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# Narrative Literature Review on MC4R rs17782313 Gene-Nutrient Interaction and Obesity Risk

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**ABSTRACT**

The Melanocortin 4 Receptor (MC4R) gene plays a critical role in appetite regulation and energy balance. The single nucleotide polymorphism (SNP) rs17782313, located near the MC4R gene, has been widely associated with an increased risk of obesity, primarily through its influence on appetite control and energy homeostasis. Understanding how this genetic variant interacts with dietary intake can offer valuable insights into the pathophysiology of obesity and inform personalized nutritional strategies. This study aims to investigate the role of SNP rs17782313 in dietary factors and obesity risk, with a particular focus on the underlying molecular mechanisms. A narrative literature review was conducted, synthesizing findings from molecular, genetic, and epidemiological studies. The review highlights how rs17782313 may influence MC4R function and how macronutrient intake, particularly carbohydrates, proteins, and fats, modulates this effect. Evidence suggests that nutritional factors can affect gene expression or interact directly with the MC4R pathway, influencing energy intake, metabolic responses, and body weight regulation. Observational studies in various populations confirm the global relevance of these gene-diet interactions. The findings highlight the need for an integrative approach that combines genetics and nutrition to develop individualized interventions for obesity prevention and treatment. Understanding these interactions may contribute to more effective management of obesity and related metabolic disorders by tailoring dietary recommendations to genetic profiles.



## INTRODUCTION

The MC4R gene (Melanocortin 4 Receptor) is located on chromosome 18q21.3 and consists of 996 base pairs, encoding a G-protein-coupled receptor that activates adenylyl cyclase (Yu et al., 2020). As a member of the melanocortin receptor family, which includes five subtypes (MC1R to MC5R), MC4R plays a critical role in regulating energy expenditure and appetite (Heyder et al., 2019). MC4R is activated by endogenous peptides such as alpha-melanocyte-stimulating hormone (α-MSH) and beta-melanocyte-stimulating hormone (β-MSH), which promote anorexigenic effects by suppressing appetite. Conversely, agouti-related peptide (AgRP) acts as an inverse agonist, stimulating appetite by inhibiting MC4R activity(Heyder et al., 2019; N. A. Heyder et al., 2021). Upon activation by its ligands, MC4R primarily couples with stimulatory G-proteins (Gs), leading to the activation of adenylyl cyclase and an increase in cyclic AMP (cAMP) levels. This, in turn, activates protein kinase A (PKA), which mediates anorexigenic effects, such as appetite suppression (Liu & Hruby, 2022). Additionally, MC4R can interact with other G-proteins, including Gi and Gq, demonstrating its versatility in modulating various physiological responses depending on the context of ligand binding (Fontaine et al., 2024; Heyder et al., 2019).

As a G-protein-coupled receptor, MC4R is predominantly expressed in the hypothalamus, where it plays an essential role in regulating appetite and energy expenditure. Activation of MC4R inhibits food intake and enhances energy expenditure, thereby contributing to body weight maintenance (Hainer et al., 2020; Metzger et al., 2024). The leptin-melanocortin pathway is a key regulatory system in this process. Leptin, a hormone secreted by adipose tissue, stimulates MC4R

activity to control food consumption and energy balance. Disruptions in this pathway, particularly involving MC4R, have been associated with obesity (Hainer et al., 2020). The endogenous agonists of MC4R, including melanocortin hormones such as α-MSH, activate signaling pathways that suppress feeding behavior and increase energy expenditure, thereby aiding in body weight regulation (NCBI, 2024). Defects in these signaling pathways, especially those linked to the MC4R gene, can lead to hyperphagia (excessive eating) and reduced energy expenditure, both of which contribute to obesity (Fairbrother et al., 2018; Kalinderi et al., 2024).

Polymorphisms in the MC4R gene are associated with specific monogenic forms of obesity. Loss-of-function variants can result in overeating and weight gain, whereas some gain-of-function mutations may enhance receptor activity, potentially offering protection against obesity (Hainer et al., 2020; Lotta et al., 2019). Notably, the single nucleotide polymorphism (SNP) rs17782313, located near the MC4R gene, has been extensively studied due to its strong association with obesity (Lotta et al., 2019).

However, despite numerous studies, findings regarding the association between rs17782313 and obesity-related traits remain inconsistent, especially in diverse ethnic populations. Furthermore, limited research has specifically explored how this SNP interacts with dietary factors such as energy and carbohydrate intake, particularly in adult Javanese populations. This represents a clear research gap that necessitates further investigation. This study addresses that gap by evaluating not only the association between rs17782313 and obesity parameters (BMI, waist circumference, and hip circumference) but also by examining potential gene-diet interactions involving energy and carbohydrate intake.

The novelty of this study lies in its integration of a nutrigenetic approach to assessing SNP-diet interactions, thereby contributing to a broader understanding of how personalized nutrition strategies can be applied to populations with distinct genetic and dietary backgrounds. Therefore, the aim of this study is twofold: first, to examine whether the rs17782313 variant located near the MC4R gene is associated with anthropometric indicators of obesity, including body mass index (BMI), waist circumference, and hip circumference, in Javanese adults. Additionally, this study aims to investigate whether this genetic variant interacts with dietary intake of energy and carbohydrates to influence the risk of obesity. The specific outcomes expected from this research include identifying significant associations between rs17782313 and obesity-related phenotypes, uncovering potential gene-diet interactions that may modify individual susceptibility to obesity, and providing scientific evidence that supports the development of personalized nutrition strategies. Through a nutrigenetic approach, this study contributes to a deeper understanding of how genetic and dietary factors jointly influence obesity, particularly within the context of a specific ethnic population.

## METHOD

### Search strategy

A systematic literature review was conducted to identify relevant studies examining the relationship between the MC4R gene and obesity. Articles were sourced from reputable medical and biological databases, including PubMed. The search was performed using the following keywords and combinations: (Obesity) AND (MC4R) 1,168 results, (MC4R rs17782313) AND (obesity) 207 results, (((Interaction) AND (MC4R)) AND (Nutrients)) AND (Obesity) 15 results, The final data analyzed and processed amounted to 5. The search was limited to peer-reviewed articles published in English from [insert years or range, e.g., 2014 to 2024].

### Inclusion and exclusion criteria

Studies were included if they met the following criteria: Focused on the MC4R gene and its role in obesity or metabolism, and included information on specific single-nucleotide polymorphisms (SNPs), such as rs17782313. Discussed the relationship between MC4R gene variants and nutrient interactions. Reported original research or meta-analysis findings. Studies

were excluded if they lacked sufficient detail on MC4R-related mechanisms. Included non-human subjects without relevance to human physiology.

### Data extraction and analysis

Relevant data from selected studies were systematically extracted and organized into categories, including variants of the MC4R gene and their effects. Nutritional factors interacting with MC4R pathways. Population-based differences in MC4R polymorphisms. The extracted data were synthesized to explore the interplay between genetic, dietary, and metabolic factors in obesity. The findings were critically analyzed to identify consistent trends and gaps in the existing research.

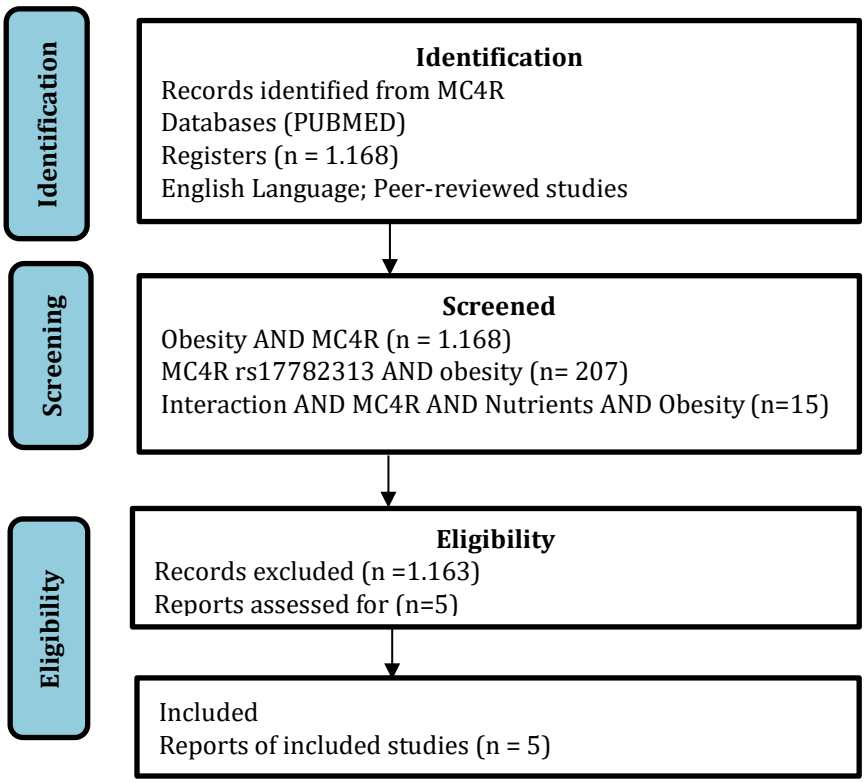


**Figure 1. PRISMA Diagram**

## RESULTS

**Table 1. Summary of Articles that meet the criteria for research objectives**

| Title | Journal | Method | Result |
|---|---|---|---|
| A polymorphism near the MC4R gene (rs17782313) is associated with serum triglyceride levels in the general Japanese population: the J-MICC Study (Katsuura-Kamano et al., 2014) | Endocrine Genetics/ Epigenetics | Study Design: A cross-sectional study.<br>Sample size: Initially, 4,512 subjects; after exclusions based on specific criteria, 2,035 subjects remained for analysis.<br>Study location: Ten areas in Japan under the framework of the Japan Multi-Institutional Collaborative Cohort (J-MICC) Study.<br>Observed data: demographic and lifestyle data, physical activity, anthropometric data, clinical and biochemical data, dietary data, genetic data | - The study also evaluated associations between rs17782313 and obesity (BMI ≥ 25, as per the Japan Society for the Study of Obesity criteria) or weight changes since age 20 (≥ 5.1 kg, the median).<br>- No significant associations were found between rs17782313 and obesity or weight change. |

| Title | Journal | Method | Result |
|---|---|---|---|
| Genetic variations in SEC16B, MC4R, MAP2K5, and KCTD15 were associated with childhood obesity and interacted with dietary behaviors in the Chinese school-age population (Lv et al., 2015) | Gene | Study Design: Cross-sectional study on metabolic syndrome in children and adolescents. Included both case (obese) and control (healthy) groups.<br>Sample Size: Obese cases: 853 children aged 7–17 years. Healthy controls: 2124 children aged 7–17 years.<br>Study Location: Conducted in six cities across China (Beijing, Shanghai, Tianjin, Hangzhou, Chongqing, Nanjing)<br>Data Collection: Anthropometric data, Epidemiological Data, SNP Genotyping, Questionnaire Validation | - The strongest association was found with rs17782313 in the MC4R gene ($P = 1.91 \times 10^{-5}$). Compared to the TT genotype, subjects with TC and CC genotypes had increased risks of obesity, with odds ratios (ORs) of 1.49 (95% CI, 1.26–1.77) and 2.15 (95% CI, 1.49–3.11), respectively.<br>- Additive interactions were observed with MC4R rs17782313 and salty flavor preference, with an attributable proportion (AP) due to an interaction of 0.38 (95% CI: 0.13–0.62).<br>- |
| The association of MC4R rs17782313 polymorphism with dietary intake in Iranian adults (Khalilitehrani et al., 2015) | Gene | Study Design: Observational cross-sectional study.<br>Sample size: 400 healthy individuals.<br>Study location: Department of Cellular-Molecular Nutrition, TUMS.<br>Data Collection: Genotyping, Anthropometric data, Dietary Intake, Physical Activity | - The CC genotype participants with BMI ≥ 25 $kg/m^2$ have a significantly higher energy and fat intake than those with BMI < 25 $kg/m^2$<br>- Individuals with the CC genotype of MC4R rs17782313 have a higher energy intake compared to those with the TT genotype. |
| Interactions with the MC4R rs17782313 variant, mental stress and energy intake and the risk of obesity in Genome Epidemiology Study (Park et al., 2016) | Nutrition & Metabolism | Study Design: The study utilized a cohort design with data collected from the Ansung and Ansan cohorts of the Korean Genome and Epidemiology Study (KoGES).<br>Sample Size: A total of 8,842 subjects participated, including 4,183 men and 4,659 women, all aged between 40 and 69 years.<br>Study Location:<br>The study was conducted in two communities: the rural community of Ansung and the urban community of Ansan, both in Korea.<br>Data Collection: Data were collected in 2001 through health interviews, physical measurements, and mental stress assessments. Nutritional intake was assessed using a Korean dish-based semi-quantitative food frequency questionnaire (FFQ).<br>Genotyping | - These findings suggest that both genetic and lifestyle factors, as well as stress, interact with the MC4R rs17782313 polymorphism to influence obesity risk.<br>- The MC4R rs17782313 minor allele (C) was associated with higher BMI across normal, overweight, and obese subjects, with a statistically significant increase in BMI seen in subjects with the minor alleles compared to those with major alleles (TT) nutrient Intake and MC4R Genotypes.<br>- Individuals with the MC4R C allele showed a higher intake of processed foods (such as ramen, canned tuna, fish cake, ham, and cheese) and a lower intake of fruits. This dietary preference might contribute to the higher obesity risk observed in individuals with this genotype. |

| Title | Journal | Method | Result |
|---|---|---|---|
| Genes Involved in Susceptibility to Obesity and Emotional Eating Behavior in a Romanian Population (Vranceanu et al., 2024) | Nutrients | Study design: cross-sectional study on gene variants, eating behavior, and obesity in adults.<br>Sample size: 220 subjects (men and women, normal weight, overweight, and obese).<br>Study location: conducted in two weight loss clinics in Romania.<br>Data collection: anthropometric data, emotional eating measurement, genetic analysis | - The study revealed that individuals with the MC4R/CC genotype exhibited a higher average BMI (28.93), weight (82.65 kg), and waist circumference (82.10 cm) compared to individuals with other genotypes, indicating a predisposition towards obesity and central obesity.<br>- Emotional eating scores (EES) showed significant effects on BMI (F = 6.831, p = 0.0013) and were independently associated with increased obesity risk in MC4R genotype carriers.<br>- However, the interaction between MC4R genotypes and EES on BMI was not significant (F = 1.115, p = 0.3505).<br>- Dietary and behavioral interventions targeting emotional eating may mitigate the risk of obesity, regardless of the MC4R genotype. |

## Nutrient interaction with MC4R

### MC4R gene variants and protein synthesis

MC4R gene variants play a crucial role in regulating energy balance and body weight. Variants in the MC4R gene can result in either loss or gain of function, directly impacting receptor signaling pathways and influencing an individual's risk of developing obesity (Lotta et al., 2019; Mohammed et al., 2023). Understanding these genetic variants is crucial for developing personalized therapeutic strategies to manage MC4R-related obesity. The MC4R gene can undergo various mutations, including missense, nonsense, and frameshift mutations. Studies have identified numerous MC4R variants across different populations, some of which are associated with an increased risk of obesity, while others confer protective effects. For instance, research on 61 nonsynonymous variants revealed that 47 led to loss of function (LoF), and 9 displayed gain of function (GoF) characteristics (Lotta et al., 2019). These variants can impair the receptor's ability to activate downstream signaling pathways, such as the production of cyclic AMP (cAMP) in response to agonists like α-MSH (alpha-melanocyte-stimulating hormone), a process critical for appetite regulation and energy homeostasis (Mohammed et al., 2023; Rodríguez Rondón et al., 2024).

Some gain-of-function variants in the MC4R gene have been found to reduce β-arrestin recruitment, which is associated with a lower risk of adiposity and improved metabolic outcomes. This suggests that targeting MC4R signaling could be a potential strategy for treating obesity by modulating its pathway (Lotta et al., 2019). Furthermore, specific mutations can disrupt the synthesis and trafficking of the MC4R protein, such as hindering its localization to the plasma membrane, an essential step for ligand activation (Brouwers et al., 2021). Understanding these functional impacts is crucial for developing therapies that enhance or restore MC4R function, particularly in individuals with specific pathogenic variants (Rodríguez Rondón et al., 2024).

One significant single nucleotide polymorphism (SNP), rs17782313, has been linked to obesity and metabolic traits, particularly in females. This SNP affects body mass index (BMI), insulin resistance, and fasting glucose levels, underscoring the role of genetic factors in the development of obesity. Further research is required to uncover the mechanisms through which this SNP influences health fully and to explore interventions that target the MC4R pathway for

effective obesity management (Adamska-Patruno et al., 2019; Carrasco-Luna et al., 2023; Chermon & Birk, 2023; Hammad et al., 2020; Sull et al., 2020).

**Types of nutrients affecting mc4r and mechanisms of nutrient interaction**

The interaction between nutrients and the melanocortin 4 receptor (MC4R) is a key focus of research, particularly regarding how different dietary components influence MC4R mechanisms involved in energy balance and obesity. Various nutrients, including proteins, carbohydrates, and fats, have been shown to impact MC4R function and gene expression, with implications for appetite regulation, energy expenditure, and metabolic health (Adamska-Patruno et al., 2021; Huang et al., 2017).

Research indicates that carbohydrate intake can also influence MC4R function. For instance, individuals with specific single-nucleotide polymorphisms (SNPs) in the MC4R gene exhibit a relative increase in carbohydrate utilization post-meal, suggesting that carbohydrate intake may modulate the effects of MC4R on energy balance. One study revealed that individuals with specific MC4R genotypes responded differently to high-protein diets in terms of appetite, suggesting that protein intake may interact with MC4R to influence satiety and food cravings. This suggests a potential gene-diet interaction, where specific MC4R variants modify the effects of dietary protein on appetite regulation (Adamska-Patruno et al., 2019).

Carbohydrate intake can also affect MC4R function. Some studies show that individuals with specific single nucleotide polymorphisms (SNPs) in the MC4R gene display an increased reliance on carbohydrates for energy after meals. This suggests that carbohydrate intake may modulate MC4R-related energy balance, underscoring the significance of macronutrient composition in influencing both genetic and physiological pathways associated with MC4R function. In particular, individuals with specific MC4R variants may metabolize carbohydrates differently, which can affect their overall energy expenditure (Adamska-Patruno et al., 2019; 2021; Park et al., 2016).

Additionally, the intake of dietary fats has been linked to the function and signaling of MC4R. High-fat diets, for instance, may upregulate MC4R expression and alter its pathways, potentially influencing both food intake and energy expenditure. Studies have also identified a relationship between MC4R-related single-nucleotide polymorphisms (SNPs) and dietary fat preferences, with some variants being associated with a higher preference for energy-dense foods, such as those high in fat. This suggests that MC4R function is sensitive to macronutrient composition, particularly in terms of fat intake and energy balance.

The interaction between MC4R genetic variants, such as SNP rs17782313, and dietary factors plays a significant role in the development of obesity and metabolic disorders. Specific MC4R genotypes may predispose individuals to higher energy intake from specific types of food, such as processed and high-calorie foods, while also correlating with lower consumption of healthier options like fruits. This gene-diet interaction underscores the complexity of MC4R's role in obesity, as different genotypes respond differently to various types of food (Adamska-Patruno et al., 2021; Park et al., 2016). Furthermore, psychological factors, such as mental stress, can influence MC4R activity and dietary choices. Stress can activate MC4R signaling pathways, leading to increased cravings for high-energy foods. This highlights the need to consider both psychological and nutritional factors when examining MC4R's involvement in obesity and its related mechanisms (Park et al., 2016).

**Mechanisms of interaction**

The melanocortin 4 receptor (MC4R) is a key regulator of appetite and energy homeostasis. It mediates the effects of melanocortins released from proopiomelanocortin (POMC) neurons in the hypothalamus. When activated, MC4R decreases food intake and increases energy expenditure, making it a critical target in understanding the mechanisms of obesity (Metzger et al., 2024). Variants in the MC4R gene can influence how the body processes energy from different macronutrients, impacting overall metabolic health and obesity risk (Adamska-Patruno et al., 2019; Metzger et al., 2024). Different MC4R genotypes can lead to variations in behavioral responses to food stimuli. For example, individuals with certain MC4R variants may experience

increased cravings for specific foods, which can influence their dietary choices and overall energy balance (Adamska-Patruno et al., 2021; Huang et al., 2017).

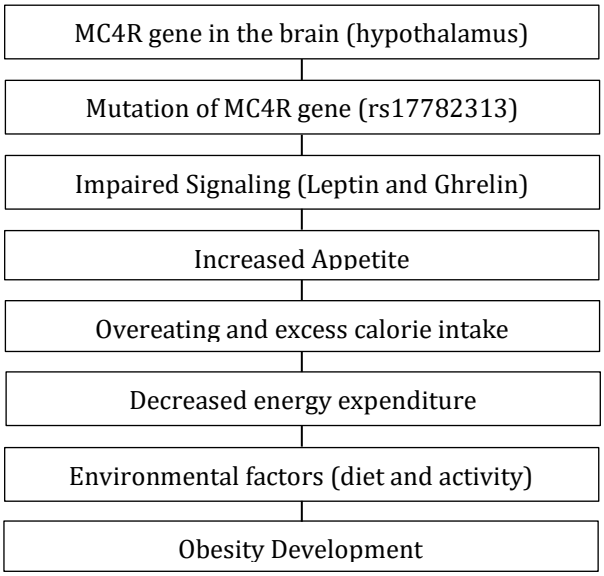


**Figure 1. Mechanisms of the process of obesity influenced by the MC4R gene (rs17782313)**

## Nutrient-induced changes in MC4R gene expression

Nutrient intake plays a significant role in modulating MC4R gene expression. Several types of nutrients have been shown to influence the function and regulation of this gene through various mechanisms. For example, high-protein diets have been shown to reduce food intake and influence appetite-related pathways regulated by MC4R. Studies in both human and animal models have demonstrated that increased dietary protein intake leads to reduced hypothalamic expression of MC4R, suggesting a regulatory effect of protein on this gene (Adamska-Patruno et al., 2021; Huang et al., 2017).

Similarly, high-fat diets have been linked to epigenetic modifications, including altered DNA methylation of the MC4R gene, which leads to decreased mRNA expression of MC4R. These findings suggest that dietary fat can influence MC4R gene expression and its associated physiological functions (Koochakpoor et al., 2016). Carbohydrate intake has also been implicated in the modulation of MC4R expression. Evidence suggests that individuals with specific genetic variants may metabolize carbohydrates differently, thereby affecting their energy balance and MC4R activity (Adamska-Patruno et al., 2021). In addition to macronutrients, micronutrients like folate and certain phytochemicals may influence MC4R expression by altering its epigenetic regulation, thereby expanding the scope of nutrient-gene interactions beyond macronutrients alone (Koochakpoor et al., 2016).

## Genetic variants, nutrients, and obesity risk

The interaction between MC4R genetic variants and nutrient intake is crucial for understanding the mechanisms of obesity. For example, the MC4R variant rs17782313 has been extensively studied about dietary intake and the development of obesity. Research involving 8,842 Korean adults found that while the daily intake of energy, carbohydrates, and protein did not vary significantly between MC4R genotypes, the percentage of energy from fat did. Individuals with the C allele of the rs17782313 variant showed a positive association with processed food intake, such as ramen and canned tuna, while having a negative association with fruit consumption. This suggests that genetic variants can influence dietary preferences and choices, which, in turn, affect energy balance. (Park et al., 2016).

Moreover, studies have shown that higher carbohydrate intake is linked to increased BMI and waist circumference in individuals with the TC+CC genotype. In contrast, individuals with the TT genotype exhibit an increase in basal metabolic rate (BMR) per kilogram of body weight (Alizadeh et al., 2022). There is a significant association between rs17782313 and body weight in the combined population (Walia et al., 2021). The rs17782313 polymorphism has also been associated with body weight and energy intake across various populations (Adamska-Patruno et al., 2019; Khalilitehrani et al., 2015; Meng et al., 2018; Rahati et al., 2022) with evidence suggesting that the C allele increases appetite and the risk of obesity (Álvarez-Martín et al., 2024). Understanding how MC4R gene variants interact with nutrient intake and other factors, such as stress, is essential for developing personalized dietary strategies to manage obesity and metabolic disorders.

This study aimed to evaluate the association between the MC4R rs17782313 genetic variant and anthropometric indicators of obesity, as well as to assess its potential interaction with energy and carbohydrate intake among Javanese adults. The analysis revealed that the rs17782313 variant was significantly associated with several anthropometric parameters, particularly body mass index (BMI), waist circumference, and hip circumference. Individuals carrying the TC and CC genotypes tended to have higher anthropometric measurements compared to those with the TT genotype, indicating that this variant contributes to an increased risk of obesity in the studied population.

Furthermore, this study examined the interaction between the rs17782313 variant and dietary intake of energy and carbohydrates. The interaction analysis showed that dietary patterns could modify the genetic effect on obesity risk. Specifically, individuals with the risk genotypes (TC/CC) who also had higher intakes of energy and carbohydrates exhibited greater increases in BMI and waist circumference compared to those with similar genotypes but lower intakes of these nutrients. These findings provide evidence of a nutrigenetic interaction, where the genetic predisposition to obesity is influenced by dietary factors, particularly carbohydrate and energy intake.

These results are consistent with biological theories suggesting that MC4R variants play a role in regulating appetite and energy metabolism and may respond differently to variations in macronutrient composition. Thus, this study not only confirms the genetic association with obesity but also reinforces the importance of considering gene-diet interactions in the development of personalized nutrition strategies. In the context of the Javanese population, the findings provide preliminary evidence for understanding how local genetic factors interact with traditional and modern dietary patterns to influence nutritional status and metabolic disease risk.

## DISCUSSION

### Association between MC4R rs17782313 and obesity parameters

The present study found a significant association between the rs17782313 variant near the *MC4R* gene and obesity-related anthropometric measures, including body mass index (BMI), waist circumference, and hip circumference, among Javanese adults. Individuals carrying the C allele (TC and CC genotypes) showed higher mean values for these parameters, supporting the hypothesis that this polymorphism contributes to increased obesity risk. These findings are consistent with studies conducted in East Asian and European populations. For instance, Lv et al., (2015) demonstrated that children with the CC genotype had more than twice the risk of obesity compared to those with the TT genotype. Similarly, a study by Vranceanu et al. (2024) found that Romanian adults with the CC genotype exhibited higher BMI and waist circumference.

However, the absence of consistent associations in all studies, as seen in the null findings in the Japanese population (Katsuura-Kamano et al., 2014), suggests potential variability across ethnic groups. This reinforces the need for population-specific investigations, such as this study, particularly in underrepresented Southeast Asian populations. The current findings thus fill a research gap by contributing genotype-phenotype data from Javanese individuals whose genetic and dietary profiles differ from previously studied cohorts.

### Interaction between MC4R rs17782313 and dietary intake

This study further revealed that the rs17782313 variant interacts with dietary intake to influence the risk of obesity. Carriers of the C allele had a higher intake of energy and carbohydrates, and this was associated with increased anthropometric measures. These results support the concept that genetic background influences dietary behavior and nutrient metabolism. Similar findings were reported by Khalilitehrani et al. (2015b), who observed increased energy and fat intake among CC genotype carriers in Iran. Adamska-Patruno et al. (2021) highlighted the differences in carbohydrate metabolism associated with the MC4R genotype, which aligns with the current study's focus on carbohydrate intake. Moreover, Carrasco-Luna et al. (2023) stressed that macronutrient response differs by genotype, advocating for genotype-specific dietary strategies.

Studies have also highlighted the potential benefits of macronutrient manipulation. High-protein diets may help specific MC4R genotypes reduce energy intake through enhanced satiety (Huang et al., 2017), while high-fat diets may influence MC4R gene expression and fat preference depending on genetic predisposition (Koochakpoor et al., 2016). These nutrigenetic insights underscore the importance of individualized dietary interventions, particularly for genetically susceptible populations.

### Psychosocial and behavioral factors

Beyond genetics and diet, psychosocial influences may modulate *MC4R*-mediated pathways. Stress and emotional eating behavior have been shown to influence food preferences and intake, particularly in individuals who are genetically susceptible. Park et al. (2016) observed that stress levels interacted with *the MC4R* genotype to elevate energy intake. Vranceanu et al. (2024) also reported higher emotional eating scores among CC genotype carriers, although the interaction term was not statistically significant. These observations suggest that the psychological context may amplify or buffer the genetic and dietary risks associated with obesity.

### Future research and personalized nutrition potential

The integration of genetic, dietary, and behavioral data has the potential to enhance the prevention and treatment of obesity. Rahati et al. (2022) and Carrasco-Luna et al. (2023) emphasized the importance of developing personalized nutrition models based on genetic information. Future directions should include mechanistic studies of MC4R signaling, particularly how it responds to different macronutrients, as well as interventions tailored to individual genotypes.

Additionally, emerging technologies such as artificial intelligence and machine learning hold promise for integrating complex data (genotype, diet, lifestyle) to produce personalized nutrition recommendations. Longitudinal studies are also needed to assess the long-term effectiveness of nutrigenetic interventions. Furthermore, the role of gut microbiota as a mediator in MC4R–diet interactions offers an exciting area for exploration.

## CONCLUSION

This study highlights the role of MC4R gene variants in energy balance regulation and obesity, as well as their interactions with various nutrients. Specific MC4R gene variants significantly impact the synthesis and function of receptor proteins, affecting signaling pathways in the body. Loss-of-function (LoF) mutations in MC4R can disrupt the activation of the cAMP pathway, which plays a crucial role in appetite regulation and energy homeostasis. In contrast, gain-of-function (GoF) mutations exhibit protective effects against obesity. One key variant, rs17782313, has been linked to an increased body mass index (BMI) and a higher risk of insulin resistance, particularly in women. Beyond genetic factors, MC4R variations also interact with environmental factors, including dietary patterns, suggesting that a nutrigenetic approach may be a potential strategy for managing obesity.

Additionally, this study found that different macronutrients, including proteins, fats, and carbohydrates, influence MC4R gene expression and function in distinct ways. High-protein diets may reduce MC4R gene expression, whereas high-fat consumption is linked to epigenetic modifications that affect MC4R expression. Individuals with specific MC4R variants tend to prefer high-fat and processed foods, increasing their risk of obesity. Apart from nutrition, psychological factors such as stress also play a role in activating the MC4R pathway, impacting food preferences and energy consumption patterns. These findings underscore the importance of a comprehensive approach that integrates genetic, nutritional, and psychosocial factors to understand better and effectively manage obesity.

Based on these insights, it is recommended that nutrition professionals and clinicians consider incorporating genetic screening, particularly SNP-based testing such as for rs17782313, into personalized obesity risk assessment and intervention planning. Researchers are encouraged to investigate genotype-specific dietary responses further to inform evidence-based dietary modifications. For policymakers, integrating genetic risk profiling into public health strategies could enhance the precision and effectiveness of national obesity prevention programs. Ultimately, diet modifications tailored to an individual's MC4R genotype hold promise for improving outcomes in obesity management and metabolic health.

## AUTHOR'S DECLARATION

### Authors' contributions and responsibilities

**MHSOY**: writing original draft, visualization; **AP:** Conceptualization, writing original draft (supporting), funding acquisition.

### Availability of data and materials

All data are available from the authors.

### Competing interests

The authors declare no competing interest.

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