	<0.001*
FFMI, Median (Q1–Q3)	15.80 (14.70–16.55)	19.90 (18.00–21.80)	<0.001*

Data was analyzed with Wilcoxon rank sum test. While the p-value was analyzed with Fisher's exact test, *p<0.05. BMI: Body mass index; TWB: Total body water; ECW: Extracellular water; ICW: Intracellular Water; BCM: Body cell mass; BMR: Basal metabolic rate; BFMI: Body fat mass index; FFMI: Fat-free mass index.

We also did trend test for the additive genetic model using Cochran-Armitage test. The Cochran–Armitage trend test revealed a borderline significant association for the *FTO* rs9939609 variant with A risk allele (p=0.053) and the *TMEM18* rs6548238 variant with C risk allele (p=0.065), while the MC4R rs17782313 variant with C risk allele showed no significant trend (p=0.724).

Association between genetic variants and BMI

The *FTO* rs9939609 variant demonstrated a significant association with BMI under the additive genetic model. Each additional A allele was associated with an increase in BMI of 2.31 kg/m² (β=2.312; 95% CI: 0.529–4.094; p=0.011), explaining approximately 5.1% of the variance. In contrast, the *MC4R* rs17782313 and *TMEM18* rs6548238

Table 2. Genotype distribution based on obesity status.

SNP	Genotype	n (%)		*p*-value
		Non-Obese	Obese	
FTO rs9939609	AA	2 (3.1)	2 (4.3)	0.102
	TA	18 (28.1)	22 (46.8)	
	TT	44 (68.8)	23 (48.9)	
MC4R rs17782313	CC	3 (4.7)	1 (2.1)	0.87
	TC	14 (21.9)	11 (23.4)	
	TT	47 (73.4)	35 (74.5)	
TMEM18 rs6548238	CC	62 (96.9)	42 (89.4)	0.247
	TC	2 (3.1)	3 (6.4)	
	TT	0 (0.0)	2 (4.3)	

Table 3. Allele frequency and HWE results, with non-obesity as control.

SNP	Risk Allele	Allele Frequency (Overall)	Allele Frequency (Non-Obese)	Allele Frequency (Obese)	HWE *p*-value (Controls)
FTO rs9939609	A	0.216	0.172	0.277	1.000
MC4R rs17782313	C	0.149	0.156	0.138	0.163
TMEM18 rs6548238	C	0.959	0.984	0.926	1.000

variants showed no significant association with BMI after adjustment for age and sex (Table 4).

The Relationship Between Genetic Variations and Body Composition

The *FTO* rs9939609 variant showed a significant association with several body composition parameters measured using BIA. In the heatmap, red indicates a positive association, blue indicates a negative association, and white represents no association. In contrast, the *MC4R* rs17782313 and *TMEM18* rs6548238 variants did not show significant associations with any of the BIA-derived parameters (Figure 2).

Mediation Analysis on Body Composition Parameters

Sveral BIA-derived parameters significantly mediated the relationship between *FTO* rs9939609 and BMI-related outcomes. For total body weight, the Average Causal Mediation Effect (ACME) was 5.675 kg (95% CI: 1.474–11.073; p=0.004), accounting for 84.6% of the total effect. Fat mass also demonstrated a significant mediating effect with ACME of 3.638 kg (95% CI: 0.876–6.860; p=0.008), mediating 90.5% of the total effect. Similarly, both the FFMI and BFMI exhibited significant mediation (ACME: 0.825 and 1.469, respectively; both $p \leq 0.006$), with more than 87% of the total effect mediated. The TBW also significantly mediated the association with ACME of 1.257 L (95% CI: 0.396–2.439; p=0.004), explaining 72.7% of the total effect (Table 5).

In all cases, the Average Direct Effect (ADE) was not statistically significant (p>0.05), suggesting that the genetic influence of *FTO* rs9939609 on BMI primarily operates indirectly through changes in body composition.

Discussion

This study is the first to investigate the relationship between genetic variations in *FTO* rs9939609, *MC4R* rs17782313, and *TMEM18* rs6548238, with BMI and body composition in a young adult population in Indonesia. The results demonstrate that the *FTO* rs9939609 variant is significantly correlated with BMI, fat mass, FFMI, and TBW, which serve as primary mediators in influencing obesity risk. The *FTO* gene plays a pivotal role in regulating adipogenesis, feeding behavior, and appetite control, primarily through its effects on hypothalamic signaling pathways. Variants or mutations in the *FTO* gene, particularly risk alleles within its first intron, are strongly associated with increased fat mass and the development of obesity by promoting adipocyte differentiation and lipid accumulation. In individuals with obesity, skeletal muscle mass often declines largely due to reduced physical activity and a sedentary lifestyle. This loss of muscle mass consequently lowers the FFMI. Because skeletal muscle tissue has a high water content, whereas adipose tissue exhibits significantly lower hydration, the progressive increase in fat mass resulting from enhanced adipogenesis, at the expense of fat-free mass, leads to a substantial reduction in both the percentage and absolute amount of TBW.(21–23)

In contrast, the *MC4R* rs17782313 and *TMEM18* rs6548238 variants showed no significant association with these parameters in this population. In previous studies, the minor allele frequency (MAF) of the T allele at the *TMEM18* gene rs6548238 in several European countries, Nigeria, Japan, and Brazil showed relatively low values of 0.15, 0.10, 0.18, and 0.12, respectively.(24) In the present study,

Table 4. Multiple linear regression of genetic variations on BMI.

SNP	Risk Allele	β (Per Allele)	95% CI (Low)	95% CI (High)	*p*-value	Adjusted for	R^2	Adj. R^2
FTO rs9939609	A	2.312	0.529	4.094	0.0115	Age, Sex	0.077	0.051
MC4R rs17782313	C	-0.724	-2.657	1.209	0.4590	Age, Sex	0.024	-0.003
TMEM18 rs6548238	C	-2.122	-5.239	0.994	0.1800	Age, Sex	0.036	0.009

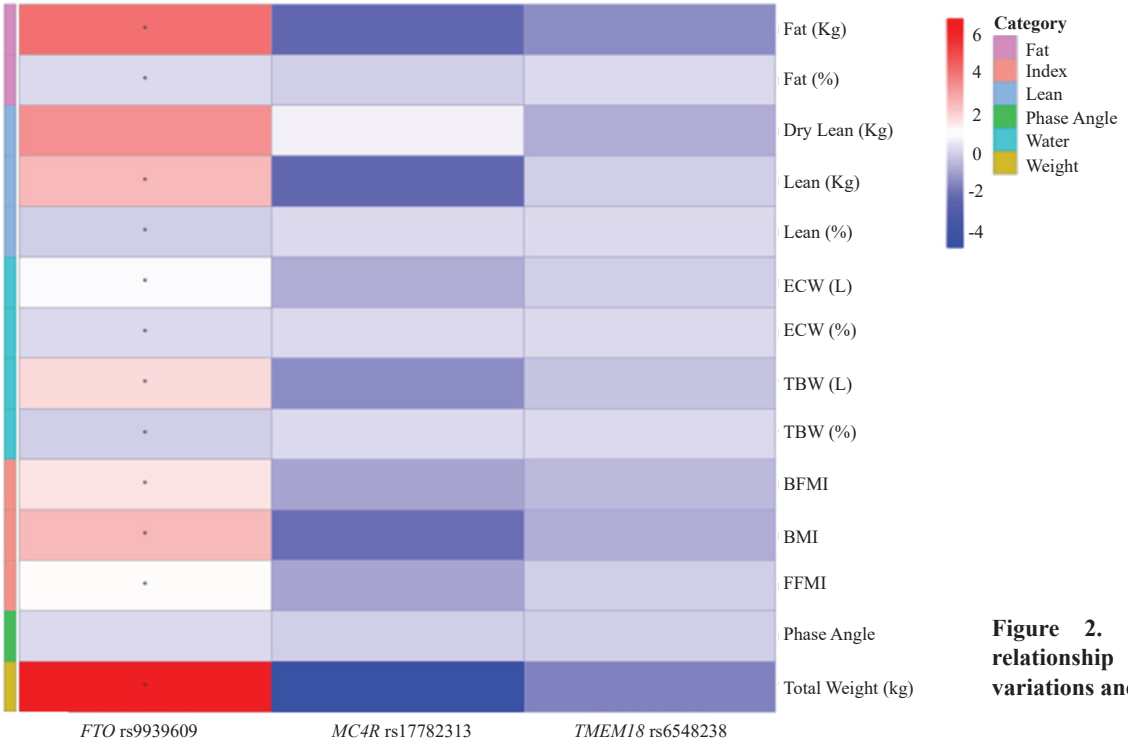

Figure 2. Heatmap of the relationship between genetic variations and BIA parameters.

the minor allele frequency obtained was also relatively low and even lower compared to those countries.

This study highlights the superiority of BIA in accurately measuring body composition compared to BMI, which only reflects total body mass without distinguishing between fat and muscle components.(19) Unlike previous studies in Indonesia that were limited to analyzing the *FTO* gene and BMI without utilizing BIA, our study helps expands the understanding of genetic influences on obesity in young adults with a more comprehensive approach especially because *FTO* rs9939609 lies in an intronic region.(16,17,25)

Previous studies in Indonesia are consistent with these findings, showing that individuals with the A allele of *FTO* rs9939609 have a higher risk of obesity compared to those with the T allele, supported by local data confirming the role of this gene in fat accumulation.(25) However, the *MC4R* rs17782313 variant showed no significant correlation with BMI or body composition in this population, despite international studies reporting an association between the C allele and an increased risk of obesity compared to the T allele, possibly influenced by differences in environmental factors or dietary patterns.(12,15) Similarly, the *TMEM18* rs6548238 variant showed no significant association with BMI or body composition in this study, although global literature suggests that the C allele increases obesity risk. (13) These differences may reflect environmental factors, such as typical Indonesian dietary patterns or physical activity levels, as well as population-specific genetic variations, warranting further research for more in-depth analysis.

The lack of significance of the *MC4R* rs17782313 and *TMEM18* rs6548238 variants on BMI in this study can be explained by several factors. First, ethnic differences and allele frequency distributions strongly influence the detectability of genetic associations. Studies across multiple populations have shown that the MAF of *MC4R* rs17782313 and *TMEM18* rs6548238 are substantially lower in Asian populations compared with European cohorts, thereby reducing the statistical power to detect genotype–phenotype effects even when biological mechanisms exist.(13) A low MAF means that fewer individuals carry risk allele, leading to smaller observable differences in BMI or body composition between genotypes. Second, gene–environment interactions, such as dietary patterns, cultural eating behaviors, habitual physical activity, and socioeconomic context, can modify genetic effects on adiposity. This may explain why these SNPs show strong associations with obesity in European populations but not in young Indonesians. Indirect mechanisms, such as the influence of *MC4R* risk alleles on appetite regulation and visceral fat accumulation may require more sensitive

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Table 5. Mediation analysis between *FTO* rs9939609 and BMI-related outcomes.

Outcome	ACME	ACME Low	ACME High	ACME *p*-value	ADE	ADE Low	ADE High	ADE *p*-value	Total Effect	Total Low	Total High	Total *p*-value	Prop Mediated	Prop Low	Prop High	Prop *p*-value
Total Weight (Kg)	5.675	1.474	11.073	0.004	1.037	-0.889	2.909	0.322	6.711	2.021	12.285	0.004	0.846	0.500	1.229	0.004
Fat (Kg)	3.638	0.876	6.860	0.008	0.382	-0.488	1.360	0.396	4.020	1.306	7.330	0.006	0.905	0.596	1.176	0.002
Lean (Kg)	2.069	0.576	3.943	0.002	0.45	-1.352	2.072	0.610	2.519	0.306	4.931	0.034	0.821	0.299	2.608	0.036
TBW (lt)	1.257	0.396	2.439	0.004	0.473	-0.541	1.375	0.358	1.730	0.491	3.145	0.006	0.727	0.347	1.758	0.010
ECW (lt)	0.631	0.172	1.241	0.000	0.149	-0.284	0.53	0.484	0.780	0.107	1.496	0.018	0.809	0.421	2.055	0.018
Fat (%)	0.025	0.007	0.049	0.016	0.000	-0.010	0.011	0.980	0.026	0.006	0.050	0.006	0.988	0.574	1.810	0.018
Lean (%)	-0.025	-0.05	-0.007	0.010	0.000	-0.011	0.009	0.964	-0.026	-0.051	-0.006	0.02	0.988	0.572	1.655	0.018
TBW (%)	-0.021	-0.038	-0.006	0.004	0.001	-0.01	0.011	0.846	-0.020	-0.041	-0.003	0.022	1.058	0.507	2.640	0.018
ECW (%)	-0.009	-0.017	-0.003	0.002	0.000	-0.004	0.004	0.964	-0.009	-0.018	-0.002	0.010	0.993	0.574	2.431	0.008
FFMI	0.825	0.225	1.549	0.006	0.116	-0.265	0.427	0.580	0.941	0.293	1.616	0.000	0.877	0.488	1.386	0.006
BFMI	1.469	0.418	2.950	0.002	0.088	-0.239	0.458	0.638	1.557	0.541	3.103	0.004	0.943	0.642	1.233	0.006

TWB: Total body water; ECW: Extracellular water; FFMI: Fat-free mass index; BFMI: Body fat mass index.

markers of adiposity than BMI alone. These population-specific differences highlight the importance of considering ancestry, allele frequencies, and environmental exposures when interpreting genetic effects on obesity.(26,27)

To strengthen these findings, this study compared BMI with body composition analysis using BIA, which provides detailed measurements of muscle mass, fat mass, visceral fat, and body water content. Although BMI is a simple and widely applicable anthropometric method, it has limitations as it does not distinguish between subcutaneous fat, visceral fat, and muscle mass, making it less accurate in assessing obesity risks related to visceral fat.(18) In contrast, BIA provides more comprehensive data, enabling a better understanding of how genetic variations affect specific physiological parameters.(19) This approach not only improves measurement accuracy but also clarifies the relationship between genetic factors and body characteristics relevant to obesity, making it a valuable tool in population health research.

This study provides important evidence on the relationship between *FTO* rs9939609, *MC4R* rs17782313, and *TMEM18* rs6548238 and their influence on BMI and body composition in young Indonesian adults. The strong and consistent association of *FTO* rs9939609 with adiposity-related traits highlights its potential value as a genetic marker for early obesity risk identification. These findings also emphasize the importance of integrating BIA-derived phenotypes, which is beyond BMI alone, when assessing genetic susceptibility to obesity in young populations. Such insights may support the development of more targeted lifestyle or nutrition-based interventions for individuals with elevated genetic risk.

This study has several strengths, including the focus on a young adult cohort and the use of BIA for detailed body composition assessment. However, some limitations should be noted. Although the total sample size exceeded the minimum requirement based on G*Power estimation, the very low MAF of *MC4R* and *TMEM18* reduced statistical power to detect small genetic effects. The cross-sectional design also prevents causal inference. In addition, lifestyle factors such as diet and physical activity were not collected, limiting the ability to evaluate gene–environment interactions. Selection bias is possible because participants were recruited from a single university through voluntary participation. Future studies with larger and more diverse cohorts, objective measures of visceral adiposity, and longitudinal follow-up are needed to validate these findings and further clarify the roles of these genetic variants in obesity risk.

Conclusion

The *FTO* rs9939609 variant was significantly associated with higher BMI and adverse body composition profiles among young Indonesian adults, with its effect primarily mediated through fat and muscle indices. In contrast, *MC4R* rs17782313 and *TMEM18* rs6548238 showed no significant associations with BMI or body composition. These findings support the integration of genetic data with BIA phenotypes to refine obesity risk assessment and inform targeted interventions in the Indonesian context, while offering indirect functional insight into the regulatory role of this intronic *FTO* variant.

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Authors Contribution

ES and MK were involved in concepting and planning the research. ES, TS and SMD performed the subject recruitment and data acquisition/collection, ICA performed laboratory works which include DNA extraction and genotyping. ES carried out the statistical analysis. All authors took parts in drafting the manuscript and giving critical revision of the manuscript.

Conflict of Interest

The authors declare no conflicts of interest or competing interests related to the content of this manuscript.

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