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Original Research Article

Ramadan Fasting and Anthropometric Parameters: The Role of *MC4R* rs17782313 Genotype in Adults Semarang, Indonesia

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Abstract

Background: The *melanocortin-4 receptor (MC4R)* gene plays a key role in regulating energy balance and food intake. The rs17782313 variant has been associated with altered eating behavior and energy homeostasis, potentially influencing anthropometric and body composition responses during Ramadan fasting.

Objective: To examine the effects of Ramadan fasting on anthropometric parameters, body composition, and macronutrient intake across different *MC4R* genotypes in adults.

Methods: Thirty-five subjects were genotyped and grouped into recessive (TT, n=15) and dominant (TC+CC, n=20) allele carriers. Anthropometric and body composition measurements, dietary intake (SQ-FFQ), and physical activity (IPAQ-SF) were assessed before, during, and after Ramadan. Genetic data for rs17782313 were based on previously confirmed genotyping data. Repeated Measures ANCOVA, adjusted for energy intake and physical activity, evaluated genotype and time effects.

Results: The recessive group (TT) showed higher values than the dominant group (TC+CC), with significant differences in body weight, BMI, hip circumference, and visceral fat across all time points ($p < 0.05$). Waist circumference differed significantly during and after Ramadan, while BMR differed only before fasting ($p < 0.05$). Macronutrient intake and physical activity did not differ significantly between groups, although protein and fat intake changes post-Ramadan were notable ($p < 0.05$). A significant time–physical activity interaction was found for body weight ($p = 0.041$). TT carriers showed more pronounced anthropometric changes during Ramadan fasting compared to TC+CC carriers.

Conclusion: Ramadan fasting significantly influences anthropometric parameters, body composition, and macronutrient intake across *MC4R* genotypes. Greater responses were observed in recessive carriers (TT), although fasting outcomes were also shaped by nutrition and physical activity. Despite the relatively small sample size, these findings highlight the interplay of genetic and environmental factors in energy regulation during Ramadan and suggest the potential importance of considering genetic background in nutritional and lifestyle interventions during fasting periods.

Keywords: Ramadan fasting; *MC4R* rs17782313; Anthropometry; Body composition; Macronutrient intake.

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INTRODUCTION

Research on the impact of Ramadan fasting on nutritional status has been widely conducted, yet findings remain inconsistent. Some studies have

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reported significant reductions in body weight, anthropometric parameters, and body composition during fasting, while others found no substantial changes.¹⁻⁴ This variation indicates that the body's response to fasting is not uniform and may be influenced by multiple factors, including genetic factors.³ However, research on the impact of genetic variation particularly *MC4R* polymorphisms on anthropometric and body composition responses to Ramadan fasting remains limited, especially in Southeast Asian populations. Given the widespread practice of Ramadan fasting worldwide, understanding its metabolic and nutritional effects is particularly relevant in countries with large Muslim Populations, such as Indonesia.

In Indonesia, 87.2% of the population is Muslim and observes Ramadan fasting annually.⁵ Ramadan fasting generally lasts from before sunrise to sunset, averaging 12–17 hours depending on geographical location.^{6,7} Physiologically, Ramadan fasting falls under the category of religious fasting and can be classified as a type of intermittent fasting (IF) known as time-restricted eating (TRE).⁸⁻¹⁰ Evidence from several meta-analyses and systematic reviews suggests that IF can serve as an effective intervention strategy for weight reduction,¹¹⁻¹⁵ achieved by limiting food intake to specific eating windows.¹⁶

Previous studies have reported reductions in body weight during Ramadan ranging from 0.59–1.93 kg in individuals with normal nutritional status and from 0.95–15.8 kg in those who are overweight or obese.¹⁷⁻¹⁹ These differences may be influenced by changes in meal frequency and physical activity during Ramadan.^{20,21} Such changes may offer an alternative approach for addressing nutritional status issues in Indonesia, where the prevalence of overweight and obesity is 14.4% and 23.4%, respectively.²² These high prevalence rates are influenced by socioeconomic factors, dietary patterns, physical activity, genetics, and other factors such as sex, sleep patterns, and gut microbiota composition.²³⁻²⁷

In addition to altering eating patterns,²⁸ fasting also affects the circadian rhythm, which regulates metabolism, energy balance, and appetite.²⁹ Changes in meal timing during fasting can influence metabolic hormones such as insulin, leptin, and ghrelin, which are involved in *melanocortin-4 receptor (MC4R)*-related pathways regulating appetite and energy balance.^{27,30-36} The *MC4R* gene encodes a G-protein-coupled receptor that plays a central role in energy homeostasis, regulation of food intake, and adipose tissue formation.³⁷⁻³⁹

MC4R has several variants that may impair its expression.^{39,40} Among the 130 pathogenic variants identified, one of the most impactful on the melanocortin system is rs17782313 (minor allele C).²⁷ This single nucleotide variant (SNV) is located in the upstream intron of the *MC4R* gene and is frequently associated with increased appetite, reduced satiety, leptin resistance, elevated ghrelin secretion, and a higher risk of obesity.³⁹⁻⁴² Such effects can increase energy intake particularly from carbohydrates and fats, contributing to fat mass accumulation.

Findings on the association between *MC4R* rs17782313 and energy intake, metabolism, and nutritional status remain inconsistent.⁴³ Several studies have reported that individuals with CC and CT genotypes tend to have higher appetite compared with those carrying the TT genotype,⁴⁴ and that the SNV is linked to macronutrient intake and anthropometric indices, although results vary.⁴⁵⁻⁴⁷ Carriers of the C allele generally present with higher BMI, metabolic rate, and energy expenditure via enhanced thermogenesis, whereas CT and TT carriers have lower metabolic rates.⁴⁷ This may explain differential responses to Ramadan fasting across genotypes.

To date, no studies in Indonesia have examined the specific effect of *MC4R* rs17782313 on changes in anthropometric parameters during Ramadan fasting. Such responses may also be influenced by the dietary habits of Indonesians, which are often high in sugar and fat during Ramadan.^{21,48,49} Therefore, this study aims to determine the impact of Ramadan fasting on nutritional status according to *MC4R* rs17782313 SNV. Based on previous evidence linking the C allele with impaired satiety signaling and altered energy regulation, it was hypothesized that carriers of the C allele (TC and CC genotypes) would exhibit less favorable anthropometric and body composition responses compared to Ramadan fasting compared with TT carriers.

MATERIALS AND METHODS

This study adopted a natural experimental cohort design conducted over the Ramadan fasting period, which lasted approximately 29-30 days, with assessments at three time points: one week before Ramadan fasting, the third week of Ramadan fasting, and two weeks after Eid al-Fitr in 2025. The primary measurements included anthropometric parameters, body composition, dietary intake, and physical activity.

Anthropometric parameters included body weight, height, body mass index (BMI), waist circumference, hip circumference, and waist-to-hip ratio (WHR). Body compositions parameters included muscle mass percentage, body fat percentage, visceral fat, and basal metabolic rate (BMR).

Participants and Study Setting

Participants were recruited in Semarang City, Indonesia using purposive sampling from a previously established cohort by re-contacting all eligible respondents from a prior study. Eligible participants were Muslim adults aged 19-59 years who observed Ramadan fasting, were not on a strict diet, were free from medical conditions requiring treatment or medication, and were not pregnant or breastfeeding. Participants were excluded if they withdrew from the study or were unable to complete the fasting period. A total of 35 participants (8 males and 27 females) consented to participate.

Sample Size Estimation

Sample size estimation was performed using GPower version 3.1 with an alpha of 0.05, statistical power of 0.95, and an effect size of 0.89,⁵⁰ yielding a

minimum of 24 participants. To accommodate a projected 10% drop out rate, the minimum target was set at 27 participants. The recruitment process was conducted by re-contacting each respondent from a previous study, resulting in 35 participants who provided a positive response and consented to take part in this research.

Anthropometric, Dietary, and Physical Activity Assessment

Body weight and body composition were measured using a digital bioelectrical impedance analyzer (Karada scan, OMRON HBF-214, accuracy ± 0.1 kg), and height was measured using a portable stadiometer (microtoise, accuracy ± 0.5 cm). Waist circumference was measured at the midpoint between the lowest rib and the iliac crest, while hip circumference was measured at the widest portion of the buttocks using a non-stretchable measuring tape (accuracy 0.1 cm).⁵¹ BMI was calculated as weight (kg) divided by height squared (m^2).⁵² Dietary intake was assessed using a Semi-Quantitative Food Frequency Questionnaire (SQ-FFQ) that has been validated for use in Indonesian adults, and analyzed to estimate mean daily energy and nutrient intakes.⁵³ Physical activity was assessed using the Indonesian validated version of the International Physical Activity Questionnaire–Short Form (IPAQ-SF) and expressed in metabolic equivalent minutes per week (MET-min/week).^{54,55}

Genotyping Procedure

Genetic data for the single nucleotide variant (SNV) rs17782313 of the *MC4R* gene were obtained from a previously conducted genotyping analysis carried out by collaborating members of the research team. These existing data were used to classify participants according to genotype in the present study.

In the previously conducted genotyping analysis, genomic DNA was extracted from peripheral blood samples using a commercial GeneAid DNA extraction kit, and DNA concentration was assessed prior to analysis. Genotyping was performed using a TaqMan allelic discrimination assay (Assay ID: C_32667060_10) on a real-time polymerase chain reaction (PCR) platform. Each 10 μ L reaction mixture contained TaqMan GTXpress Master Mix (2 \times), TaqMan SNV Genotyping Assay (20 \times), and genomic DNA. PCR conditions consisted of an initial enzyme activation at 95°C for 10 minutes, followed by 40 cycles of denaturation at 95°C for 15 seconds and annealing/extension at 60°C for 60 seconds. Genotype classification (TT, TC, and CC) was determined based on allele-specific fluorescence signals measured at the endpoint of amplification using TaqMan Genotyping Software.

Statistical Analysis

Data normality was assessed using the Shapiro–Wilk test. Changes in anthropometric and body composition parameters over time were analyzed using repeated-measures analysis of covariance (ANCOVA), with genotype as the between-subject

factor and time as the within-subject factor. Energy intake and physical activity were included as covariates to account for behavioral influences on fasting-related outcomes. Post hoc comparisons across time points were performed using Tukey’s test. All statistical analyses were performed using IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA), with statistical significance set at $p < 0.05$.

Participants were classified according to a dominant genetic model, with TC and CC genotypes combined as C allele carriers and compared with TT homozygotes. This approach was adopted due to the established biological relevance of the C allele and the limited number of CC carriers, which precluded separate genotype-level analyses. Baseline differences in age, BMI, and body fat percentage were observed between genotype groups. Together with the small sample size, particularly for the CC genotype, these baseline imbalances may have limited statistical power and contributed to variability in observed responses. Accordingly, these factors are acknowledged as methodological limitations and were carefully considered in the interpretation of the findings.

Ethical Approval

This study was approved by the Health Research Ethics Committee, Faculty of Medicine, Universitas Diponegoro, Ministry of Higher Education, Science, and Technology, Indonesia (No. 058/EC/KEPK/FKK-UNDIP/III/2025). All participants received a detailed explanation regarding the study objectives, procedures, and potential risks prior to participation. Written informed consent was obtained from all participants. The confidentiality of participants’ identities and personal data was strictly maintained throughout the study.

RESULTS

A total of 35 participants were included in this study, comprising 15 (42.9%) with the TT genotype, 17 (48.6%) with the TC genotype, and 3 (8.6%) with the CC genotype (Table 1). The allele frequencies of T and C were 67.1% and 32.9%, respectively, with a minor allele frequency (MAF) of 32.9%. The genotype distribution was in Hardy–Weinberg equilibrium ($p = 0.551$).

Participants were categorized into two groups: TT ($n = 15$) and TC+CC ($n = 20$) (Table 2). The TT group had a significantly higher mean age than the TC+CC group ($p = 0.043$). In both groups, females predominated. At baseline, body weight, BMI, hip circumference, visceral fat, and BMR were significantly higher in the TT group ($p < 0.05$), whereas height, waist circumference, waist-to-hip ratio (WHR), muscle mass, and body fat percentage did not differ significantly ($p > 0.05$). Based on mean BMI, the TT group was classified as overweight, while the TC+CC group was within the normal range. The proportion of participants with normal nutritional status was lower in the TT group. Energy and macronutrient intake assessed by SQ-FFQ, as well as total physical activity, did not differ significantly between groups ($p > 0.05$).

Table 1. Proportion of SNV rs17782313 in the *MC4R* Gene

N	Genotype			Allele		p-value ^a
	TT	TC	CC	T	C	
35	15 (42.9%)	17 (48.6%)	3 (8.6%)	47	23	0.551
	MAF			67.1%	32.9%	

^aHardy-Weinberg Equilibrium for SNV rs17782313 *MC4R* Gene
MAF, Minor Allele Frequency

Table 2. Characteristics of Subjects in the TT and TC+CC Groups

Characteristic	TT (n=15)	TC+CC (n = 20)	p-value
Age (years)	29.73 ± 10.61	23.20 ± 7.82	0.043 ^{a*}
Sex			
Male	4 (26.7%)	4 (20.0%)	
Female	11 (73.3%)	16 (80.0%)	
Anthropometric Measurements			
Height (cm)	159.62 ± 9.79	160.13 ± 5.95	0.850 ^b
Body Weight (kg)	70.74 ± 16.61	58.60 ± 11.53	0.015 ^{b*}
BMI (kg/m ²)	27.66 ± 5.09	22.84 ± 4.17	0.004 ^{a*}
Nutritional Status			
Underweight	0 (0.00%)	2 (10.0%)	
Normal	6 (40.0%)	12 (60.0%)	
Overweight	5 (33.3%)	5 (25.0%)	
Obese	4 (26.7%)	1 (5.0%)	
Waist Circumference (cm)	85.87 ± 12.76	79.90 ± 10.87	0.102 ^c
Hip Circumference (cm)	100.91 ± 10.13	91.85 ± 9.34	0.017 ^{c*}
WHR	0.85 ± 0.07	0.87 ± 0.08	0.764 ^c
Body Compositions			
Muscle Mass (%)	27.22 ± 4.81	29.29 ± 4.62	0.162 ^a
Body Fat (%)	31.78 ± 6.65	27.87 ± 6.65	0.057 ^a
Visceral Fat	11.43 ± 7.06	5.61 ± 4.02	0.004 ^{a*}
BMR (cal/day)	1474.29 ± 289.59	1318.72 ± 206.35	0.049 ^{a*}
Macronutrient Intake (SQ-FFQ)			
Energy (cal/day)	1572.59 ± 577.77	1376.48 ± 407.06	0.247 ^a
Proteins (g/day)	65.66 ± 26.03	59.92 ± 19.07	0.456 ^b
Fats (g/day)	61.55 ± 27.07	56.58 ± 20.88	0.543 ^a
Carbohydrates (g/day)	190.74 ± 81.02	160.36 ± 52.64	0.219 ^b
Physical Activity (MET-minutes/week)	2509.93 ± 2722.59	2149.50 ± 2458.98	0.684 ^b
IPAQ-SF			
Low	1 (6.7%)	1 (5.0%)	
Moderate	11 (73.3%)	17 (85.0%)	
High	3 (20.0%)	2 (10.0%)	
Occupation			
Student	14 (93.3%)	12 (60.0%)	
Employee	1 (6.7%)	8 (40.0%)	
Type of residence			
Boarding / Dormitories	14 (93.3%)	10 (50.0%)	
Family Home	1 (6.7%)	10 (50.0%)	

^aVariables (log transformed) analyzed using Independent T-Test

^bVariables analyzed using Independent T-Test

^cVariables analyzed using Mann-Whitney Test

**p* < 0.05, considered statistically significant

BMI, Body Mass Index; WHR, Waist-to-Hip Ratio; BMR, Basal Metabolic Rate; SQ-FFQ, Semi-Quantitative Food Frequency Questionnaire; IPAQ-SF, International Physical Activity Questionnaire-Short Form

Table 3. Repeated Measures ANCOVA in TT and TC+CC Groups with Energy Intake and Physical Activity as Covariates

Characteristic	<i>p</i> -value Tests of Within-Subjects				<i>p</i> -value Tests of Between-Subjects		
	Time	Time x Group (Recessive vs Dominant)	Time x Energy Intake	Time x Physical Activity	Group (TT vs TC+CC)	Energy Intake	Physical Activity
Anthropometric Measurements							
Body Weight (kg) ^a	0.074	0.182	0.309	0.041*	0.021*	0.359	0.834
BMI (kg/m ²) ^a	0.622	0.294	0.800	0.422	0.007*	0.565	0.746
Waist Circumference (cm) ^b	0.474	0.866	0.639	0.714	0.010*	0.324	0.965
Hip Circumference (cm) ^b	0.951	0.665	0.855	0.707	0.057	0.990	0.739
WHR ^b	0.977	0.553	0.912	0.825	0.996	0.356	0.959
Body Compositions							
Muscle Mass (%) ^a	0.678	0.622	0.729	0.619	0.423	0.933	0.462
Body Fat (%) ^a	0.423	0.393	0.495	0.776	0.101	0.972	0.570
Visceral Fat ^a	0.692	0.850	0.314	0.145	0.008*	0.522	0.928
BMR (cal/day) ^a	0.123	0.558	0.211	0.364	0.051	0.383	0.880

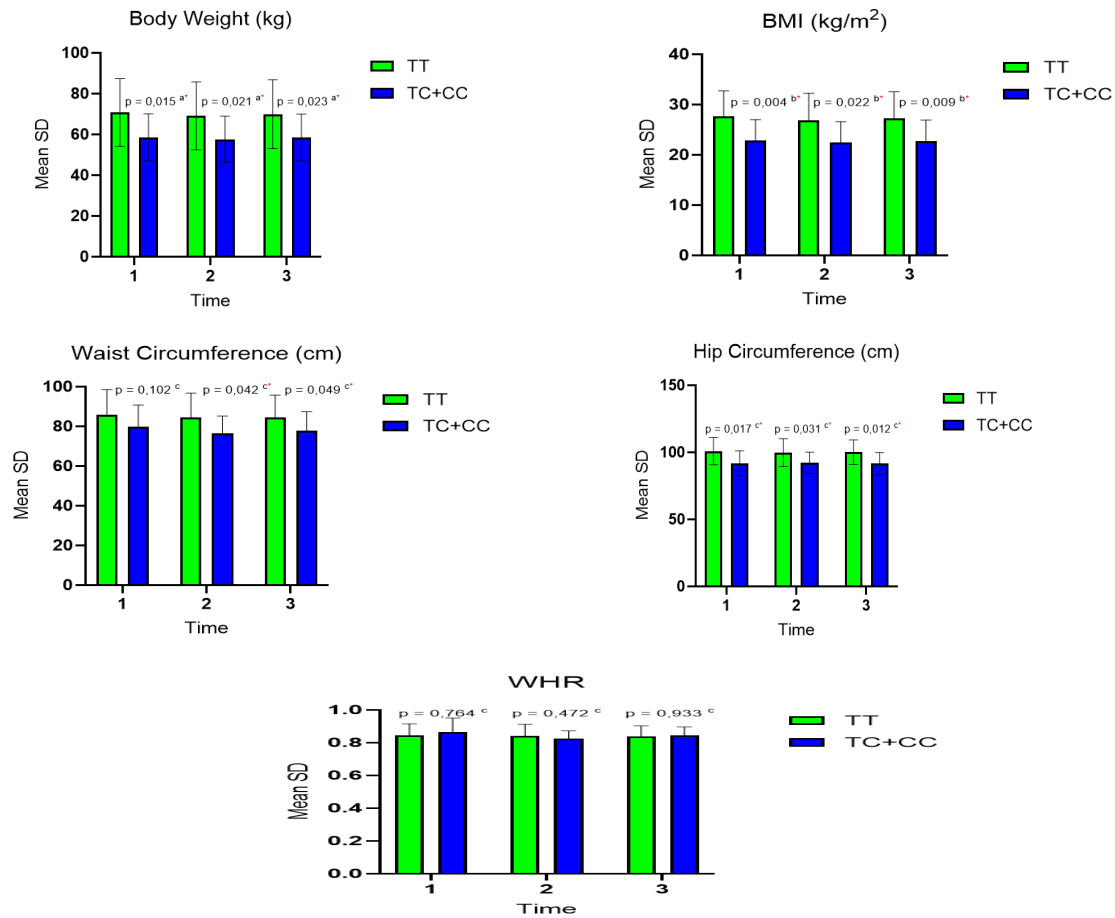
^aLog-transformed variable and covariates (energy intake and physical activity)

^bRank-transformed variable and log-transformed covariates (energy intake and physical activity)

**p* < 0.05, considered statistically significant

BMI, Body Mass Index; WHR, Waist-to-Hip Ratio; BMR, Basal Metabolic Rate

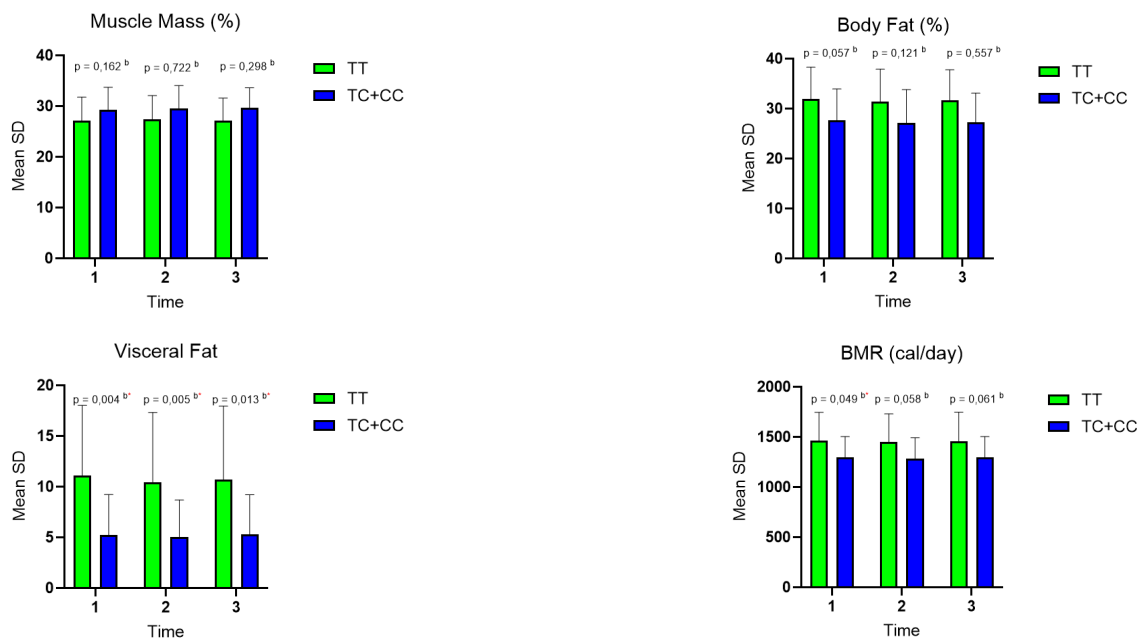
ANTHROPOMETRIC MEASUREMENTS



^a Data were analyzed using the independent t-test| ^b log-transformed data were analyzed using the independent t-test| ^c data were analyzed using the Mann–Whitney test| *p* < 0.05 indicates statistical significance| BMI, body mass index; WHR, waist-to-hip ratio.

Figure 1. Repeated Measures ANOVA of Anthropometric Parameters by TT and TC+CC Groups Across Three Measurement Time Points

BODY COMPOSITIONS



^b Log-transformed data were analyzed using the independent t-test| $p < 0.05$ indicates statistical significance| BMR, basal metabolic rate.

Figure 2. Repeated Measures ANOVA of Body Compositions by TT and TC+CC Groups Across Three Measurement Time Points

Across the three measurement time points (before, during, and after Ramadan), body weight, BMI, hip circumference, and visceral fat remained consistently higher in the TT group, with significant differences observed at all time points ($p < 0.05$) (Figure 1). Waist circumference differed significantly during and after Ramadan ($p < 0.05$), but not at baseline ($p = 0.102$). No significant differences were observed in WHR, muscle mass, or body fat percentage at any time point ($p > 0.05$), although muscle mass and body fat percentage tended to be higher in the TC+CC group before and after Ramadan. BMR differed significantly between groups only at baseline ($p = 0.049$) (Figure 2).

Energy intake was generally higher in the TT group across time points, although most differences were not statistically significant ($p > 0.05$). Significant between-group differences were observed for protein ($p = 0.040$) and fat intake ($p = 0.021$) two weeks after Ramadan. Physical activity levels did not differ significantly between groups at any time point ($p > 0.05$) (Figure 3).

Within-group analysis showed dynamic changes over time (Figure 4-6). During Ramadan, both groups exhibited reductions in most anthropometric measures, followed by increases after Ramadan. A similar pattern was observed for dietary intake, with decreased energy and macronutrient intake during Ramadan and increased intake afterward, while physical activity levels declined in both periods.

Repeated measures ANCOVA (Table 3) demonstrated a significant interaction between time and physical activity on body weight ($p = 0.041$). The

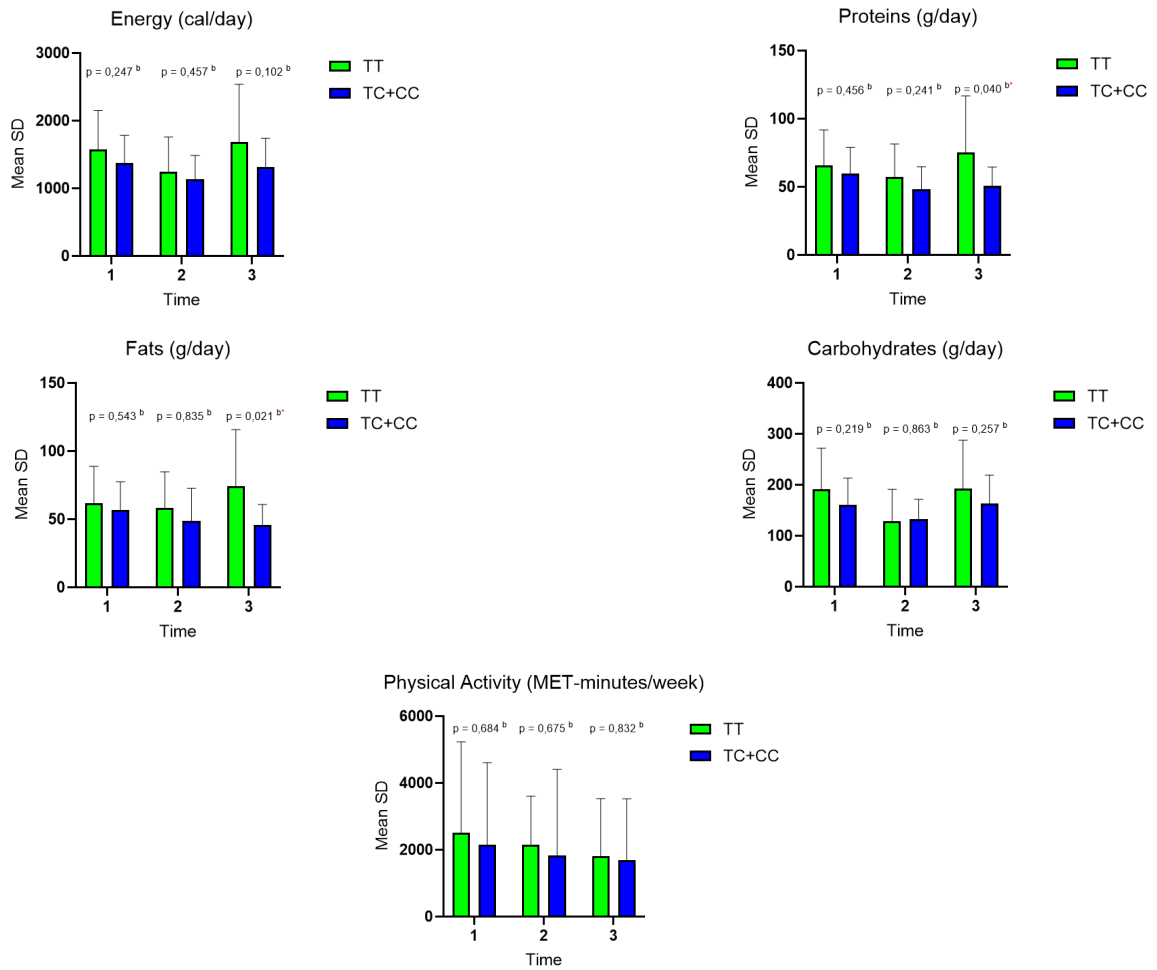
genotype group (TT vs. TC+CC) had significant effects on body weight ($p = 0.021$), BMI ($p = 0.007$), waist circumference ($p = 0.010$), and visceral fat ($p = 0.008$) after adjustment for energy intake and physical activity. No significant effects were observed for hip circumference, WHR, muscle mass, body fat percentage, or BMR.

DISCUSSION

The *MC4R* gene plays a key role in regulating energy balance and eating behavior through the hypothalamic neuroendocrine pathway.^{56,57} In this study, the rs17782313 genotype distribution was in Hardy–Weinberg equilibrium ($p = 0.551$), indicating no deviation in allele distribution within the study population.⁵⁸ The minor allele frequency (MAF) of the C allele was 32.9%, which falls within the reported range for Southeast/East Asian populations. Data from Ensembl indicate a C allele MAF of approximately 18.7%–32% in these populations,⁵⁹ while global estimates from GWAS Catalog are around 24%.⁶⁰

Compared with other Indonesian studies, a lower C allele MAF (10.91%) has been reported in the Jambi Malay population, suggesting potential genetic heterogeneity across subpopulations in Indonesia.⁶¹ These differences may reflect variations in ethnic background, population structure, and sampling characteristics. However, the relatively small sample size in the present study should be considered, as it may limit the generalizability of the observed MAF and Hardy–Weinberg equilibrium to the broader Javanese population.⁵⁸

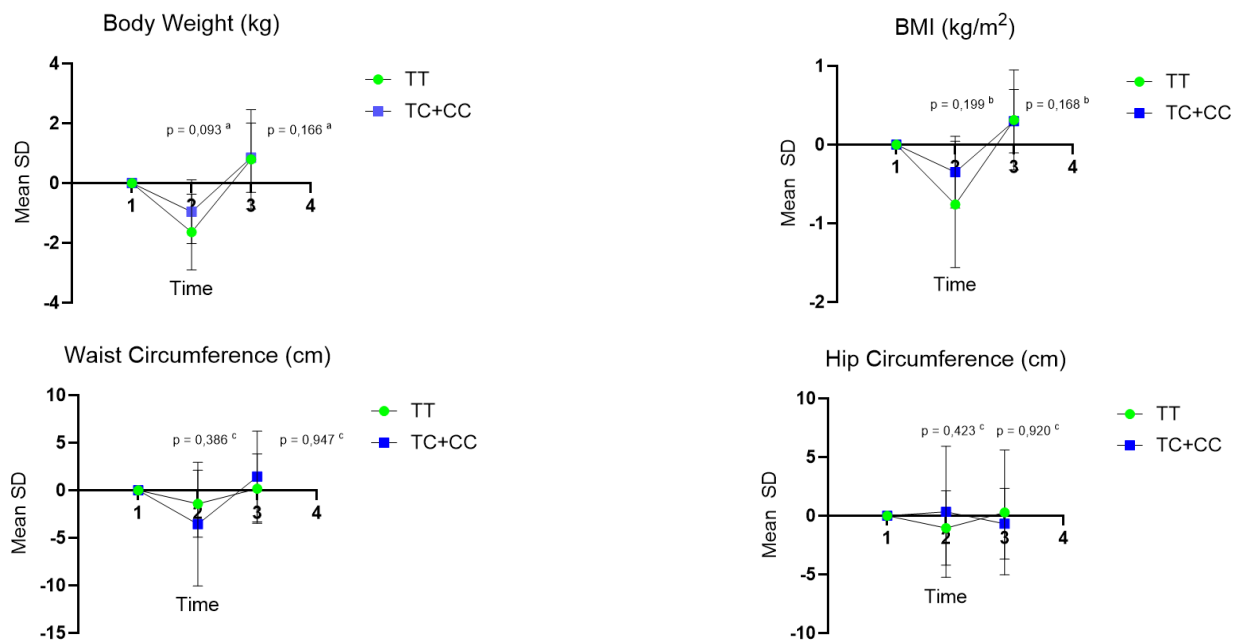
MACRONUTRIENT INTAKE (SQ-FFQ) & PHYSICAL ACTIVITY (IPAQ-SF)

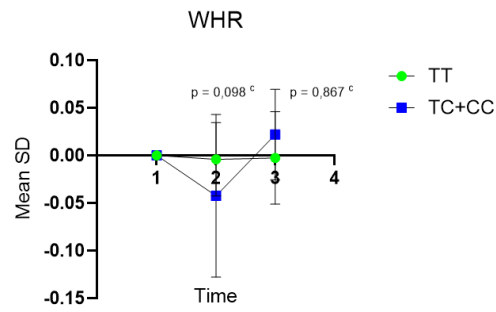


^b Log-transformed data were analyzed using the independent t-test | $p < 0.05$ indicates statistical significance | SQ-FFQ, Semi-Quantitative Food Frequency Questionnaire; IPAQ-SF, International Physical Activity Questionnaire–Short Form.

Figure 3. Repeated Measures ANOVA of Macronutrient Intake and Physical Activity by TT and TC+CC Groups Across Three Measurement Time Points

ANTHROPOMETRIC MEASUREMENTS

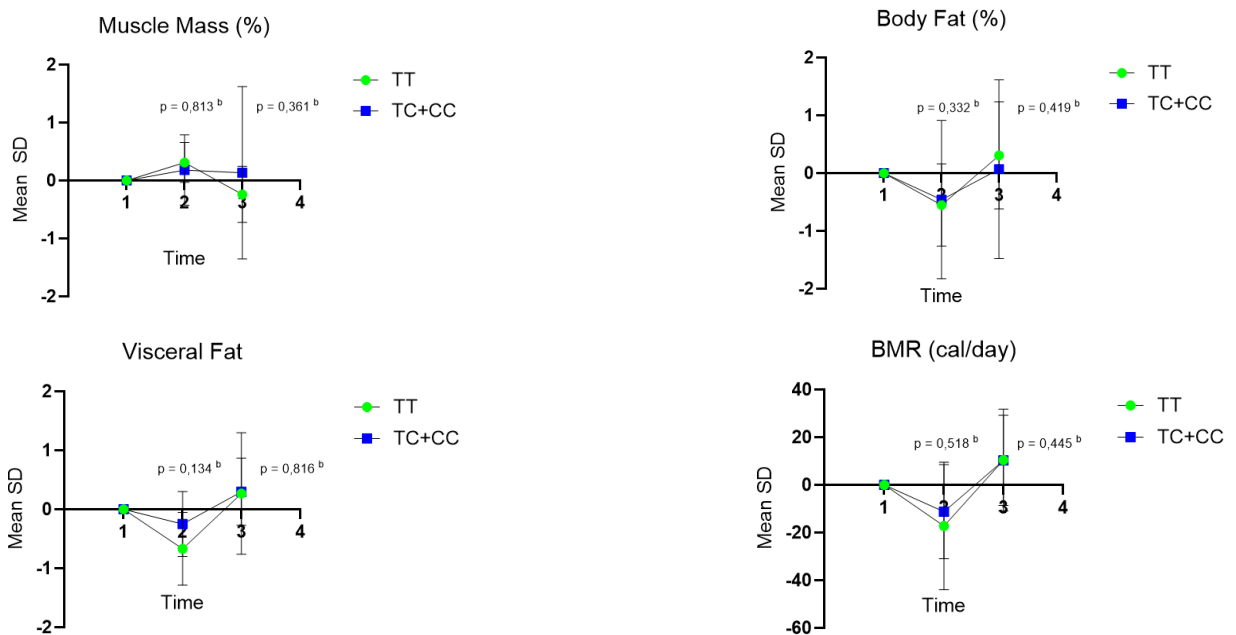




^a Data were analyzed using the independent t-test| ^b log-transformed data were analyzed using the independent t-test| ^c data were analyzed using the Mann–Whitney test| $p < 0.05$ indicates statistical significance| BMI, body mass index; WHR, waist-to-hip ratio.

Figure 4. Changes Over Time in Anthropometric Measurements in Both Groups

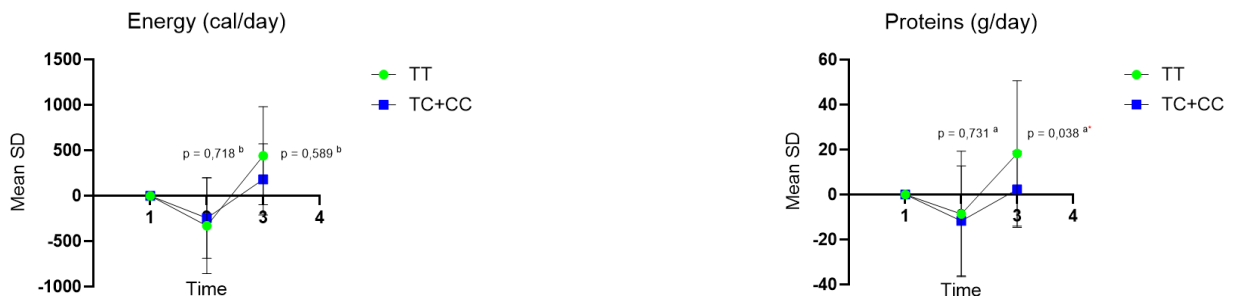
BODY COMPOSITIONS

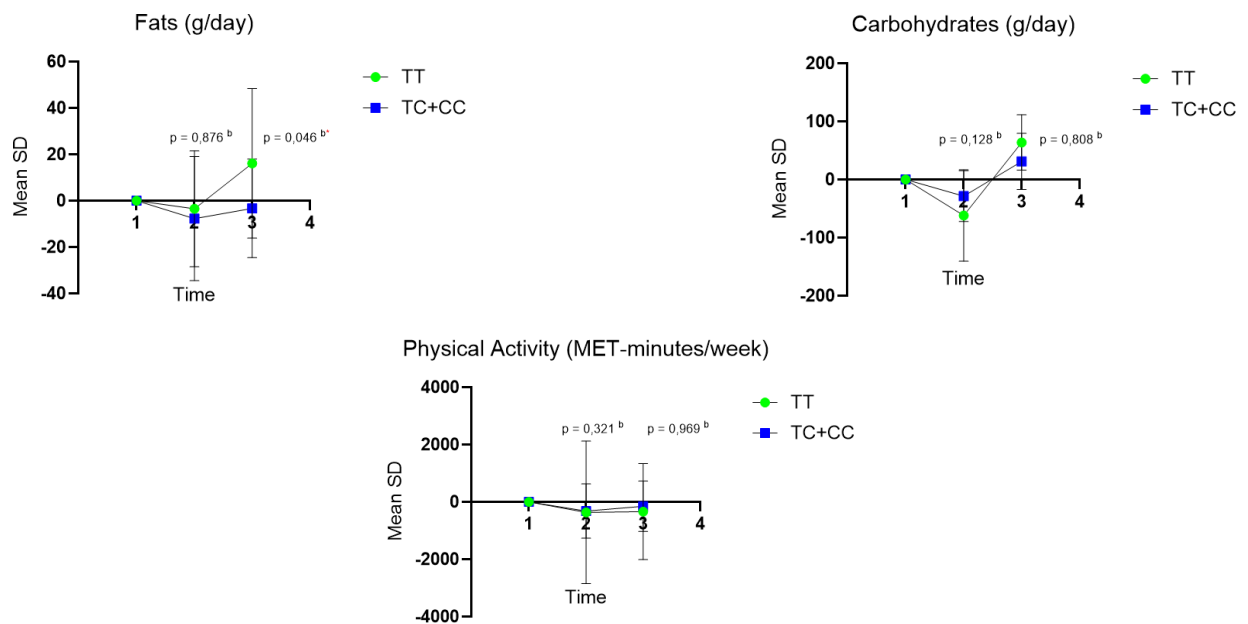


^b Log-transformed data were analyzed using the independent t-test| $p < 0.05$ indicates statistical significance| BMR, basal metabolic rate.

Figure 5. Changes Over Time in Body Compositions in Both Groups

MACRONUTRIENT INTAKE (SQ-FFQ) & PHYSICAL ACTIVITY (IPAQ-SF)





^b Log-transformed data were analyzed using the independent t-test| $p < 0.05$ indicates statistical significance| SQ-FFQ, Semi-Quantitative Food Frequency Questionnaire; IPAQ-SF, International Physical Activity Questionnaire–Short Form.

Figure 6. Changes Over Time in Macronutrient Intake and Physical Activity in Both Groups

Previous studies have consistently reported that C allele of rs17782313 is associated with increased appetite and higher anthropometric measures including body weight, BMI, waist circumference, and hip circumference primarily due to impaired satiety signaling.^{40,43,47} Interestingly, the present study found the opposite. The homozygous recessive T allele carriers (TT) experienced greater changes in anthropometric parameters, body composition parameters, and macronutrient intake during Ramadan fasting compared to the TC + CC group. Ramadan fasting affected both groups, however the TT group exhibited more pronounced changes, suggesting potentially greater short-term responsiveness rather than definitive benefits during fasting period.

Baseline differences partly explain this observation. Individuals in the TT group had higher baseline body weight and BMI, providing a greater potential for reduction during fasting. These findings suggest that variability in fasting responses may be influenced not only by genetic background but also by baseline phenotypic characteristics, which may interact with genetic regulation of energy balance.

MC4R, Ghrelin, and Leptin Signaling

The discrepancy between the present findings and previous literature may be explained by differences in the efficiency of the *MC4R*-mediated hormonal adaptation during fasting. Prior studies indicate that C allele carriers tend to exhibit impaired appetite regulation, characterized by higher ghrelin and lower glucagon-like peptide-1 (GLP-1) levels, resulting in reduced satiety and greater difficulty achieving weight loss.⁴⁶ In the current study, however, changes in anthropometric measures and dietary intake among C allele carriers (TC + CC) were relatively modest compared with TT carriers, suggesting a potentially more attenuated adaptive response to fasting.

Mechanistically, ghrelin activates agouti-related peptide (AgRP) and neuropeptide-Y (NPY) neurons, which inhibiting *MC4R* signaling and increasing hunger. Conversely, leptin activates proopiomelanocortin (POMC) neurons to produce α -melanocyte stimulating hormone (α -MSH), which binds to *MC4R* to suppress appetite and increase energy expenditure.^{42,62,63} In addition *MC4R* activation in intestinal enteroendocrine L cells also promotes the release of peptide-YY (PYY) and GLP-1, thereby slowing gastric emptying, enhancing satiety, and improving glucose regulation.⁶⁴

During fasting or energy restriction, circulating leptin levels decline substantially as a result of reduced energy intake and fat mass. This decline functions as a biological signal of negative energy balance, activating adaptive hypothalamic responses primarily through the melanocortin system, particularly *MC4R* signaling. In individuals with preserved *MC4R* function (TT genotype), fasting-induced leptin reduction may lead to coordinated changes in POMC/CART and NPY/AgRP signaling. This response reduces thermogenesis and increases hunger within a physiologically adaptive range, allowing energy expenditure to recover after refeeding.^{42,65}

In contrast, carriers of the C allele exhibit impaired melanocortin signaling. When leptin levels decrease during fasting, *MC4R* activation may be further reduced due to pre-existing receptor insensitivity. As a consequence, thermogenesis may be more strongly suppressed, metabolic efficiency may increase, and recovery of energy expenditure during refeeding is delayed. This adaptive profile may favor energy conservation, potentially limiting fat loss during fasting and increases susceptibility to weight regain after fasting ends.^{42,65}

These mechanisms are consistent with studies reporting distinct hormonal fluctuations during

Ramadan fasting. Alogaiel et al. (2025) reported a significant post-Ramadan increase in ghrelin (SMD = +0.31 pg/mL), while leptin remained unchanged (SMD = -0.11 µg/mL).⁶⁶ Similarly, Al-Rawi et al. (2020) found ghrelin decreased at the end of Ramadan but rose sharply thereafter, with leptin continuing to decline. Such imbalances are particularly relevant in obese individuals with leptin resistance, where post-fasting ghrelin surges are insufficiently countered by satiety signals. If *MC4R* responsiveness is reduced potentially due to lower receptor affinity, leptin resistance, and relatively stable ghrelin levels as suggested in previous studies among C allele carriers, changes in energy intake and body composition during and after fasting tend to be minimal.³¹ Thus, the C allele carriers in this study may represent a more attenuated hormonal response profile, whereas TT carriers demonstrate a more dynamic and adaptive hormonal response. It should be emphasized that these mechanistic interpretations are hypothesis driven and inferred from existing literature, as direct measurements of hormonal biomarkers were not available in the present study.

Links to Overweight/Obese Phenotype, Dietary Intake, and Physical Activity

Beyond hormonal regulation, baseline nutritional status and body weight also shape metabolic responses to fasting. Obese individuals have larger fat reserves and relatively less efficient metabolism, facilitating a faster shift to lipolysis during fasting and increased fat utilization as an energy source.^{67,68} This aligns with reports showing greater Ramadan weight loss in obese individuals compared with those of normal weight.^{17,19} In the present study, the recessive group showed greater weight loss than the dominant group, suggesting that while TT carriers may have more efficient genetic energy regulation, obesity can amplify short-term fasting responses but may also contribute to rapid weight regain post-fasting without continued intervention.

These findings are consistent with previous literature reporting that the rs17782313 variant of the *MC4R* gene is associated with increased abdominal fat.^{45,46,69-71} Although Ramadan fasting has been shown to reduce visceral fat, these effects may be transient.⁷²⁻⁷⁵ Interestingly, although the recessive group in this study had an average BMI within the overweight category, the characteristic influence of the C risk allele remained evident. This was reflected in variables such as body weight, body fat percentage, and visceral fat, where the TC+CC group experienced smaller reductions during fasting and greater increases after fasting compared to the TT group. In contrast, for muscle mass, the TC+CC group exhibited only modest increases during Ramadan, whereas the TT group showed more favorable responses. These findings suggest that *MC4R*-related genetic effects may persist beyond baseline phenotypic status and influence body composition dynamics during energy restriction.

Dietary patterns and food accessibility also influence body composition changes. Ramadan alters meal timing and food choices, often favoring energy-dense foods consumed during limited eating windows.⁴⁸ In this study, 93.3% of TT group

participants lived independently in dormitories, potentially limiting access to high-quality, varied foods compared with those living with family. Although between group differences in dietary intake were not statistically significant ($p > 0.05$), the TT group exhibited larger reductions during fasting and increases afterward. In contrast, approximately half of the TC+CC group lived with family. This aligns with findings from Hawlader et al. (2025) and Septiasari et al. (2023), which indicated that individuals living with family consumed more nutritionally balanced home-cooked meals, while those living alone relied more on ready-to-eat or instant foods.^{49,76} Physical activity significantly influenced weight changes over time ($p < 0.05$) but did not differ between groups. Consistent physical activity plays a key role in weight control during and after fasting.⁷⁷ Apriliansyah et al. (2023) similarly reported that 209 minutes/day of activity could reduce body weight by 1 kg in one week, while 236 minutes/day could reduce BMI by 1 kg/m².⁷⁸

Implications and Limitations

These findings indicate that the metabolic effects of fasting are not solely determined by energy deficit. Rather, they are also influenced by individual genetic capacity to maintain energy expenditure during caloric restriction. The *MC4R* rs17782313 polymorphism may modulate fasting responses through alterations in leptin sensitivity, melanocortin signaling, and thermogenic efficiency. These mechanisms may contribute to inter-individual variability in anthropometric and body composition outcomes. This highlights the potential value of incorporating genetic information into personalized fasting or dietary interventions.

Several limitations should be acknowledged. Hormonal biomarkers such as leptin, ghrelin, GLP-1, and PYY were not directly measured, limiting mechanistic confirmation of the proposed pathways. Baseline differences in anthropometric status and living arrangements may have influenced dietary access and adaptive responses to fasting. The relatively small sample size and potential selection bias due to recontacting participants from a previous cohort may limit generalizability. Measurement errors inherent to self-reported SQ-FFQ and IPAQ-SF data, as well as residual confounding, may have occurred and should also be considered. Additionally, the relatively short observation period precludes conclusions regarding long-term weight maintenance or post-fasting weight regain.

CONCLUSION

Ramadan fasting was associated with changes in nutritional status across *MC4R* rs17782313 genotype groups in this adult population. Variations in genotype were related to differences in anthropometric and body composition changes observed before, during, and after fasting. Both groups exhibited reductions in body weight and BMI during Ramadan, followed by partial regain afterward, with differing patterns and magnitudes of response. The TT group showed relatively greater reductions during fasting, whereas the TC+CC group demonstrated a more pronounced

rebound in several parameters post-Ramadan. These findings suggest that the effects of Ramadan fasting on nutritional status are influenced not only by genetic variation but also by energy intake and physical activity, highlighting a complex interaction between genotype, dietary patterns, and lifestyle factors.

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