Interaction between a refined carbohydrate dietary pattern and genetic risk score for obesity in the Korean population

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Data availability: Eligible researchers may access the datasets used and analysed for this study at https://www.nih.go.kr/ko/main/contents.do?menuNo=300563 (Korean) after receiving permission from the Korea Disease Control and Prevention Agency. Further details in English are available at https://www.nih.go.kr/eng/main/main.do.

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Abstract

Objective*:* Genetic predisposition to obesity can stimulate an increase in adiposity throughout adulthood. However, the interaction between genetic factors and dietary habits may modify the genetic association with obesity. Thus, this study aimed to investigate the dietary patterns that influence the genetic risk of obesity in a Korean population using a large cohort study and genome-wide association study.

Design: Prospective cohort study.

Setting: The genetic risk score (GRS) was calculated based on six identified single nucleotide polymorphisms of the *OTOL1*, *NMBR*, *DNAJB9*, *ASCC1*, *NT5C2*, and *FTO* genes associated with obesity, as ascertained by body mass index. Dietary patterns were determined using food intake data from a food frequency questionnaire and factor analysis.

Participants: This study included data from 8,458 adults aged 40-69 years from the Ansan and Ansung cohorts of the Korean Genome and Epidemiology Study.

Results*:* The refined carbohydrate dietary pattern showed a significant inverse association with obesity in the highest GRS group with a non-significant interactive association (odds ratio [OR], 0.801; 95% confidence interval [CI], 0.662—0.969; *P* for trend = 0.0251, *P* for interaction = 0.571). However, participants with the highest refined carbohydrate dietary pattern score and highest GRS had an increased prevalence of obesity (OR: 1.288, 95% CI: 1.068–1.554, *P* for trend = 0.0251) compared with the prevalence of those with the lowest dietary pattern score and GRS.

Conclusions: Reducing refined carbohydrate consumption may be helpful for Korean adults with a greater genetic susceptibility to obesity.

Keywords: Genetic risk factor, obesity, dietary pattern, refined carbohydrates

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Introduction

Obesity is a global health concern, with a third of the world's population being overweight or obese. The current prevalence of obesity is two-fold compared with that recorded in 1980.[1] Obesity is associated with chronic metabolic diseases, including cardiovascular diseases, diabetes, fatty liver disease, and several cancers,[2] leading causes of mortality globally. The aetiology of obesity is multifactorial,[3] and several metabolic pathways contribute to obesity. Moreover, numerous genetic variants have been linked to obesity.[4] Genetic predispositions to obesity can stimulate increased adiposity throughout adulthood.[5] However, increasing evidence suggests that the interaction between genetic factors and healthy dietary habits may modify the genetic association with obesity.[6]

Several epidemiological studies have revealed an attenuated genetic association with obesity by consuming healthy diets, including fruits, vegetables, and whole grains. A study of two large cohorts in the United States (US) showed that increasing fruit and vegetable intake can mitigate body mass index (BMI) and body weight increases among individuals with a greater genetic susceptibility to obesity.[7] A plant-based dietary pattern was associated with low adiposity and reduced risk of high blood pressure and stroke among individuals with a genetically higher risk of obesity in a large cohort study from the United Kingdom (UK).[8]

In contrast, unhealthy eating habits, such as high fat or sugar consumption, increase the genetic association with obesity. The intake of total and saturated fats had a stronger positive association with BMI in individuals with a higher genetic risk score (GRS) for obesity than in those with a lower GRS.[9] In particular, interactions between GRS and poor fat quality were shown to influence obesity and metabolic syndrome.[10,11] Moreover, the genetic association with BMI was elevated in individuals with a high intake of sugar-sweetened beverages. The relative risks for incident obesity per increment of 10 risk alleles were more than three-fold higher in the highest consumption group than in the lowest intake group.[12] These findings underscore the need to evaluate how different dietary patterns interact with genetic predisposition.

Several studies have investigated the effect of dietary intake on the genetic association with obesity in the Korean population. Variants of *COBLL1*, a gene related to weight maintenance and appetite, was associated with fat intake and BMI and incidence of obesity in a prospective cohort of the Korean population.[13] However, it has been suggested that modifying environmental factors such as diet may exert a stronger impact on obesity than

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genetic variants.[14,15] Therefore, exploring the interaction of dietary factors and genes with a genome-wide predisposition to obesity is important.

The GRS is a useful measurement that improves the predictive value of a genetic variant by simultaneously combining multiple loci.[16] The relationship between the obesity-related genetic (polygenic) risk score and calorie intake has been investigated in a previous study that employed three large Korean cohorts, revealing no significant interaction.[17] Meanwhile, the interactive association between healthy dietary patterns and BMI-GRS was non-significant in a European cohort.[18] Food consumption patterns are widely used to capture the overall effects of complex dietary consumption rather than a single dietary intake,[19] and may be more effective in capturing a genetic association with obesity. However, whether dietary patterns and the GRS interact to develop obesity in the Korean population remains unclear. Therefore, we explored the dietary patterns that influence the genetic risk of obesity in a Korean population using a large cohort study and a genome-wide association study (GWAS).

Methods

Study design and population

This study included participants from the Ansan and Ansung cohorts of the Korean Genome and Epidemiology Study (KoGES), a prospective study conducted by the Korea Disease Control and Prevention Agency between 2001 and 2002 to examine common chronic diseases among Koreans. The initial cohort consisted of 10,030 Korean adults aged 40–69 years. This study involved whole-genome single nucleotide polymorphism (SNP) genotyping to identify the genetic and environmental factors contributing to obesity-related diseases. The inclusion criterion was participation in the baseline Ansan and Ansung cohort. After applying specific exclusion criteria, the study sample was refined. The exclusion criteria were as follows: participants with missing dietary intake data (n = 697); participants with missing height and weight information (n = 4); participants with missing data on obesity measurements (e.g. waist, hip) (n = 12); participants with implausible total energy intakes (< 2,093 or > 20,930 kJ/day [500 or 5,000 kcal/day]), which is commonly applied criterion in large-scale nutritional epidemiology studies to remove physiologically unrealistic values,[20,21]; or a BMI > 50 kg/m² (n = 381); and those with incomplete genotype data (n = 478). This led to a final sample of 8,458 individuals; 52.5% were female, and 47.5% were male (Figure S1). The study was conducted in accordance with the Korean Genome and Epidemiology Study

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GWAS and GRS calculation

Genomic DNA was extracted from peripheral blood leukocytes collected from the participants in the Ansan and Ansung cohorts. Genotyping was conducted using the Affymetrix Genome-Wide Human SNP Array 5.0 (Affymetrix, Inc., Santa Clara, CA, USA). The whole-genome imputed data for the cohort were obtained from the Korea Disease Control and Prevention Agency. SNP markers were filtered based on call rate, minor allele frequency, and Hardy–Weinberg equilibrium, following the criteria from a previous study.[22] SNP imputation was performed using the IMPUTE software (version 1; University of Oxford, Oxford, UK),[23] referencing the NCBI build 35 and dbSNP build 126, with an initial reference set consisting of 90 individuals from the JPT and CHB populations in HapMap (release 22). SNPs with a minor allele frequency < 0.01 and missing rate > 0.05 were excluded. The SNP data from the Ansan and Ansung cohorts were then merged with 1.5 million imputed SNPs for association analysis with a chosen quantitative trait. A GWAS analysing the interaction between SNPs and BMI was performed using PLINK v1.90, employing a linear regression model adjusted for sex and age as covariates, analysing a total of 1,591,162 SNPs.[24] Significant SNPs were identified using a threshold of $-\log_{10}P$-value > 5. Linkage disequilibrium clumping and analysis were performed with PLINK, and Haploview v4.2 was used to visualise linkage disequilibrium blocks. The SNP positions and nomenclature were annotated according to the Ensembl release 54. The GRS for each participant was calculated using the six SNPs most strongly associated after clumping, following the model outlined below:

$$\mathrm{GRS} = \sum_{i=1}^{n} risk\ allele\ in\ SNP_i \times \beta_i$$

Participants were divided into three groups based on their GRS distributions. Beta values represent the effect size of each SNP with increasing BMI. Therefore, participants with a low GRS are associated with a lower risk of having a higher BMI, whereas those with a

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high GRS are associated with a higher risk. Accordingly, the low, medium, and high-genetic risk groups represent participants with low, intermediate, and high GRS levels, respectively (Table S3).

Covariates

General characteristics of the study population were collected using questionnaires and various anthropometric and clinical assessments, including height, weight, and BMI (calculated as weight in kilograms divided by height in meters squared [kg/m^2]). Demographic data were organised according to the two cities (Ansan and Ansung) and household income levels (categorised as monthly income in Korean won [KRW], where 1 million KRW is approximately 750 USD, into three brackets: < 1 million, 1–3 million, and > 3 million KRW). Although education level was also assessed, only household income was included in the multivariable models to avoid redundancy and potential multicollinearity between socioeconomic variables. In addition, drinking status (current, former, or never) and smoking status (current, former, or never) were each categorized into three groups. Daily physical activity duration was categorized into the following groups: none, < 30 min, 30–60 min, 60–90 min, 90 min to 2 h, 2–3 h, 3–4 h, 4–5 h, or > 5 h. Physical activity was quantified using metabolic equivalents (METs) following the International Physical Activity Questionnaire,[25] which categorised participants into three levels: “low,” “moderate,” and “high” physical activity.[26] Individuals classified as having “high activity” engaged in vigorous-intensity activities for at least thrice weekly, totalling at least 1,500 MET-min per week, or participated in a combination of various activities for ≥7 days per week, achieving at least 3,000 MET-min per week. The “moderate activity” category included those who met any of the following conditions: vigorous-intensity activity for at least 20 min per day on ≥3 days per week, moderate-intensity activity and/or walking for at least 30 min per day on ≥5 days per week, or a combination of walking, moderate, and vigorous activities on ≥5 days per week, totalling at least 600 MET-min per week. Those who did not meet any of these criteria were classified as “low activity.”

Dietary pattern analysis

Dietary intake was assessed using a semi-quantitative food frequency questionnaire that provided data on the average consumption frequencies and portion sizes of 103 food items.[27] Principal component analysis was employed to extract dietary factors, and varimax rotation was used to enhance interpretability. We retained dietary factors with eigenvalues of

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≥ 1.0 based on the Kaiser criterion, supported by scree-plot inspection and the interpretability of the extracted factors within our dataset. Four factors met these criteria, and we subsequently focused on components with substantial variance contributions and loadings of ≥ 0.3 (Table S1). Based on these criteria, we identified four distinct dietary patterns and named them according to the characteristic food groups they included (Figure 2). To examine the association between these dietary patterns and obesity, we divided the factor scores into tertiles (T1, T2, and T3). The nutrient intake levels representative of each dietary pattern were calculated based on these tertiles.

Statistical analysis

Statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA) with the threshold for statistical significance set at a *P*-value < 0.05. Categorical and continuous variables were compared using chi-squared tests and regression models, respectively. Multivariable-adjusted logistic regression and interaction analyses were used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) for obesity across the tertiles of each dietary factor and the three GRS groups, with adjustments for relevant covariates. Regression models were also used to assess *P*-values for trends.

Results

Basic characteristics of the study population

The basic characteristics of the study participants, categorised by GRS tertiles for obesity, are summarised in Table 1. The participants were divided into the following groups based on their GRS: T1 (lowest risk), T2 (moderate risk), and T3 (highest risk). Notable variations were observed in the demographic and lifestyle characteristics across these groups. The average age showed a decreasing trend from T1 to T3; however, this trend was non-significant ($P = 0.0620$). BMI showed a significant increase across the GRS tertiles, with the highest GRS group (T3) exhibiting a higher average BMI (25.06 ± 3.17 kg/m^2) than the lowest GRS group (T1, 24.17 ± 3.07 kg/m^2) ($P < 0.0001$), indicating a strong association between higher genetic risk for obesity and increased BMI. Household income distribution varied among the GRS groups but was non-significant ($P = 0.0943$). Drinking status, smoking status, and physical activity levels also showed similar proportions of current alcohol drinkers across the groups.

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GWAS of obesity

A GWAS was conducted to identify genetic loci associated with obesity using BMI as the phenotypic trait. A total of 1,590,162 SNPs were analysed across all chromosomes in the Ansan and Ansung cohorts. The number of SNPs varied across chromosomes, with the highest number identified in chromosome 2 (142,070 SNPs) and the lowest in chromosome 22 (17,942 SNPs). The average interval between SNPs across all chromosomes was approximately 1,856 base pairs (bp). Chromosome 19 had the largest average interval of 3,549 bp, whereas chromosome 6 had the smallest average interval of 1,422 bp. The total genomic distance covered by the SNPs was approximately 2.78 billion bp, with an average standard deviation of 20,801.7 bp for SNP intervals. These results provide a detailed landscape of SNP distribution across the human genome, enabling a comprehensive association analysis for obesity (Table S2).

The GWAS results were visualised using Manhattan plots to assess the distribution of the observed *P*-values against the expected values (Figure 1). Thirty-four SNPs showed significant associations with BMI, surpassing the threshold of $-\log_{10}P$-value > 5. After applying linkage disequilibrium clumping, six SNPs exhibited the most robust associations with BMI and the calculated GRS for each participant (Table 2). These SNPs are located on different chromosomes and are annotated with specific genes. The effect sizes (beta values) for these SNPs ranged from −0.327 to 0.423, indicating positive and negative effects on BMI. For example, rs1436740 in *OTOL1* demonstrated a beta value of 0.423 (95% CI: 0.238 to 0.608, *P* = 7.92E-06), suggesting a strong positive association with increased BMI. Conversely, rs17178527 in the *NMBR* gene exhibited a beta value of −0.327 (95% CI: −0.437 to −0.218, *P* = 5.05E-09), indicating a negative association with BMI. The results suggested that these genetic loci may play a role in regulating BMI and obesity. Several of these loci have also been previously associated with adiposity-related or metabolic traits, supporting the biological plausibility of their involvement in BMI regulation.

Dietary pattern analysis

Four major dietary patterns were identified from the factor analysis and named after foods or food groups with high factor-loading values (Table S1 and Figure 2). The “Vegetables and Kimchi” pattern was characterised by high consumption of fermented paste, sauces and seasonings, vegetables, and Kimchi. The “Eggs, fish, and dairy products” pattern was characterised by high consumption of eggs, fish and shellfish, and dairy products such as

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milk. The “Refined carbohydrate” pattern was typified by highly positive factor loadings for white rice and negative factor loadings for whole grains. The “Wheat flour, bread, and noodles” pattern was classified by high consumption of noodles, dumplings, wheat flour, bread, and sweets.

Interactive effects of dietary patterns and GRS on obesity prevalence

The ORs and 95% CIs for obesity prevalence across the interactions of the dietary pattern tertiles and GRS levels are summarised in Table 3 (Table S4). Obesity prevalence was assessed using dietary pattern tertiles, with the lowest tertile (T1) of each pattern at each GRS level serving as the reference. In the “Vegetables and Kimchi” pattern, participants in the GRS T2 group exhibited an increased OR for obesity compared with the OR of those in T1 in model 1 (*P* for trend = 0.0260). For the “Eggs, fish, and dairy products” pattern, participants in the GRS T2 group showed a marginal increase in obesity prevalence compared with the prevalence in T1 in model 1 (*P* for trend = 0.0382). Conversely, the “Refined carbohydrate” pattern showed a significant decrease in obesity prevalence for participants in the highest tertile (T3) of the GRS T3 group in model 1 (*P* for trend = 0.0092). This association persisted in model 2 (*P* for trend = 0.0251). For the “Wheat flour, bread, and noodles” pattern, participants in the highest tertile (T3) of the GRS T2 group exhibited a decreased OR in model 2 (*P* for trend = 0.0226).

The joint effects of dietary patterns and GRS based on BMI were analysed, with low dietary pattern scores and low GRS serving as reference points. The results demonstrated varying associations between dietary patterns and obesity risk across GRS tertiles (Table 4). For the “Vegetables and Kimchi” dietary pattern, the lowest prevalence was observed in those with the lowest pattern scores and GRS T1 (reference group), whereas the highest prevalence of obesity was observed in individuals with GRS T3 and intermediate pattern score (OR: 1.841, 95% CI: 1.524–2.225, *P* for trend 0.4726). In the “Eggs, fish, and dairy products” pattern, the lowest prevalence was observed in GRS T1 with T3 pattern scores (OR: 0.977, 95% CI: 0.799–1.194, *P* for trend = 0.4530), and the highest prevalence was noted in the GRS T3 with T3 pattern scores (OR: 1.719, 95% CI: 1.408–2.098, *P* for trend: 0.4654). In the “Refined carbohydrate” dietary pattern, the lowest prevalence was observed in those with the highest pattern scores and GRS T1 group (OR: 0.870, 95% CI: 0.719–1.053, *P* for trend = 0.1687), whereas the highest prevalence was observed in the lowest pattern scores with GRS T3 (OR: 1.594, 95% CI: 1.323–1.919, *P* for trend = 0.0251). For the “Wheat flour, bread, and

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noodles" dietary pattern, individuals with GRS T1 and the highest dietary pattern scores had the lowest odds of obesity (OR: 0.875, 95% CI: 0.719–1.065, *P* for trend = 0.1954), whereas GRS T3 and high dietary pattern scores showed the highest odds of obesity (OR: 1.543, 95% CI: 1.279–1.861, *P* for trend = 0.8060).

Discussion

Herein, we demonstrated that the refined carbohydrate dietary pattern in a Korean population was significantly associated with a high GRS for obesity using a large-population-based cohort and six SNPs derived from a GWAS for BMI. The refined carbohydrate dietary pattern showed a significant inverse association for obesity in the highest GRS group, with no significant interactive association. Conversely, participants with the highest refined carbohydrate dietary pattern score and the highest GRS had an increased prevalence of obesity compared with the prevalence of those with the lowest dietary pattern score and GRS. Accordingly, reducing refined carbohydrate consumption may benefit individuals with greater genetic susceptibility to obesity.

Most genes with obesity-related SNPs identified in the current study, including *OTOL1*, *NMBR*, *DNAJB9*, *ASCC1*, *NT5C2*, and *FTO*, have been previously associated with obesity. *FTO* is a well-known gene associated with obesity in several populations.[28,29] The association of *OTOL1* and BMI, confirmed in the Korean and Japanese populations, was also replicated in Filipino women.[22,30] *ASCC1* SNPs were strongly associated with obesity and osteoporosis in postmenopausal Korean women.[31] In the Framingham Heart Study, *NTC52* was recently identified to be associated with elevated BMI.[32] *NT5C2* was also observed to be associated with reduced visceral and subcutaneous fat in Japanese females.[33]

Although the mechanisms of the genetic variants identified in this study for the development of obesity are not clear, the genes associated with the link between obesity and BMI are expressed in the hypothalamus, hippocampus, and limbic system and regulate energy expenditure, satiety, and appetite.[34-36] The gene pool varies according to ethnicity, and Asians have a higher metabolic risk than Europeans with a similar BMI.[37] Therefore, identifying novel genetic variants and genome-wide scanning from various ethnicities are required. In this context, *NMBR* and *DNAJB9* are promising new genetic factors that should be further explored to determine their effects on obesity among Asian populations.

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Refined carbohydrate diet has primarily been associated with a high risk of obesity-related diseases. For example, an increased prevalence of high liver fat was observed with the intake of starch from refined grains, which decreased with fibre and starch intake from whole grains in a study of 22,973 adults in the UK.[38] In three large prospective cohort studies in the USA, a 100 g per day increase in carbohydrate intake from refined grains was associated with 0.8 kg more long-term weight gain, whereas that from whole grain, fruit, and non-starchy vegetables was negatively associated with 0.4–3 kg less long-term weight gain.[39] In addition, a Japanese cohort study reported that higher consumption of white rice—a major source of refined carbohydrates in Asian diets—was associated with more than 3 kg of body weight gain in one year, whereas consumption of brown/multi-grain rice showed no significant association.[40] These findings are consistent with our results showing that participants who were in the highest tertiles for both the refined carbohydrate dietary pattern and GRS had higher odds of obesity compared with those were in the lowest tertiles for both variables. Thus, our results suggest that individuals with a high genetic predisposition to obesity and a high refined carbohydrate dietary pattern are susceptible to obesity.

The mechanism of the interaction between the obesity-related genetic variants identified in this study and carbohydrate intake remains unclear. Nevertheless, the mechanism underlying another genetic variant related to a carbohydrate digestive enzyme has been identified. Salivary α-amylase hydrolyses starch in the bloodstream; the difference in activity of this enzyme is partly determined by copy number variants of the salivary a-amylase gene (*AMY1*). In a study involving 32,054 adults from four prospective cohort studies in the USA and UK conducted among females with higher GRS calculated using nine *AMY1* SNPs, higher *AMY1*-GRS signifying higher salivary amylase activity was related to notable central adiposity gain upon high-carbohydrate consumption.[41]

However, the refined carbohydrate dietary pattern was negatively associated with obesity among individuals in the highest GRS group in our study. Although the refined carbohydrate dietary pattern showed an inverse association with obesity within the high GRS group, the joint analysis demonstrated that individuals with both high GRS and high refined carbohydrate dietary pattern score had the highest obesity risk. These findings are not contradictory, as the stratified analysis reflects the within-stratum association of dietary pattern among individuals with similar genetic risk, whereas the joint analysis evaluates the combined effect of two high-risk conditions occurring simultaneously. Thus, the joint model captures a different dimension—cumulative risk—while the stratified model highlights

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potential effect modification by genetic susceptibility.

Nonetheless, this inverse association is in line with several previous studies conducted in Asian populations, which have reported an inverse relationship between the refined carbohydrate dietary pattern—where white rice had the highest factor loading—and overweight or obesity.[42] A possible explanation for this association is that the rice-based dietary pattern is typically characterized by a traditional diet accompanied by higher vegetable intake, lower consumption of processed foods, and healthier lifestyle behaviors.[43] These characteristics could influence obesity risk independently of the dietary pattern score, thus may contribute to residual confounding, which could partly explain this inverse association. Moreover, potential measurement error inherent in FFQ-based dietary assessment could have attenuated or distorted the observed associations. These factors should be considered when interpreting the unexpected inverse association found in the high GRS group. Another potential mechanism may involve rice-derived proteins, which have been suggested to stimulate lipolysis and suppress lipogenesis, thereby reducing body weight gain and adiposity.[44]

Although data regarding the associations between the genetic variants identified in this study, dietary patterns, and obesity, along with related mechanisms, remain limited, several studies have reported the interaction of these factors. *FTO* reportedly exerts the greatest effect on BMI[45] and was found to be associated with obesity and high carbohydrate intake.[46] In a meta-analysis of 56 studies with 213,173 adults, the *FTO* risk allele was associated with low total energy intake and high fat and protein intake.[47] Nevertheless, no significant interaction has been reported.[48]

Future studies should explore the biological mechanisms underlying the interaction between refined carbohydrate intake and obesity-related genetic variants. In particular, identifying metabolic pathways through which high-carbohydrate dietary patterns may differentially influence individuals with distinct genetic predispositions will help clarify causality. Further research is also needed to evaluate these associations using repeated dietary assessments and broader genomic profiling to account for additional variants involved in carbohydrate metabolism. Such work will contribute to establishing clinically meaningful gene–diet interactions and inform precision nutrition strategies.

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In addition to the refined carbohydrate dietary pattern, other dietary patterns and genetic variants are associated with obesity. The dietary patterns of vegetables and Kimchi, eggs, fish, and dairy products, and wheat flour, bread, and noodles were associated with obesity only in the intermediate GRS level in this study. Nonetheless, a plant-based diet, such as a high intake of vegetables and fruit, can attenuate body weight increase and cardiovascular risk factors among individuals with high GRS-associated BMI.[7,8] High adherence to healthy diets, including the Healthy Eating Index, Mediterranean Diet, and Dietary Approach to Stop Hypertension, can mitigate genetic predisposition to obesity.[49] Conversely, positive interactions of dietary pattern with the omega-6/omega-3 ratio, the GRS and metabolic parameters were observed among individuals with obesity.[10,11] Moreover, a dietary pattern of highly salty snacks and fast-food intake, extracted from the Iranian population with A and T alleles of *APOA1* SNP, was positively associated with the risk of metabolic syndrome.[50]

This study has several limitations. First, we could not examine the association of various obesity outcomes with genetic factors and dietary patterns, given that the phenotype of genetic variants was limited to only BMI. Second, although the KoGES cohort is longitudinal, our analysis relied on dietary patterns derived solely from baseline FFQ data, and therefore reflects cross-sectional associations. As a result, causal inference cannot be made, and the possibility of reverse causation or residual confounding remains. Our primary objective was to examine these cross-sectional relationships, as repeated dietary assessments were not available for the present analysis. Thus, the findings should be interpreted as associative rather than causal. Third, the usual food intake was possibly underestimated, as it was assessed using a semi-quantitative food frequency questionnaire. Moreover, determining dietary patterns, including the number of dietary pattern groups and food item classification, and the rotation method could be subjective.

Despite these limitations, this study has several strengths. First, it utilized a large, community-based Korean cohort with well-characterized phenotypic and genotypic data, allowing the examination of BMI-related genetic variants that have been repeatedly validated in Asian populations. Second, by investigating the interaction between the refined carbohydrate dietary pattern and the GRS, our findings provide additional evidence supporting the relevance of diet–gene interactions in obesity risk. These results underscore the potential implications for developing personalized nutrition strategies tailored to genetic susceptibility within the Korean population.

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Conclusions

Collectively, our results indicate that the refined carbohydrate dietary pattern of the Korean population was substantially associated with a high GRS for obesity derived from SNPs of *OTOL1*, *NMBR*, *DNAJB9*, *ASCC1*, *NT5C2*, and *FTO*, using a large-population-based cohort. Accordingly, reducing refined carbohydrate consumption may benefit individuals with greater genetic susceptibility to obesity.

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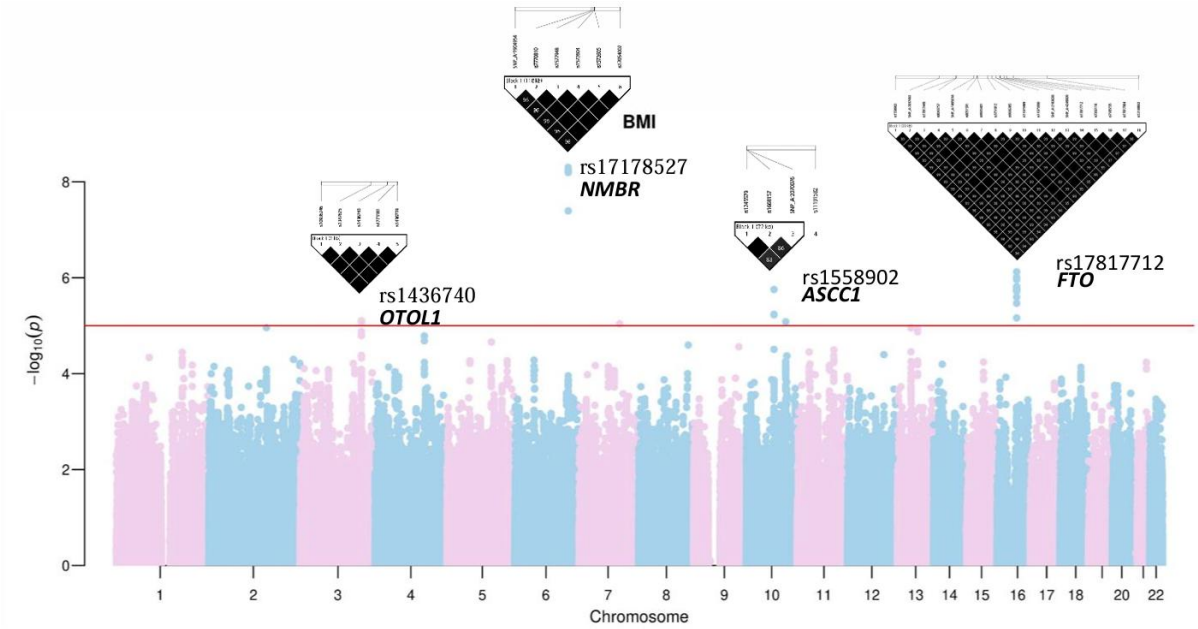


Figure 1. Genome-wide Manhattan plot for BMI. The $-\log_{10}P$ values are presented using the trend test for SNPs distributed across the entire genome. The red line indicates the signals with $-\log_{10}P$ value > 5 detected in the genome-wide association study. A total of 1,590,162 SNPs were used to generate the plot. BMI, body mass index; SNP, single nucleotide polymorphism.

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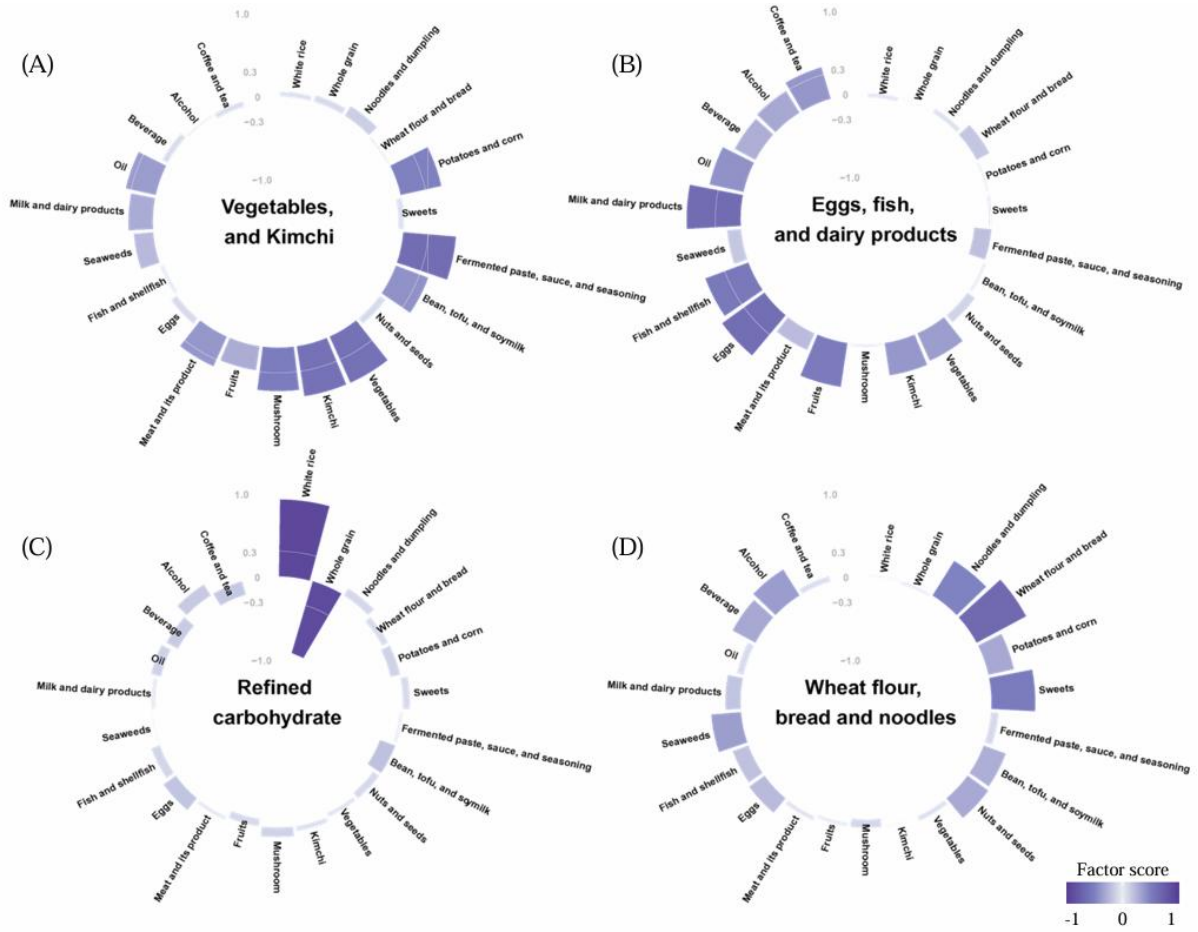


Figure 2. Factor loading for major dietary patterns identified according to factor analysis. (A) "Vegetables and Kimchi" pattern, (B) "Eggs, fish, and dairy products" pattern, (C) "Refined carbohydrate" pattern, (D) "Wheat flour, bread and noodle" pattern. The dietary patterns were named based on the top food groups with the highest factor-loading values.

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Table 1. Basic characteristics according to genetic risk of obesity among Korean adults from the Ansan and Ansung cohorts

	GRS T1	GRS T2	GRS T3	*P*-value
N	2,802	2,871	2,785	
Males (%)	1,301 (46.43)	1,413 (49.22)	1,307 (46.93)	0.0808
Age (year)	52.47±9.02	51.96±8.83	52.01±8.81	0.0620
BMI (kg/m^2)	24.17±3.07	24.60±3.07	25.06±3.17	<.0001
Household income				
< 1,000,000 KRW	999 (35.65)	945 (32.92)	941 (33.79)	0.0943
< 3,000,000 KRW	1,297 (46.29)	1,388 (48.35)	1,275 (45.78)	
≥ 3,000,000 KRW	458 (16.35)	508 (17.69)	530 (19.03)	
Drinking status				
Current alcohol drinker	1,303 (46.50)	1,420 (49.46)	1,278 (45.89)	0.1191
Past alcohol drinker	182 (6.50)	185 (6.44)	169 (6.07)	
Non-drinker	1,306 (46.61)	1,257 (43.78)	1,327 (47.65)	
Smoking status				
Current smoker	722 (26.83)	732 (26.09)	674 (25.17)	0.4063
Past smoker	430 (15.35)	464 (16.16)	425 (15.26)	
Nonsmoker	1,620 (57.82)	1,658 (57.75)	1,659 (59.57)	
Physical activity				
Low	1,116 (39.83)	1,212 (42.22)	1,169 (41.97)	0.3879
Moderate	578 (20.63)	564 (19.64)	559 (20.07)	
High	1,108 (39.54)	1,095 (38.14)	1,057 (37.95)	

BMI, body mass index; GRS, genetic risk score; KRW, Korean won

Values are the number of participants with percentages for categorical variables and mean ± standard deviation for continuous variables. Categorical and continuous variables were compared using chi-squared tests and regression models, respectively.

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Table 2. Genetic characteristics of the 6 SNPs associated with BMI among Korean adults from the Ansan and Ansung cohorts

Chr	SNP	Gene	Position	Effect alleles	Other alleles	MA	MAF	BETA	SE	Lower 95% CI	Upper 95% CI	*P*-value	$-\log_{10}$*P*value
3	rs1436740	*OTOL1*	163, 005,436	C	T	C	0.069	0.423	0.095	0.238	0.608	7.92E-06	5.101
6	rs17178527	*NMBR*	141, 947,773	G	A	A	0.248	-0.327	0.056	-0.437	-0.218	5.03E-09	8.299
7	rs9987062	*DNAJB9*	108,195,347	A	G	A	0.075	0.402	0.091	0.225	0.580	9.09E-06	5.042
10	rs11000212	*ASCC1*	73,625,658	G	C	G	0.207	0.282	0.059	0.166	0.397	1.76E-06	5.754
10	rs11191582	*NT5C2*	104,903,643	A	G	A	0.224	0.262	0.059	0.147	0.376	8.26E-06	5.083
16	rs17817712	*FTO*	52,378,626	G	A	G	0.121	0.362	0.073	0.219	0.505	7.57E-07	6.121

Chr, chromosome; CI, confidence interval; MA, minor allele; MAF, minor allele frequency; SE, standard error; SNP, single nucleotide polymorphism; BMI, body mass index

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Table 3. Odds ratios of obesity according to the dietary pattern score tertiles stratified by the GRS among Korean adults from the Ansan and Ansung cohorts

		Tertile of each pattern score			
		T1	**T2**	**T3**	
		OR	OR (95% CI)	OR (95% CI)	***P for trend***
Vegetables and Kimchi					
Model 1	GRS T1	1.00 (ref.)	1.194 (0.923–1.545)	1.249 (0.965–1.616)	0.1422
	GRS T2	1.00 (ref.)	1.124 (0.870–1.451)	1.308 (1.013–1.689)	0.0260
	GRS T3	1.00 (ref.)	1.147 (0.955–1.377)	1.059 (0.882–1.272)	0.6528
	P for interaction	0.431			
Model 2	GRS T1	1.00 (ref.)	1.130 (0.863–1.478)	1.087 (0.812–1.457)	0.4895
	GRS T2	1.00 (ref.)	1.077 (0.828–1.402)	1.218 (0.914–1.621)	0.2168
	GRS T3	1.00 (ref.)	1.162 (0.961–1.402)	1.091 (0.892–1.334)	0.6528
	P for interaction	0.428			
Eggs, fish, and dairy products					
Model 1	GRS T1	1.00 (ref.)	1.012 (0.780–1.314)	0.892 (0.680–1.169)	0.5516
	GRS T2	1.00 (ref.)	1.098 (0.847–1.423)	1.073 (0.818–1.408)	0.0382
	GRS T3	1.00 (ref.)	1.003 (0.833–1.209)	1.154 (0.953–1.397)	0.1161
	P for interaction	0.524			
Model 2	GRS T1	1.00 (ref.)	1.090 (0.829–1.432)	0.940 (0.694–1.273)	0.4530
	GRS T2	1.00 (ref.)	1.213 (0.919–1.601)	1.174 (0.865–1.594)	0.3254
	GRS T3	1.00 (ref.)	0.949 (0.781–1.154)	1.070 (0.862–1.328)	0.4654
	P for interaction	0.533			
Refined carbohydrate					
Model 1	GRS T1	1.00 (ref.)	0.879 (0.681–1.135)	0.972 (0.754–1.254)	0.0564
	GRS T2	1.00 (ref.)	0.844 (0.654–1.089)	1.009 (0.783–1.301)	0.9028
	GRS T3	1.00 (ref.)	0.903 (0.753–1.084)	0.781 (0.650–0.938)	0.0092
	P for interaction	0.572			
Model 2	GRS T1	1.00 (ref.)	0.848 (0.651–1.104)	0.877 (0.672–1.144)	0.1687
	GRS T2	1.00 (ref.)	0.809 (0.621–1.054)	0.962 (0.738–1.255)	0.7763
	GRS T3	1.00 (ref.)	0.917 (0.760–1.106)	0.801 (0.662–0.969)	0.0251
	P for interaction	0.571			
Wheat flour, bread, and noodles					
Model 1	GRS T1	1.00 (ref.)	0.897 (0.695–1.159)	0.996 (0.769–1.292)	0.8914
	GRS T2	1.00 (ref.)	1.136 (0.880–1.467)	0.885 (0.682–1.148)	0.3638
	GRS T3	1.00 (ref.)	0.938 (0.781–1.128)	1.011 (0.841–1.216)	0.8318
	P for interaction	0.746			
Model 2	GRS T1	1.00 (ref.)	0.894 (0.685–1.166)	0.974 (0.730–1.300)	0.1954
	GRS T2	1.00 (ref.)	1.151 (0.884–1.499)	0.827 (0.617–1.108)	0.0226
	GRS T3	1.00 (ref.)	0.942 (0.779–1.139)	1.019 (0.826–1.257)	0.0860
	P for interaction	0.641			

CI, confidence interval; GRS, genetic risk score; OR, odds ratio

Model 1 was adjusted for sex (male and female) and age (continuous). Model 2 was adjusted for sex (male and female), age (continuous), body mass index (continuous), energy intake (continuous), household income level (< 1 million, 1–3 million, and > 3 million Korean won), drinking status (current, former, or never), smoking status (current, former, or never), and daily physical activity duration (none, < 30 min, 30–60 min, 60–90 min, 90 min to 2 h, 2–3 h, 3–4 h, 4–5 h, or > 5 h), and physical activity (low, moderate, or high activity).

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Table 4. Odds ratios of obesity according to the joint categories of each dietary pattern score and the GRS among Korean adults from the Ansan and Ansung cohorts

	Tertile of each pattern score			
	T1	**T2**	**T3**	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	***P for trend***
Vegetables and Kimchi				
GRS T1	1.00 (ref.)	1.121 (0.926–1.358)	1.123 (0.923–1.367)	0.4895
GRS T2	1.177 (0.974–1.422)	1.373 (1.138–1.658)	1.401 (1.155–1.698)	0.2168
GRS T3	1.638 (1.356–1.978)	1.841 (1.524–2.225)	1.656 (1.364–2.010)	0.4726
Eggs, fish, and dairy products				
GRS T1	1.00 (ref.)	1.116 (0.919–1.354)	0.977 (0.799–1.194)	0.4530
GRS T2	1.215 (1.006–1.468)	1.227 (1.012–1.487)	1.317 (1.079–1.606)	0.3254
GRS T3	1.617 (1.339–1.953)	1.557 (1.285–1.888)	1.719 (1.408–2.098)	0.4654
Refined carbohydrate				
GRS T1	1.00 (ref.)	0.887 (0.731–1.072)	0.870 (0.719–1.053)	0.1687
GRS T2	1.161 (0.965–1.396)	0.973 (0.807–1.173)	1.231 (1.022–1.484)	0.7763
GRS T3	1.594 (1.323–1.919)	1.494 (1.240–1.801)	1.288 (1.068–1.554)	0.0251
Wheat flour, bread, and noodles				
GRS T1	1.00 (ref.)	0.895 (0.739–1.083)	0.875 (0.719–1.065)	0.1954
GRS T2	1.182 (0.980–1.425)	1.204 (0.999–1.453)	0.985 (0.810–1.198)	0.0226
GRS T3	1.543 (1.279–1.861)	1.399 (1.159–1.690)	1.434 (1.181–1.743)	0.8060

CI, confidence interval; GRS, genetic risk score; OR, odds ratio

Adjusted for sex, age, body mass index, energy intake, household income level, drinking status, smoking status, and physical activity.

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