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Original Research Article

Relationship between MC4R rs17782313 Polymorphism and Body Mass Index and Appetite Regulation in Young Adults in Indonesia

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Abstract

Background: Obesity is an increasing public health problem, including among young adults in Indonesia. Genetic, environmental, and behavioral factors contribute to obesity. One of the genetic variants associated with obesity is the MC4R rs17782313 polymorphism, which plays a role in appetite regulation and energy balance.

Objective: This study aims to determine the relationship between the MC4R rs17782313 polymorphism and Body Mass Index (BMI) in young adults in Indonesia and to evaluate its effect on feelings of hunger, satiety and eating satisfaction.

Method: We conducted a cross-sectional study involving 152 young adults at Universitas Tarumanagara. Genotyping was done using the real-time PCR method with the KASP™ system. To evaluate hunger, satiety, and eating satisfaction, we used the Visual Analog Scale (VAS; 0–100 mm, where 0 = 'not at all hungry/full/satisfied' and 100 = 'extremely hungry/full/satisfied' before and after meals and calculated the difference scores. We analyzed the data using R software.

Results: The results showed no significant relationship between the MC4R rs17782313 polymorphism and BMI ($p = 0.7$). However, there was a significant difference in hunger scores between the TT and CT genotypes ($p = 0.024$), where individuals with the TT genotype experienced a greater reduction in hunger after eating than individuals with the CT genotype. In addition, we also found a significant difference in BMI based on gender in our young adult population ($p = 0.0032$).

Conclusion: This study found that MC4R rs17782313 was not significantly associated with BMI in this population. However, the variant may influence appetite regulation, as individuals with the TT genotype showed a greater reduction in hunger after eating. A significant BMI difference between sexes was also observed; these findings suggest a role for MC4R in eating behavior, warranting further investigation in larger, diverse populations.

Keywords: *Obesity; MC4R; rs17782313; Appetite; BMI*
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INTRODUCTION

Obesity is an increasingly prevalent global health problem. Although obesity itself does not directly cause fatal diseases, people with obesity have a high risk of various other diseases that have the potential to result in death, such as hypertension, diabetes, heart disease, and various types of cancer.[1] In Indonesia, the incidence of obesity continues to increase, prompting attention from the Indonesian Ministry of Health, especially the Directorate of Prevention and Control of Non-Communicable Diseases. According to national data, the overall prevalence of obesity reached 23.4% in 2023(2). Notably, the prevalence of obesity among young adults also showed an upward trend, increasing from 18.8% in 2018 to 20.8% in 2023.[2,3]

The development of obesity involves a complex interplay of genetics, behavior, physiological, environmental and psychosocial factors.[4] In some cases, genetic predispositions also play a significant role in determining an individual's susceptibility to obesity.

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Studies show that individuals with specific genetic variations have a greater tendency to gain weight despite having similar lifestyles to individuals without these genetic variations.[5] One of the most common SNPs associated with obesity is FTO rs9939609.[6,7,8]

Another important genetic factor linked to obesity is the MC4R (Melanocortin-4 Receptor) gene variant, which plays a role in appetite regulation and energy balance.[9,10] However, recent research shows that genetic influence on body mass index (BMI) is not deterministic but is influenced by other factors, such as the regulation of satiety and hunger levels before eating.[11] Several studies showed that individuals with the C allele have a higher risk of obesity than individuals with the T allele.[12,13] Additionally, research also finds that this variant can influence eating behavior, levels of the hormone ghrelin, and other metabolic factors.[14,15]

Despite extensive research in other populations, studies on the prevalence of the MC4R rs17782313 polymorphism in Indonesia is still limited. Considering that Indonesia has ethnic diversity that can influence genetic expression and customs that affect eating patterns, this research is important to explore how these polymorphisms contribute to obesity in Indonesia's young population. Therefore, this research aims to determine the relationship between the MC4R rs17782313 polymorphism and obesity in the young Indonesian population; while also evaluating behavioral factors such as pre-meals hunger levels and satiety. A better understanding of how genetic and behavioral factors interact may provide foundation for developing more effective and evidence-based strategies for obesity prevention.

MATERIALS AND METHODS

Study Design

This cross-sectional study was conducted at Universitas Tarumanagara. This study received ethical approval from the Universitas Tarumanagara Research Ethics Committee (UTHREC) with project number 003-UTHREC/UNTAR/I/2024. Before the research was conducted, all subjects were given information regarding the aims and procedures of the research and signed informed consent. The data collected is kept confidential and is only used for research purposes.

Research Subjects

The subjects in this study consisted of 152 young adults selected based on predetermined inclusion and exclusion criteria. Anthropometric data such as height and weight were measured directly by researchers to ensure data accuracy. BMI categorization was done using the Asia-Pacific Standard

DNA Extraction

We extracted genomic DNA each subject's saliva using the Quick-DNA miniprep plus kit (Zymo Research, USA, Catalog # D4069) following the manufacturer's instructions. To collect saliva, participants were asked to rinse their mouth with 400 µl of sterile water, hold it briefly, and then spit into a sterile collection tube. We then obtain 200 µl of saliva from each sample, added the biofluid and cells buffers (provided in the kit) performed proteinase K digestion at 55ºC. The samples were then subjected to a series of centrifugation steps to remove contaminants and isolate high-quality genomic DNA.

MC4R rs17782313 Genotype Analysis

MC4R rs17782313 genotype analysis was carried out by the real-time PCR method using Rotorgene Q (Qiagen, USA), and allele detection was carried out with the KASP™ system (LGC Biosearch Technologies, UK) according to the manufacturer's instructions. C allele of MC4R srs17782313 were labelled with FAM, while T allele were labelled with HEX

The real time PCR thermal cycling conditions were as follows:

- Initial denaturation at 94ºC for 15 minutes,
- Touchdown phase of 10 cycles:
  - Denaturation at 94ºC for 20 seconds
  - Annealing starting at 68ºC for 1 minutes, decreasing by 0.8ºC per cycle
- Then 26 cycles of:
  - Denaturation at 94ºC for 20 seconds,
  - Annealing at 60ºC for 1 minutes with fluorescence signal acquisition at the end of cycle.

Table 1. Demographic data of the study

Variable	N =152
MC4R Genotype	
CC	6 (4%)
CT	39 (26%)
TT	107 (70%)
Age (years old, Mean ± SD / Median (Min-Max)	19.8 ± 2.27 / 20 (17 – 31)
BMI (Mean ± SD / Median (Min-Max)	25 ± 5.5 / 23.7(15.7 – 45.7)
BMI Category	
Underweight	11 (7%)
Normal	54 (37.5)
Overweight	22 (14.5)
Obese I	38 (25%)
Obese II	27 (18%)
Gender	
Male	52 (34%)
Female	100 (66%)
Hunger, Satiety and Satisfaction	
Hunger difference score (Mean ± SD)	2.38 ± 2.35
Satiety difference score (Mean ± SD)	2.19 ± 2.21
Satisfaction difference score (Mean ± SD)	1.94 ± 2.10

Evaluation of Hunger, Satiety, and Satisfaction

Hunger, Satiety and Satisfaction were evaluated using the Visual Analog Scale (VAS; 0–100 mm, where 0 = 'not at all hungry/full/satisfied' and 100 = 'extremely hungry/full/satisfied' before and after eating. Difference scores were calculated based on the difference between VAS scores before and after meals to assess subjective changes in sensations of hunger, satiety and satisfaction.

Statistical Analysis

Statistical analysis was conducted using R software (version 4.4.0) and R studio (version 2024.121+563). Data was analyzed to test the relationship between the MC4R rs17782313 genotype and body mass index (BMI) as well as hunger, satiety and satisfaction scores. Specifically, we first conduct normality testing to determine the appropriate statistical approach and for non-parametric data we used the Kruskal-Wallis test to evaluate differences in BMI across genotypes, used Wilcoxon rank-sum test to assess BMI differences between genders, used Kruskal-Wallis test and followed by pairwise Wilcoxon rank-sum post-hoc test to identify significant differences between specific genotype group. Data visualization was done using the ggplot2 package.

RESULTS

Table 1 presents the basic characteristics of the 152 subjects involved in this study, including the distribution of the MC4R rs17782313 genotype, age, body mass index (BMI), hunger, satiety and satisfaction difference scores. Most subjects had the TT genotype (70%), followed by CT (26%) and CC (4%). The average age of the subjects was 19.8 ± 2.27 years, with an average BMI value of 25 ± 5.5. Evaluation of the differences in hunger, satiety and satisfaction scores showed that the hunger difference score had the highest average (2.38 ± 2.35), followed by the satiety difference score (2.19 ± 2.21) and satisfaction difference score (1.94 ± 2.10). This information provides an initial picture of the genotype distribution, and the physiological factors analyzed in this study.

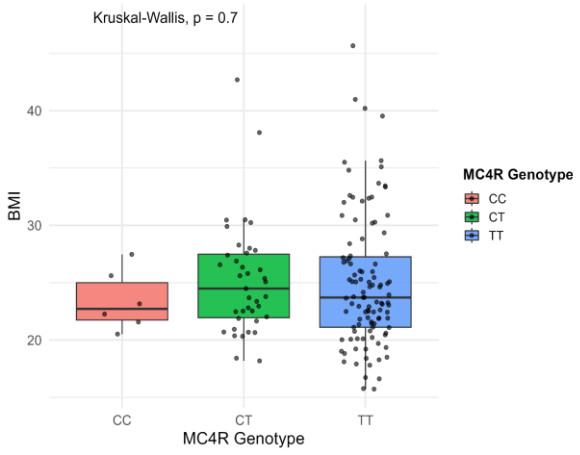

Figure 1. BMI differences Across MC4R rs17782313 Genotypes (CC group n = 6, CT group n =39, TT group n = 107)

Figure 1 shows the relationship between the MC4R rs17782313 genotype and BMI in boxplot form with a scatter plot overlay. Each point represents an individual's BMI value, grouped by CC, CT, and TT genotypes. The results of the Kruskal-Wallis test (p = 0.7) displayed in the graph show no significant difference in BMI between MC4R genotype groups. This indicates that in this study sample, the MC4R rs17782313 genotype did not significantly affect BMI. Further analysis may be needed to understand the role of other factors, such as diet, physical activity, and appetite regulation, in obesity. Power analysis of this analysis shows a value of 78.5%, which means that the probability of detecting a significant difference in BMI between MC4R rs17782313 genotype groups is quite high; nevertheless, further analysis shows a relatively small effect size (f = 0.25) and still underpowered due to imbalance of MC4R rs17782313 genotype distribution. Therefore, the non-significant results in this analysis could be caused by a small genetic effect or limited sample size when detecting such differences.

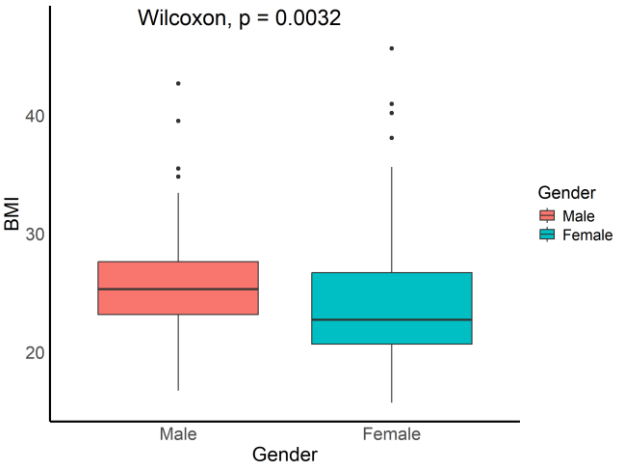

Figure 2. Male Participants (n = 52) Exhibited Significantly Higher BMI Values Compared to Female Participants (n = 100).

Figure 2 compares Body Mass Index (BMI) by gender. The statistical analysis results showed a significant difference in BMI between men and women (p = 0.0032); these findings indicate that gender may be a factor influencing BMI, possibly due to physiological, hormonal, or lifestyle differences between men and women. Further analysis is needed to understand how genetic and behavioral factors contribute to these differences.

Figure 3 shows the relationship between the MC4R rs17782313 genotype and differences in hunger, satiety, and satisfaction scores. The results of the Kruskal-Wallis analysis showed that only the Hunger Difference score showed a trend approaching significance (p = 0.073). Post-hoc analysis showed a significant difference between CT and TT genotypes (p = 0.024). This indicates that individuals with the TT genotype experience a greater reduction in hunger after eating compared to CT genotype. However, this finding should be interpreted with caution, as no adjustment for multiple comparisons was applied, and the CC group had a very small sample

size (n = 6) which may limit statistical power and increase the risk of Type 1 error.

No significant differences were found in the Satiety Difference (p = 0.87) and Satisfaction Difference (p = 0.81), indicating that the MC4R rs17782313 genotype may specifically influence pre-meal hunger regulation, rather than post meal satiety or satisfaction. These findings align with MC4R's proposed role in appetite signaling, particularly in modulating hunger prior to food intake.

DISCUSSION

This research investigated the relationship between the MC4R rs17782313 polymorphism and Body Mass Index (BMI) in a sample of 152 young adults in Indonesia. In addition, this study also evaluated feelings of hunger, satiety, and satisfaction after eating among different MC4R genotypes. Although previous studies showed a significant association between MC4R polymorphisms and obesity in various populations (12,15), our findings did not show a significant association between the MC4R rs17782313 genotype and BMI (p = 0.7).

In this study, we reported no significant relationship between MC4R rs17782313 and BMI (p = 0.7). A similar study was done by Alizadeh *et al*. (2022). on Iranian women, also did not find a significant association of the MC4R rs17782313 genotype with BMI, BMR, and BMR/kg.[15] However, many studies, such as the meta-analysis by Ali (2022) and Yu K *et al*. 2020 show a significant association of MC4R rs17782313 in Asian ethnicity.[5,14] This discrepancy in results is likely due to sample size and statistical power, where an imbalance in the distribution of genotypes in this study may have limited the ability to detect a real effect. Although the statistical power of this study was estimated at 78.5%, the imbalance of genotype distribution (70% TT, 26% CT, and only 4% CC) may limit the ability to detect a real effect. With a small effect size (f = 0.25), research with a larger sample is needed to achieve statistical significance.

In addition to sample size, genetic and ethnic variability may also influence the study results. Some populations had genetic backgrounds that were more susceptible to the effects of MC4R rs17782313. Behavioral and environmental factors, such as diet, physical activity, and socioeconomic status, also play a role in influencing the expression of this gene on BMI. The study by Corella *et al*. (2012) emphasizes that individuals with the same MC4R variant may have different risks of obesity depending on their lifestyle and diet.[16]

In this study, several studies have shown that the effect of MC4R rs17782313 on BMI may vary between populations, possibly due to differences in genetic background and environmental factors.[17,18] An individual's diet, body composition, and metabolism can also play a role in determining whether a genetic polymorphism influences obesity. The Indonesian population has high genetic diversity, so other genetic or epigenetic factors may influence MC4R expression about BMI. Additionally, interactions between genetics and local diet may affect the observed differences. In this study, the majority of ethnicity was of Chinese pure descent (52%), followed by a small percentage of various ethnicities of Javanese (11%), Sundanese (4%), Bataknese (3.3%), Dayak (2,6%), and the rest of mixed ethnicities. Further analysis by ethnicity shows no association between ethnicity with BMI and genotype (table 1).

We observed a significant difference in BMI between male and female participants (p = 0.0032). This finding aligns with previous research showing that differences in hormones, metabolism, and eating habits contribute to differences in BMI based on gender Estrogen and testosterone are known to influence fat distribution and energy metabolism, so sex-specific genetic effects need to be considered in the analysis of genetics-related obesity.[5]

This study also evaluated the impact of MC4R rs17782313 on feelings of hunger, satiety, and meal satisfaction using the Visual Analog Scale (VAS). Interestingly, the difference in hunger approached statistical significance (p = 0.073), with a significant difference between CT and TT genotypes (p = 0.024). This indicates that individuals with the TT genotype experience a greater reduction in hunger after eating than individuals with the CT genotype, which is in accordance with previous findings that the MC4R polymorphism affects the regulation of appetite and energy intake.[15]

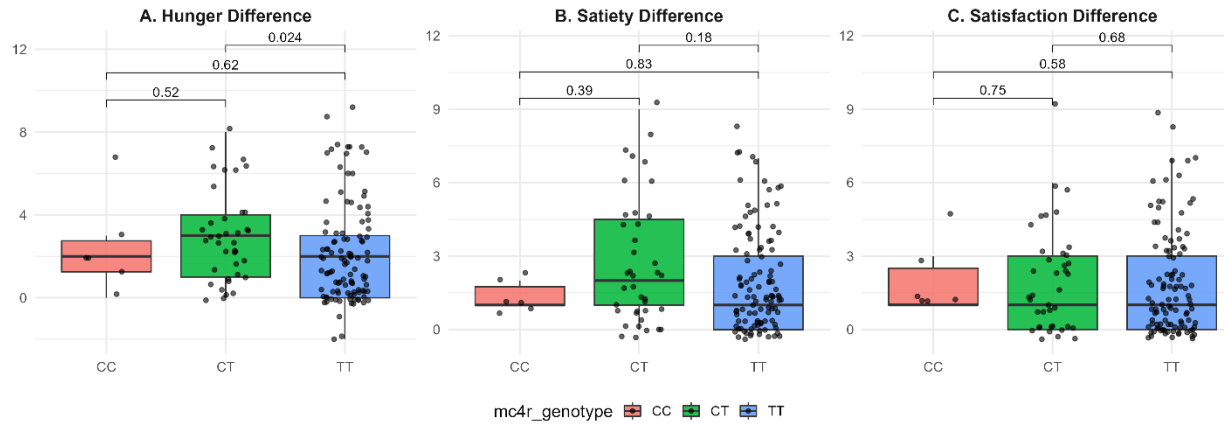

Figure 3. Comparison of Hunger, Satiety, and Satisfaction Difference Score by Genotype (CC group n = 6, CT group n =39, TT group n = 107).

However, no significant differences were found in satiety (p = 0.87) or meal satisfaction (p = 0.81), indicating that the MC4R rs17782313 polymorphism plays a more important role in hunger regulation than post-meal satisfaction. The implications of these findings suggest that although MC4R rs17782313 does not have a substantial direct impact on BMI, this gene may still contribute to obesity risk through its role in appetite regulation. Individuals with the TT genotype may be more susceptible to more frequent eating patterns due to a lower satiety response, which may increase body weight in the long term.

Several limitations of this study should be addressed. The very low frequency of the CC genotype (4%) may result in low statistical power, so studies with larger samples and a more balanced distribution of genotypes may provide clearer insights. Power analysis from this study suggests 51 subjects for each genotype. In addition, this study did not control factors such as food intake, meal times, and physical activity, which may influence the results. Therefore, future studies must include these variables better to understand the interactions between genetics and the environment. Obesity is also influenced by many other genetic variants, such as FTO, LEPR, and POMC.[6,7,18,19] Future studies should use a polygenic risk score approach to assess the influence of SNP combinations on obesity more comprehensively.[19] In addition, the cross-sectional design of this study only captures images at one point in time, so it does not allow for assessing the causal relationship between genetic factors and the development of obesity. Longitudinal studies with long-term follow-up would better assess these relationships more accurately. Lastly, one of this research's limitations is using the Visual Analog Scale (VAS) to assess hunger, satiety, and eating satisfaction. Although frequently used in appetite-related research, its validity in the context of genetics and obesity needs to be researched. Psychological and environmental factors may influence variability in subject responses, potentially influencing the interpretation of results. Nevertheless, this study has already shown the prevalence of the MC4R rs17782313 genotype in Indonesian young adults and explored the possibility of the risk's allele contributing to obesity in such a population.

Despite its limitations, this study adds a valuable data on the MC4R rs17782313 genetic landscape of obesity in Indonesian young adults. Our findings support the need of future research using a polygenic risk score approach and considering gene-lifestyle interactions. Understanding how obesity related genotype contribute to obesity risks in diverse populations may help guide the development of personalized nutrition and gene informed interventions to prevent obesity in Indonesia.

CONCLUSION

This study explores the relationship between the MC4R rs17782313 polymorphism and BMI in young adults in Indonesia and assesses its influence on hunger, satiety, and eating satisfaction. While we found no significant association between this genetic variant and BMI (p = 0.7), this result should be interpreted cautiously due to the limited sample size and imbalanced genotype distribution. We also found a significant difference in BMI between males and females (p = 0.0032). Interestingly, we observed a significant difference in hunger reduction between the TT and CT genotypes, with individuals carrying the TT genotype experiencing a smaller reduction in hunger after eating. These findings highlight the need for further research with more extensive and diverse populations to understand better the genetic and behavioral contributors to obesity in Indonesia.

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