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Bitter Taste Receptor *TAS2R38* Genetic Variation (rs10246939), Dietary Nutrient Intake, and Bio-Clinical Parameters in Koreans

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Conflict of Interest
The authors declare that they have no competing interests.

ABSTRACT

Differential bitterness perception associated with genetic polymorphism in the bitter taste receptor gene taste 2 receptor member 38 (*TAS2R38*) may influence an individual's food preferences, nutrition consumption, and eventually chronic nutrition-related disorders including cardiovascular disease. Therefore, the effect of genetic variations on nutritional intake and clinical markers needs to be elaborated for health and disease prevention. In this study, we conducted sex-stratified analysis to examine the association between genetic variant *TAS2R38* rs10246939 A > G with daily nutritional intake, blood pressure, and lipid parameters in Korean adults (males = 1,311 and females = 2,191). We used the data from the Multi Rural Communities Cohort, Korean Genome and Epidemiology Study. Findings suggested that the genetic variant *TAS2R38* rs10246939 was associated with dietary intake of micronutrients including calcium (adjusted p = 0.007), phosphorous (adjusted p = 0.016), potassium (adjusted p = 0.022), vitamin C (adjusted p = 0.009), and vitamin E (adjusted p = 0.005) in females. However, this genetic variant did not influence blood glucose, lipid profile parameters, and other blood pressure markers. These may suggest that this genetic variation is associated with nutritional intake, but its clinical effect was not found. More studies are needed to explore whether *TAS2R38* genotype may be a potential predictive marker for the risk of metabolic diseases via modulation of dietary intake.

Keywords: Blood pressure; Genetic variation; Lipids; Nutrient intake; Taste

INTRODUCTION

Earlier studies reported that dietary intake, tobacco smoking, physical activity, and other lifestyle factors are significant risk modifying factors in the etiology of obesity, hypertension, and dyslipidemia, which are subsequently associated with cardiovascular disorders [1,2]. Although it is clear that an individual's genetic traits are decisive factors in health issues, the interaction between gene and those factors could control the effect of genetic susceptibility to common chronic diseases [3]. Therefore, it emphasizes the importance of epidemiological studies focusing on the associations of genetic characteristics and nutrition – the most common environmental factors related to disease that would help better understanding the health and disease etiology.

Author Contributions

Conceptualization: Choi JH; Data curation: Choi JH, Benish; Formal analysis: Benish; Funding acquisition: Choi JH; Supervision: Choi JH; Visualization: Benish; Writing - original draft: Benish; Writing - review & editing: Choi JH, Benish.

The individual's sense of taste could play a crucial role in detecting the nature and quality of food and related health conditions [4,5]. One of the significant sensory elements is the ability to sense bitterness [6-8]. Bitter taste sensitivity is a trait that could serve as a marker for differential food preferences [9]. Individuals exhibit differential bitter taste sensitivity, influencing their food preferences and body composition. Research also confirms that many bitter compounds are medicinal in nature such as those found in cruciferous vegetables [10]. Therefore, individuals who perceive bitter compounds differently may end up with different dietary habits that could lead to adverse metabolic and health effects [11]. Thus, bitterness sensitivity and the genetics behind it are an exciting area of research, and the most extensively studied bitterness receptor gene taste 2 receptor member 38 (*TAS2R38,* T2R38) mediates the mechanism of bitter taste perception [6,12].

The genetic variation of the bitter taste receptor gene *TAS2R38* has been associated with an individuals' differential sensitivity to bitter taste and food intake. Hence, these genetic variants could modify the risk for diet-related diseases and become a potential biomarker for disease conditions. It is known that the consumption of vegetables, fruits, cereals, mushrooms, wildflowers, and medicinal plants could serve as a protective factor against several chronic diseases [13]. A healthy diet also benefits vascular condition by affecting risk markers such as blood pressure and blood lipid profiles. The genetic variants of *TAS2R38* leading to differential taste sensitivity could play as a decisive marker of disease, including obesity and metabolic disorder. A number of previous studies showed associations of the intake of vegetables with 6-n-propylthiouracil (PROP) bitterness and *TAS2R38* genotype [14-16]. In a Korean study, food group-based consumption analyses suggested that fruit intake and body mass index (BMI) were significantly associated with *TAS2R38* rs10246939 [17]. In addition, the *TAS2R38* genetic variation has also been linked to the perception of fat [18]. A study in a group of Iraqi individuals also reported that in phenylthiocarbamide (PTC) non-taster male's higher intake of salts lead to higher blood pressure [19]. Although limited association was evident, *TAS2R38* genetic variants were tested and their effects on the determinants of coronary heart disease were studied in a British cohort [20]. These may indicate that through dietary behavior, *TAS2R38* genetic variants could become a potential reason for the variability in health status. Thus, the variants appear to contribute to dietary consumption, body weight, and related metabolic phenotypes even though there were ethnicity-based differences in relevant research. However, little is known about its association with daily nutritional intake, which should be explored to study the effect of this genotype on the intake of essential nutrients to explore further the metabolic pathways related to diet.

Therefore, to further explore the effect of *TAS2R38* rs10246939 A > G as a prediction marker for the risk of disease through dietary consumption, this study aimed to analyze its associations with daily dietary nutritional intake in a Korean population. Furthermore, the association between the genetic variation and markers for blood pressure, glucose, and lipid profile were also examined.

MATERIALS AND METHODS

Study population

The present study was performed with dataset from Multi Rural Communities Cohort (MRCohort) study, which is a section of Korean Genome and Epidemiology Study (KoGES). KoGES was initiated by the Korean government funding: National Research Institute of

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Health, Centers for Disease Control and Prevention (KCDC) and the Ministry of Health and Welfare, Korea [21]. All data regarding epidemiology, clinic, diet, and genetics were obtained from the organization (KCDC). The subjects were mainly recruited from rural areas of the country using multistage cluster technique in certain villages of selected areas including Namwon, Yangpyeong, Goryeong, Wonju, Pyeongchang, and Ganghwa from January 2005–February 2010. From the MRCohort dataset with the genetic information of *TAS2R38* rs10246939 genotype (n = 3,666), the subjects were excluded: if they were having missing genetic data for target locus (n = 9); and were already diagnosed with hypertension (n = 46), hyperlipidemia (n = 6), or diabetes mellitus (n = 22). Additionally, those individuals who lacked records from lifestyle characteristics smoking (n = 2), alcohol drinking (n = 3), marital status (n = 18), education (n = 5), exercise (n = 36), and height (n = 8), as well as individuals with an implausible total energy intake < 500 or > 5,000 kcal/day (n = 9) were also excluded. Finally, a total of 3,502 participants (1,311 males and 2,191 females) aged from 40 to 89 years were analyzed in the study (**Figure 1**). The study protocol of MRCohort was approved by three Institutional Review Boards (IRBs; Hanyang University, Chonnam National University, and Keimyung University). Before the commencement of the study, all participants provided with written informed consent. Ethical approval for this study was also obtained after evaluation by the IRB (40525-201802-HR-121-07).

Descriptive data of the study subjects

Data on descriptive and lifestyle characteristics, including age, sex, smoking, alcohol drinking, education and regular exercise, were collected by trained investigators using questionnaires. Both tobacco use and alcohol consumption status was defined as never, past, or current. The BMI was calculated by dividing the body weight (kg) by the squared height (m^2). The educational levels were defined as elementary graduate (≤ 6 years), high school graduate (7–12 years), and college-level education or higher (> 12 years). Regular exercise was also defined as "Yes," when they exercised ≥ 3 times per week for about half an hour or more [22].

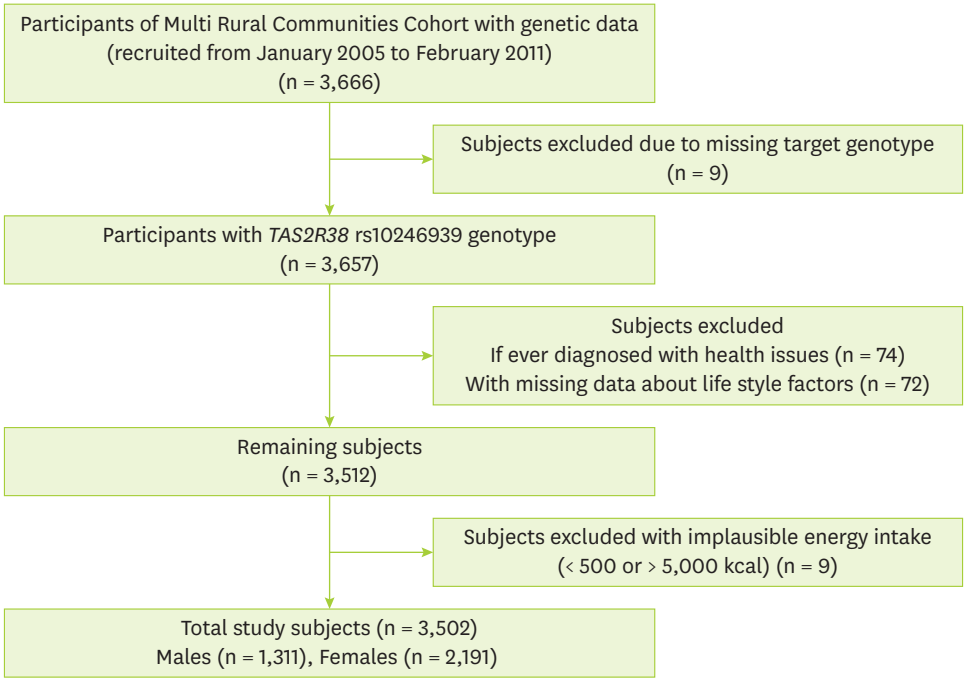

Figure 1. Subject selection process in the present study.

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Dietary intake data collection

The dietary data were collected using a validated food frequency questionnaire [23]. The trained technicians interviewed the participants. To analyze the influence of *TAS2R38* rs10246939 variant on nutritional intake, nutritional data including daily intake of energy, fat, proteins, carbohydrates as well as micronutrients (minerals and vitamins) were estimated established by using the nutrient database of the Korean Nutrition Society, and the Korean Food Consumption Table (7th edition) [24].

Assessment of blood biochemical profile

The standardized protocols were followed to measure biochemical markers [25,26]. The blood pressure markers including the systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate (times/minute) were measured with a standard mercury sphygmomanometer (Baumanometer; WA Baum Co., Inc., Copiague, NY, USA) using the first and fifth Korotkoff sounds, to the nearest 2 mmHg [25]. The average value of the last two measurements was considered. For blood analysis, the blood samples were collected in the morning from the antecubital vein. The lipid profile parameters including total cholesterol, triglycerides, high-density lipoprotein, and fasting glucose were measured enzymatically using a 747 Chemistry Analyzer (Hitachi, Tokyo, Japan) [25,26].

Genotyping

Genotyping data was conducted and obtained from KCDC, as described above. Genomic DNA from fasting peripheral blood samples was used genotype determination. Illumina Omni 1 Quad bead microarray (Illumina Inc., San Diego, CA, USA) was used to genotype as instructed by manufacturer. To ensure the quality of the genotyping data, samples with low call rate (< 99%), had excessive heterozygosity, or sex inconsistency and cryptic first-degree relatives were excluded from subsequent analyses. Furthermore, as an additional step to ensure the quality of the genotyping data, single nucleotide polymorphisms (SNPs) that exhibited high missing genotype call rates (> 5%), low minor allele frequency (MAF) (< 0.01), and significant deviation from Hardy-Weinberg equilibrium ($P < 10^{-6}$) were excluded from the analysis [27-29]. Finally, among obtained approximately 730,000 SNPs, *TAS2R38* rs10246939 variant genotype was analyzed for this study.

Statistical analyses

The influence of bitterness genotype on dietary intake and associated factors could vary with sex [17,30-33]. Therefore, sex-stratified analysis was conducted in the current study. The categorical variables were reported as frequencies and percentages, while continuous variables were reported as means ± standard deviation. Prior to analysis, the continuous variables such as age, BMI, nutrients, and biochemical variables were changed to the logarithmic form. Using residual method, the nutritional intake data was adjusted for total energy intake [34]. The association of *TAS2R38* rs10246939 genotypes with general characteristics including age, BMI, education, alcohol drinking, smoking status, and regular exercise was analyzed using general linear model (GLM) and chi-squared tests. The GLM was also used to evaluate the effect of genotype on all continuous variables including nutrients intake and blood parameters, either presence (adjusted) or absence (crude) of covariates. *Post hoc* tests were performed to verify the differences between pair of genotypes following Tukey's honest significant difference rule. A p value < 0.05 was considered statistically significant. Statistical analyses were conducted using SAS version 9.3 (SAS institute Inc., Cary, NC, USA) and SPSS version 22 (SPSS Inc., IBM Corp., Armonk, NY, USA).

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RESULTS

General characteristics and TAS2R38 genotype distribution

The general characteristics of the study population and genetic distribution of *TAS2R38* rs10246939 are presented in **Table 1**. A total of 3,502 individuals (37.4% males and 62.5% females) were selected for study. The subject's ages ranged from 40 to 89 years. In males, 36.3, 48.7, and 15.0% of subjects had the GG, AG, and AA genotypes, respectively, while in females, 33.4, 48.4, and 18.2% of the subjects possessed the GG, AG, and AA genotypes, respectively. The overall MAF was 0.412, which was similar to earlier reports [12,17]. The subjects' general characteristics showed that tobacco use (p = 0.027) and BMI (p = 0.003) were associated with genotype in females only.

Dietary nutritional intake in association with *TAS2R38* rs10246939

The daily nutritional intake levels for each *TAS2R38* rs10246939 genotype in males and females are shown in **Tables 2**, **3**, and **4**. It was evident that the consumption of macronutrients was not associated with the genotype as shown in **Table 2**. However, the effect of genotype on daily intake of micronutrients varied with sex. In males, the daily intake of vitamins and minerals was not significantly associated with the genetic variant (**Table 3**). On the other hand, females show significant associations of *TAS2R38* rs10246939 with few minerals and vitamins intake (**Table 4**). In females, the *TAS2R38* rs10246939 genotype was associated with the daily intake of calcium (adjusted p = 0.007), phosphorous (adjusted p = 0.016), potassium (adjusted p = 0.022), vitamin C (adjusted p = 0.009), and vitamin E (adjusted p = 0.005). Following *post hoc* tests, the GG genotype had significant effects on intake of nutrients. The GG genotype had the higher level of daily nutritional intake of calcium, phosphorus, potassium, and vitamin E than females with the AG genotypes, and also had more vitamin C, compared to AG and AA genotypes.

Table 1. General characteristics of the subjects in association with the *TAS2R38* rs10246939 genotype

Variables	Males				Females			
	GG (n = 476, 36.3%)	AG (n = 638, 48.7%)	AA (n = 197, 15.0%)	p	GG (n = 731, 33.4%)	AG (n = 1,061, 48.4%)	AA (n = 399, 18.2%)	p
Age (yr)	60.85 (10.1)	61.59 (10.0)	61.42 (8.7)	0.613	58.68 (9.7)	59.23 (10.0)	58.03 (10.0)	0.110
BMI (kg/m^2)	23.41 (2.9)	23.48 (2.9)	23.56 (2.9)	0.819	23.81 (2.9)	23.89 (3.1)	24.47 (3.2)	0.003
Tobacco smoking				0.057				0.027
Never	122 (25.6)	138 (21.6)	34 (17.3)		702 (96.0)	1,003 (94.5)	376 (94.2)	
Past	178 (37.4)	231 (36.2)	87 (44.2)		10 (1.4)	23 (2.2)	2 (0.5)	
Current	176 (37.0)	269 (42.2)	76 (38.6)		19 (2.6)	35 (3.3)	21 (5.3)	
Alcohol drinking				0.854				0.323
Never	128 (26.9)	159 (24.9)	46 (23.4)		449 (61.4)	701 (66.1)	259 (64.9)	
Past	49 (10.3)	68 (10.7)	19 (9.6)		20 (2.7)	21 (2.0)	10 (2.5)	
Current	299 (62.8)	411 (64.4)	132 (67.0)		262 (35.8)	339 (32.0)	130 (32.6)	
Education level				0.222				0.176
Elementary school or less	241 (50.6)	346 (54.2)	100 (50.8)		523 (71.5)	723 (68.1)	280 (70.2)	
Middle-high school	188 (39.5)	238 (37.3)	70 (35.5)		174 (23.8)	300 (28.3)	99 (24.8)	
College /more	47 (9.9)	54 (8.5)	27 (13.7)		34 (4.7)	38 (3.6)	20 (5.0)	
Regular exercise				0.624				0.623
No	346 (72.7)	480 (75.2)	147 (74.6)		533 (72.9)	789 (74.4)	301 (75.4)	
Yes	130 (27.3)	158 (24.8)	50 (25.4)		198 (27.1)	272 (25.6)	98 (24.6)	

Values represent the means ± standard deviations for age, BMI; otherwise, the data present numbers of subjects and percentages are in parentheses. The p values are calculated from the χ^2 tests among three genotypes except for age and BMI. The p values for age and BMI are from the general linear model among the three genotypes.
BMI, body mass index.

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Table 2. Intake levels of energy and macronutrients in the subjects according to the *TAS2R38* rs10246939 genotype

Variables	GG	AG	AA	p_{crude}	$p_{adjusted}$
Males	n = 476	n = 638	n = 197		
Total energy (kcal/day)	1,586.8 ± 474.2	1,571.4 ± 481.1	1,601.2 ± 521.3	0.758	0.702
Carbohydrates (g/day)	301.2 ± 26.3	300.3 ± 25.6	302.8 ± 23.1	0.454	0.452
Proteins (g/day)	48.4 ± 10.2	47.7 ± 9.9	47.6 ± 8.9	0.536	0.517
Fats (g/day)	19.3 ± 8.8	19.7 ± 9.8	18.7 ± 8.3	0.708	0.668
Females	n = 731	n = 1,061	n = 399		
Total energy (kcal/day)	1,608.6 ± 517.6	1,596.2 ± 476.0	1,656.7 ± 506.0	0.110	0.098
Carbohydrates (g/day)	302.1 ± 27.1	302.7 ± 26.6	302.6 ± 26.7	0.906	0.879
Proteins (g/day)	48.2 ± 9.8	47.4 ± 9.4	48.5 ± 10.1	0.090	0.138
Fats (g/day)	19.6 ± 9.8	18.9 ± 9.3	19.4 ± 8.8	0.179	0.230

Values represent the means ± standard deviations. The nutrients are adjusted for total energy intake with the residual method.
p_{crude} was calculated from the crude general linear model among the three genotypes.
$p_{adjusted}$ were estimated from the general linear model adjusted for age, body mass index, education level, alcohol consumption, tobacco use, regular exercise, and total energy intake, as appropriate.

Table 3. Intake levels of selected micronutrients in the male subjects according to the *TAS2R38* rs10246939 genotype

Variables	GG (n = 476)	AG (n = 638)	AA (n = 197)	p_{crude}	$p_{adjusted}$
Minerals					
Calcium (mg)	371.2 ± 193.6	360.3 ± 177.9	363.6 ± 162.3	0.757	0.788
Phosphorus (mg)	772.0 ± 168.1	759.9 ± 160.0	765.2 ± 150.0	0.491	0.489
Iron (mg)	7.8 ± 3.1	7.6 ± 2.3	7.6 ± 2.0	0.801	0.823
Potassium (mg)	1,902.0 ± 701.4	1,868.2 ± 648.2	1,916.3 ± 599.2	0.432	0.465
Sodium (mg)	2,583.5 ± 1,474.5	2,476.7 ± 1,330.8	2,555.7 ± 1,173.6	0.489	0.517
Zinc (mg)	6.4 ± 1.2	6.4 ± 1.4	6.4 ± 1.4	0.780	0.800
Vitamins					
Vitamin A (mg)	380.1 ± 279.7	354.1 ± 252.0	348.1 ± 203.6	0.431	0.488
Vitamin B1 (mg)	0.8 ± 0.1	0.8 ± 0.2	0.8 ± 0.1	0.785	0.799
Vitamin B2 (mg)	0.7 ± 0.2	0.7 ± 0.2	0.6 ± 0.2	0.720	0.713
Niacin (mg)	11.7 ± 2.7	11.5 ± 2.6	11.7 ± 2.6	0.450	0.458
Vitamin C (mg)	89.2 ± 52.0	85.9 ± 48.0	88.2 ± 42.7	0.256	0.286
Vitamin B6 (mg)	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.2	0.567	0.593
Folic acid (ug)	179.9 ± 86.3	176.6 ± 78.4	175.3 ± 60.8	0.778	0.816
Vitamin E (mg)	6.4 ± 2.4	6.2 ± 2.2	6.2 ± 2.1	0.433	0.425

Values represent the means ± standard deviations. The nutrients are adjusted for total energy intake with the residual method.
p_{crude} was calculated from the crude general linear model among the three genotypes.
$p_{adjusted}$ were estimated from the general linear model adjusted for age, body mass index, education level, alcohol consumption, tobacco use, regular exercise, and total energy intake.
The superscripts denote the differential level of consumption among the genotypes as determined by Tukey's honest significant difference tests.

Blood biochemical markers with *TAS2R38* rs10246939

To ascertain the association between *TAS2R38* rs10246939 and bio-clinical markers including blood pressure markers, glucose levels, and lipid parameters, sex stratified analysis was performed. The results revealed that the multiple blood pressure markers, including (SBP, DBP, and pulse rate) (**Table 5**), as well as the blood glucose levels and lipid parameters (total cholesterol, triglycerides, and high-density lipoproteins) (**Table 6**) were not significantly associated with the genotype under study.

DISCUSSION

The present study investigated the association of the genetic variant in the *TAS2R38* bitterness receptor (rs10246939 A > G) with daily nutritional intake and biochemical parameters in the Korean population. The findings suggested that the Korean female's dietary intake of few micronutrients is influenced by this genotype. However, there is no evidence for its association with bio-clinical markers in both genders.

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Table 4. Intake levels of selected micronutrients in the female subjects according to the *TAS2R38* rs10246939 genotype

Variables	GG (n = 731)	AG (n = 1,061)	AA (n = 399)	p_{crude}	$p_{adjusted}$
Minerals					
Calcium (mg)	364.4 ± 177.5[a]	340.1 ± 168.8[b]	359.0 ± 177.0[ab]	0.005	0.007
Phosphorus (mg)	767.7 ± 157.6[a]	748.4 ± 151.0[b]	769.8 ± 164.6[ab]	0.011	0.016
Iron (mg)	7.7 ± 2.4	7.4 ± 2.2	7.6 ± 2.4	0.150	0.184
Potassium (mg)	1,906.7 ± 684.8[a]	1,817.9 ± 658.0[b]	1,856.2 ± 643.7[ab]	0.019	0.022
Sodium (mg)	2,513.0 ± 1,354.9	2,396.8 ± 1,205.4	2,460.3 ± 1,238.4	0.336	0.370
Zinc (mg)	6.4 ± 1.2	6.4 ± 1.7	6.6 ± 2.0	0.112	0.203
Vitamins					
Vitamin A (mg)	358.1 ± 247.2	339.0 ± 232.3	349.3 ± 243.8	0.273	0.322
Vitamin B1 (mg)	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.1	0.444	0.412
Vitamin B2 (mg)	0.7 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	0.103	0.126
Niacin (mg)	11.7 ± 2.5	11.5 ± 2.5	11.8 ± 2.6	0.071	0.100
Vitamin C (mg)	89.8 ± 50.8[a]	84.4 ± 50.4[b]	81.5 ± 45.9[b]	0.009	0.009
Vitamin B6 (mg)	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.2	0.168	0.159
Folic acid (ug)	179.2 ± 79.7	171.8 ± 76.3	169.4 ± 70.8	0.081	0.082
Vitamin E (mg)	6.4 ± 2.4[a]	6.1 ± 2.3[b]	6.1 ± 2.1[ab]	0.005	0.005

Values represent the means ± standard deviations. The nutrients are adjusted for total energy intake with the residual method.
p_{crude} was calculated from the crude general linear model among the three genotypes.
$p_{adjusted}$ were estimated from the general linear model adjusted for age, body mass index, education level, alcohol consumption, tobacco use, regular exercise, and total energy intake.
The superscripts denote the differential level of consumption among the genotypes as determined by Tukey's honest significant difference tests.

Table 5. Blood pressure markers of the male and female subjects according to the *TAS2R38* rs10246939 genotypes

Variables	GG	AG	AA	p_{crude}	$p_{adjusted}$
Males	n = 476	n = 638	n = 197		
Pulse rate (times/min)	68.5 ± 9.2	69.0 ± 9.7	66.9 ± 9.1	0.086	0.093
SBP (mmHg)	117.5 ± 11.0	118.7 ± 10.6	118.7 ± 10.0	0.274	0.380
DBP (mmHg)	76.8 ± 7.6	76.7 ± 7.3	77.0 ± 7.6	0.961	0.998
Females	n = 731	n = 1,061	n = 399		
Pulse rate (times/min)	68.6 ± 9.1	68.8 ± 9.1	69.7 ± 8.8	0.176	0.150
SBP (mmHg)	115.2 ± 11.9	114.1 ± 11.8	115.7 ± 10.9	0.089	0.113
DBP (mmHg)	74.3 ± 7.4	74.3 ± 7.2	74.6 ± 7.5	0.882	0.984

SBP, systolic blood pressure; DBP, diastolic blood pressure.
Values represent the means ± standard deviations.
p_{crude} was calculated from the crude general linear model among the three genotypes.
$p_{adjusted}$ were estimated from the general linear model adjusted for age, body mass index, education level, alcohol consumption, tobacco use, regular exercise, and total energy intake.

Table 6. Blood glucose and lipid parameters of the male and female subjects according to the *TAS2R38* rs10246939 genotype

Variables (mg/dL)	GG	AG	AA	p_{crude}	$p_{adjusted}$
Males	n = 476	n = 638	n = 197		
Total cholesterol	185.8 ± 33.1	189.9 ± 34.7	189.0 ± 35.1	0.165	0.171
Triglycerides	140.4 ± 91.5	146.8 ± 101.9	146.9 ± 96.7	0.456	0.540
High density lipoproteins	43.3 ± 10.7	44.3 ± 11.5	45.1 ± 13.0	0.223	0.141
Blood glucose	95.0 ± 9.5	95.8 ± 9.9	94.8 ± 9.6	0.283	0.286
Females	n = 731	n = 1,061	n = 399		
Total cholesterol	200.7 ± 35.5	200.3 ± 36.2	201.6 ± 34.9	0.755	0.721
Triglycerides	141.6 ± 76.3	143.4 ± 87.5	143.9 ± 82.4	0.779	0.739
High density lipoproteins	46.4 ± 10.7	46.4 ± 10.5	45.5 ± 9.6	0.384	0.593
Blood glucose	92.9 ± 8.8	93.1 ± 9.3	92.9 ± 9.9	0.806	0.621

Values represent the means ± standard deviations.
p_{crude} was calculated from the crude general linear model among the three genotypes.
$p_{adjusted}$ were estimated from the general linear model adjusted for age, body mass index, education level, alcohol consumption, tobacco use, regular exercise and total energy intake.

From the analyses between the *TAS2R38* rs10246939 genetic variation and study population's general characteristics, the results suggest that the lifestyle factors, including age, alcohol consumption, behavior, education, and regular exercise were not associated with the distribution of the variation. However, the distribution of the *TAS2R38* genotype was

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associated with BMI and smoking behavior, which is consistent with earlier studies [17,35]. There has been considerable interest in the association between the bitterness variations and markers of adiposity. The potential regulatory role of T2R38 in sensory and appetite mechanism, and furthermore with metabolism in energy balance and adiposity-related digestive system, may be linked to the association between the bitterness genetic variation and BMI [8,17,18,36,37]. The genetic variation was also associated with females' smoking behavior. Earlier studies showed that the *TAS2R38* genetic variation is associated with tobacco smoking. The differential bitterness perception could be a modifying role in the use of substance such as tobacco [38]. However, in this study, the genetic effect was only evident in females' smoking. Self-reported data could underestimate smoking status and should be considered while interpreting the results. In this study, only approximately 5%–6% of females were ever-smoker, which was similar to the WHO 2017 report [39]. The underreporting issue in females for tobacco use has been widely spread due to multiple reasons, including social pressure [40]. Therefore, this rarity may underlie in this gene-health behavior association.

Inconsistencies based on ethnic-specific differences in taste responses and perception that contribute to the development of different dietary preferences were reported. One Korean cancer case-control study reported that there were no clear relationship between the *TAS2R38* genetic variation and macronutrients and dietary consumption [41]. The use of strongly flavored condiments in Korean cuisine may potentially mask the bitter taste of foods, hence, making it difficult to study the associations between *TAS2R38* and dietary nutrients consumption [41,42]. Other studies from various ethnicities including African-American, Hispanic, Latino, Caucasian, and Asian also supported the null effect of *TAS2R38* genetic variation on dietary intake [31,43,44]. However, several studies still reported the association of polymorphism in *TAS2R38* causing alterations in bitterness perception leading to differential dietary intake. The association between PROP bitterness, *TAS2R38* genotype, and vegetable intake has been consistent in the number of earlier studies [14-16]. The *TAS2R38* genetic variation has also been associated with the perception of fat [18], dietary intake of total vegetables, cruciferous vegetables, sweets, tobacco, and alcohol, which may in turn could affect micronutrient intake [8,17,36,37]. The present study shows the evidence that the bitterness genotype is associated with differential nutrients intake. An earlier study did not support the influence of *TAS2R38* diplotypes on dietary intake of micronutrients (vitamin C), but it highlighted the possible nutrient-nutrient effect on bioavailability of nutrients [45]. Vegetables and fruits contain major nutrients such as carbohydrates, proteins, lipids, vitamins, and minerals. They also possess some crucial phytonutrients which are mostly bitter in taste, including polyphenols, flavonoids, isoflavones, terpenes, and glucosinolates [7]. The consumption of these nutrients could potentially lower the risk of chronic diseases such as cancer and cardiovascular disease [46]. Fruits do not contain bitter compounds called glucosinolates, but they are a rich source of many essential nutrients such as potassium, vitamins E and C, folate, and dietary fiber. Furthermore, vitamin E is fat-soluble, essential micronutrient, and an exogenous antioxidant. The most prominent sources of vitamin E are edible vegetable oils, such as those of corn, olive, palm, rice bran, and peanut [47]. Thus, the genotype could be associated with fat-soluble nutrients consumption [48].

In addition to ethnicity-based variations, the sex was found to be correlated with the genetic effect on dietary behavior. Earlier, among Japanese females the PTC/PROP-nontaster *TAS2R38* genotype/haplotype was found to be correlated with height and weight leading to higher daily energy consumption [32]. A previous Korean study utilizing the MRCohort reported that the genetic variant *TAS2R38* rs10246939 showed moderate association with Korean females' total

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fruit intake [17]. In line with this, present study also shows the evidence that the bitterness genotype is associated with differential nutrients intake in females. In current study, although the findings of our study showed little correlation with nutritional intake, but in line with previous Korean study, sex-genotype association was clear. This may be resulted from the differential health behavior of males and females. According to various reports, females tend to exhibit a greater level of concern regarding their dietary habits in comparison to males. Females possess a more thorough understanding of issues related to food, nutrition, and diet [49-51], which leads to higher intake of fruits, vegetables, dietary fibre and lower intake of fats and salts [52]. It is also a well-established fact that behaviours associated with unhealthy dietary habits, such as smoking and alcohol use, tend to be more prevalent among males than females. Therefore, this differential nature of sex-disparity about health may lead to varied health behaviors and outcome, interacting with the genetic factor including *TAS2R38*. Moreover, this may also suggest that to study the potential role of the bitterness gene as a predictive marker of the underlying mechanisms that contribute to the development of obesity, it is crucial to take into account the influence of sex as a contributing factor. Further research should be conducted based on sex differences in individuals to have more comprehensive understanding of the role of the *TAS2R38* gene in health and disease etiology in both males and females.

Limited evidences only exist surrounding bitterness genetic variation and saltiness and sodium intake [45-48]. However, a study with young Japanese females suggested that the genetic variation in *TAS2R38* contributed to increased sodium intake [48]. A study with small number of Iraqi males investigated the PTC phenotype and blood pressure marker. They reported that most non-tasters had high blood pressure and higher intake of salty foods [19]. It has been well-known that consuming excessive sodium is a major risk factor for hypertension [53,54]. In line with this, the current study examined the effect of the bitterness genotype on dietary sodium intake and blood pressure markers (SBP, DBP, and pulse rate), yet we did not find clear evidence. In Korea, Kimchi is one of the most consumed side dishes. A recent report revealed that it is one of the most significant contributors to salt intake among Koreans and is mainly prepared from cabbage (cruciferous vegetables) [55]. Therefore, it may be possible that the *TAS2R38* genetic variation may be associated with salt intake and further blood pressure markers by the differential cruciferous vegetable's consumption. However, this was not evident in the current study. One interesting Korean study suggested that the cluster of differentiation 36 fat sensory related gene was associated with cruciferous vegetable intake, but not *TAS2R38* bitterness receptor [56]. The use of various condiments and higher overall sodium consumption level is common in this Korean population [57,58]. Thus, it is possible that the SNP is not associated with significant sources of dietary sodium, sodium intake itself, and blood pressure biomarkers. Additionally, the hypertensive individuals were excluded from the data set under study. Thus, the effect of *TAS2R38* genetic variation may not be clearly observed in the subjects.

To date, only a few studies have investigated the relationship between *TAS2R38* genetic variations and metabolic phenotypes. The findings in the Sorbs cohort provided evidence for the association of biochemical variables and the *TAS2R38* genotype: 30-minute plasma glucose and the area under the curve for plasma glucose and *TAS2R38* genotype in men [37]. The increased plasma leptin levels in Amish females also showed significant associations with the "PROP insensitive" allele of rs1726866 *TAS2R38* [33]. The altered glucose and insulin homeostasis were associated with *TAS2R* haplotype, which links alimentary chemosensation and metabolic disease [59]. According to a previous report, the risk of dyslipidemia in Korean

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men was 45.6% and 31.3% for women. Moreover, there is a drastic rise in the prevalence of dyslipidemia in the elderly population [60,61]. However, the effect of the *TAS2R38* genetic variation has not yet been explored in the Korean population and our study did not report such evidence for the measured level of plasma glucose. The lipid profile parameters, particularly total cholesterol, triglycerides, and high-density lipoproteins were also examined in present study. However, the results did not confirm a decisive association with *TAS2R38* rs10246939 genotype. A large population-based sample of British women provided evidence that the *TAS2R38* status was not an important determinant of bio-clinical markers analyzed [20]. Similarly, the findings of an earlier study about the polymorphism rs713598 of the *TAS2R38* gene reported no association with a wide range of biochemical parameters in Italian adults [18]. An American breast cancer–control study also reported no evidence for a significant association between PROP responsiveness and plasma lipids in females [62]. As described previously, the genetic variation in bitterness receptor gene *TAS2R38* could modify the dietary behavior, intake, and, hence, nutritional intake and lipid parameters. However, such genotypic effect on taste perception, food preference, and consumption could be modified by multiple other biological and milieu factors [63,64]. This requires further studies for better understanding of the role of taste genetics in human health and disease.

The current study has several limitations. First, the study population (n = 3,502) did not represent the entire Korean population. Although data was from the MRCohort, one of the largest epidemiological study cohorts in Korea, participants are mainly from rural areas. Additionally, only a single locus *TAS2R38* rs10246939 was studied, although three SNP are known to show strong association [17]. Daily nutrient intake was collected using food frequency questionnaire assessment method, which involves the use of closed-ended questionnaires that could affect the precision of dietary data [65]. It is also important to note that there was no information on medications used, which may have potentially affected taste perception and bio-clinical markers.

In conclusion, this study suggests that the *TAS2R38* rs10246939 genetic variation could influence the dietary nutritional intake in a Korean female population. Although the study provided no evidence that *TAS2R38* polymorphism had a measurable influence on biochemical markers, the findings emphasize the possible associations of a genetic variant of bitter taste receptor gene through eating behavior that could become a potential reason for the variability in dietary intake and human health and disease.

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