

# Analysis of the Interaction between Polygenic Risk Score and Calorie Intake in Obesity in the Korean Population

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## Keywords

Polygenic risk score · Calorie intake · Interaction · Obesity · Body mass index

## Abstract

**Introduction:** Obesity results from an imbalance in the intake and expenditure of calories that leads to lifestyle-related diseases. Although genome-wide association studies (GWAS) have revealed many obesity-related genetic factors, the interactions of these factors and calorie intake remain unknown. This study aimed to investigate interactions between calorie intake and the polygenic risk score (PRS) of BMI. **Methods:** Three cohorts, i.e., from the Korea Association Resource (KARE;  $n = 8,736$ ), CardioVascular Disease Association Study (CAVAS;  $n = 9,334$ ), and Health EXaminee (HEXA;  $n = 28,445$ ), were used for this study. BMI-related genetic loci were selected from previous GWAS. Two scores, PRS, and association (a)PRS, were used; the former was determined from 193 single-nucleotide polymorphisms (SNPs) from 5

GWAS datasets, and the latter from 62 SNPs (potentially associated) from 3 Korean cohorts (meta-analysis,  $p < 0.01$ ). **Results:** PRS and aPRS were significantly associated with BMI in all 3 cohorts but did not exhibit a significant interaction with total calorie intake. Similar results were obtained for obesity. PRS and aPRS were significantly associated with obesity but did not show a significant interaction with total calorie intake. We further analyzed the interaction with protein, fat, and carbohydrate intake. The results were similar to those for total calorie intake, with PRS and aPRS found to not be associated with the interaction of any of the 3 nutrition components for either BMI or obesity. **Discussion:** The interaction of BMI PRS with calorie intake was investigated in 3 independent Korean cohorts (total  $n = 35,094$ ) and no interactions were found between PRS and calorie intake for obesity.

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## Introduction

Obesity is a major risk factor for lifestyle-related diseases, such as type 2 diabetes, hyperlipidemia, and hypertension, and its prevalence has steadily increased in the past few decades [1]. Overweight individuals have a reduced capacity to cope with emergency situations and are more susceptible to joint diseases [2]. Furthermore, the most prominent cause of sleep apnea is obesity, and obese individuals are frequently diagnosed with various mental illnesses, such as attention deficit hyperactivity disorder and Asperger syndrome [3].

Individuals consuming excess calories are highly susceptible to obesity if they do not also ingest enough nutrients [4–7]. A lack of exercise and unstable lifestyle can induce obesity [8]. Stress, in particular, is one of the most prominent causes of obesity and is often caused by a lack of sleep and can lead to eating disorders or a decreased metabolic rate [9–11]. Although the environmental risk factors for obesity have been characterized, the associated genetic etiologies are only gradually being defined via genome-wide association studies (GWAS) [12–15].

Since the discovery of the *FTO* and *MC4R* variants [16, 17], serial GWAS have focused on individuals with obesity [12–15]. One such study comprised approximately 700,000 individuals including 450,000 UK Biobank participants, and reported a total of 536 loci, accounting for approximately 6% of BMI variations [15]. Although most GWAS on obesity have involved European populations, several have also included Asian populations [18, 19]. Specifically, Akiyama et al. [19] identified 112 new BMI-related genetic loci using 173,430 Japanese participants.

Among the obesity loci identified by various GWAS, genetic variants of *FTO* and *MC4R* have been assessed for their interactions with environmental factors and suggest that multiple environmental factors affect the effect size of these genetic variants [20–23]. These results imply that the carriers of alleles associated with a risk of obesity may be less affected by their genetic factors if environmental factors like diet and physical activity are modified. The polygenic risk score (PRS), determined from a GWAS dataset of single-nucleotide polymorphisms (SNPs) often serves as an index for the genetic susceptibility of individuals to a disease, and the identification of environmental factors interacting with the PRS can, potentially, help individuals with a high genetic risk [24–26].

Numerous studies have reported the interaction between PRS and environmental factors in obesity. The obesity PRS reportedly interacts with sedentary behavior such as watching television [27], the consumption of

high-sugar-containing beverages [28], and fried food [29]. Several lifestyle-related factors, including nutrient and alcohol intake and exercise, were reported for their interaction in Japanese individuals [30]. Recently, Tyrrell et al. [31] assessed 12 obesogenic environments to determine their interactions with the PRS composed of 69 BMI-related GWAS loci in the UK Biobank, involving 120,000 participants, and reported PRS-environment interactions with Townsend deprivation index, watching television, and physical activity. However, no study has yet assessed the interaction between BMI PRS and total calorie intake [31].

In this study, the interactions of PRS and association PRS (aPRS) with calorie intake, including total calorie intake and protein, fat, and carbohydrate intake, in BMI and obesity, were investigated in the Korean population.

## Materials and Methods

### Study Participants

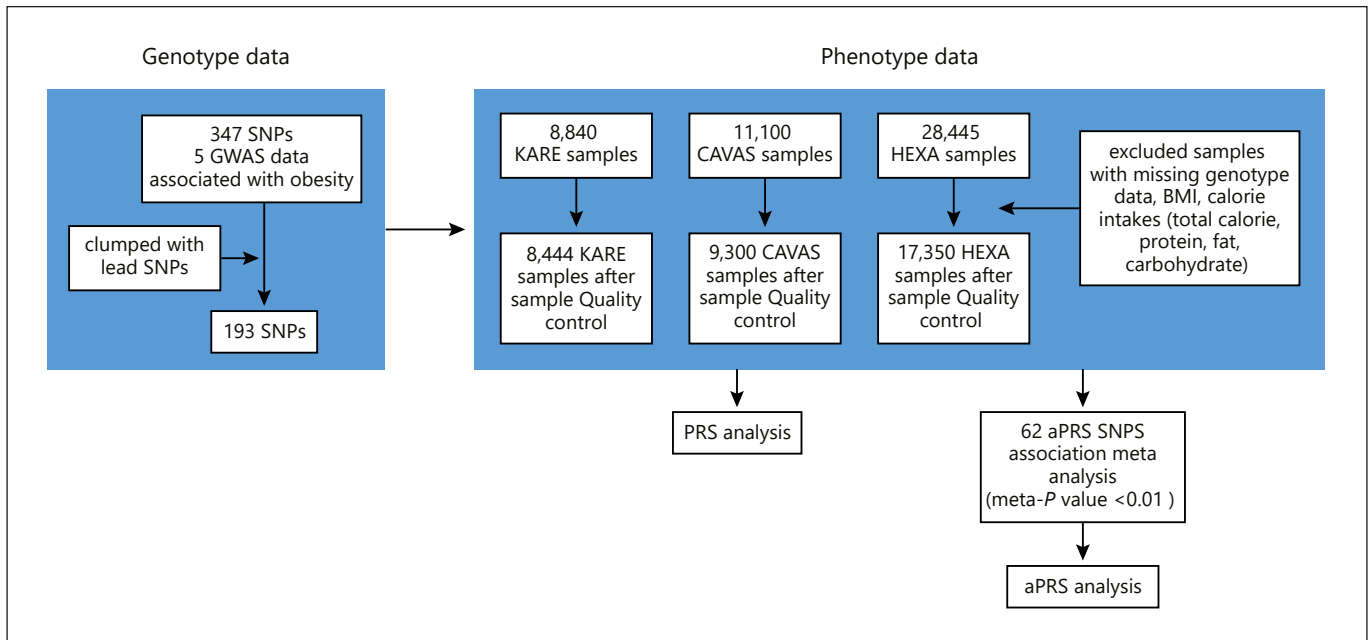
We used 3 Korean cohorts for identifying the association and interaction of BMI and obesity: the Korea Association REsource (KARE;  $n = 8,444$ ), the CARDioVAscular Disease Association Study (CAVAS;  $n = 9,300$ ), and the Health EXaminee (HEXA;  $n = 17,350$ ) cohorts. All 3 cohorts are currently being assessed as part of the Korean Genome and Epidemiology Study (KoGES) [32]. The KARE was initiated in 2001 and contains epidemiological and genetic data from 10,038 participants aged 40–69 years, 8,840 of whom were included in this study after a sample quality control assessment in accordance with the following exclusion criteria: history of cancer, sex inconsistencies, cryptic relatedness, low genotype call rate (<95%), and sample contamination. For BMI analysis, 8,444 subjects with complete data on BMI and total calorie, protein, fat, and carbohydrate intake were included. For obesity case-control analysis, subjects were divided into 2 groups based on their BMI. The obese group ( $n = 3,632$ ) with a BMI  $\geq 25$  and the normal group ( $n = 4,812$ ) with a BMI <25 [33]. The study design is summarized in Figure 1.

The CAVAS population-based cohort comprises 28,338 subjects aged 40–69 years. We selected 11,100 who were recruited from Yangpyeong, Namwon, and Goryeong in South Korea from 2005 to 2011 [34]. The quality control criteria were the same as for the KARE cohort. For the BMI analysis, 9,300 subjects were assessed, including 3,764 obese and 5,536 normal subjects for the obesity case-control analysis.

The HEXA population-based cohort comprises 173,357 subjects aged 40–79 years, 28,445 of whom were included in this study according to the same inclusion criteria as for the KARE cohort. For the BMI analysis, 17,350 subjects were assessed, including 5,170 obese and 12,180 normal subjects for the obesity case-control analysis.

### Genotyping Analysis

Genotyping analysis for the KARE cohort was performed using a genome-wide human SNP array 5.0 (Affymetrix, Santa Clara,



**Fig. 1.** Schematic diagram of the study design. Summary of data included in this study. A total of 193 genetic variants selected from 5 GWAS publications were used in the PRS analysis and 62 variants potentially associated in 3 Korean cohorts were used in the aPRS analysis, resulting in 35,094 Korean samples (8,444 from KARE, 9,300 from CAVAS, and 17,350 from HEXA) being included in the PRS and aPRS analyses.

CA, USA), as previously described [32], and SNP imputation was performed with IMPUTE2 [35] using phase 1 of the 1000 Genomes Project as a reference panel. Genetic variants with a high missing call rate (>5%), a low minor allele frequency (MAF < 0.05), a Hardy-Weinberg equilibrium (HWE) of  $p \leq 1 \times 10^{-6}$ , and a low imputation quality (info score < 0.4) were excluded.

The CAVAS and HEXA population were genotyped using the Korea Biobank array (KoreanChip), designed by the Center for Genome Science, Korea National Institute of Health (KNIH), based on the platform of UK Biobank axion array and manufactured by Affymetrix [36]. The SNP imputation method and genotype quality control criteria were the same as for KARE.

#### Selection of BMI-Associated SNPs and Determination of the PRS and aPRS

In total, 347 BMI-related SNPs were identified from 5 BMI-related GWAS that included analyses of Asian populations [13, 14, 18, 19, 32]. Independent SNPs were identified using clumping analysis in PLINK v1.9, with the following set parameters:  $p$  value ( $< 5 \times 10^{-8}$ ), genomic distance (< 1 Mb), and linkage disequilibrium ( $r^2 > 0.2$ ). Thereafter, we selected only 1 top-ranked SNP with the lowest  $p$  value from each clump within a 1-Mb range based on GWAS data. We then obtained a total of 193 independent SNPs and verified whether they were included in the imputed genotype data of each cohort. Consequently, 193 SNPs were selected for the PRS in KARE, 152 in CAVAS, and 192 in HEXA. We calculated each individual PRS using the selected SNPs, by summing risk alleles with weighting the effect size of each allele or without weighting (PRS<sub>unweighted</sub>) [31]. The unweighted PRS were calculated by summing the number of risk alleles without applying the weight of

effect size ( $unweighted\ PRS = SNP_1 + SNP_2 + \dots + SNP_n$ ). Meanwhile, the weighted PRS were calculated according to Equation 1, by creating a weighted score by summing the number of risk allele multiplied by the effect size ( $weighted\ score = \beta_1 \times SNP_1 + \beta_2 \times SNP_2 + \dots + \beta_n \times SNP_n$ ), followed by rescaling the weighted score to represent the number of risk alleles [31].

$$weighted\ PRS = \frac{weighted\ score \times number\ of\ available\ SNPs}{sum\ of\ the\ \beta\ coefficients\ of\ available\ SNPs} \quad (1)$$

To determine the aPRS, we carried out association meta-analyses of BMI using the 3 cohorts, and selected SNPs that were BMI-associated (meta-analysis,  $p < 0.01$ ; online suppl. Table S1; see [www.karger.com/doi/10.1159/000511333](http://www.karger.com/doi/10.1159/000511333) for all online suppl. material). Consequently, 62 SNPs were selected for the aPRS in each cohort. We calculated each individual aPRS using the selected SNPs, by summing risk alleles with weighting the effect size of each allele or without weighting (aPRS<sub>unweighted</sub>). The average PRS and aPRS in each cohort are shown in online supplementary Table S2.

We also created an additional PRS<sup>2</sup> using a total of 941 independent SNPs more recently identified in a BMI GWAS of approximately 700,000 individuals with European ancestry [15]. After selection of SNPs for the imputed genotype data of each cohort, 768 were selected for the PRS<sup>2</sup> in KARE, 634 in CAVAS, and 823 in HEXA (online suppl. Table S3). We then calculated each individual PRS<sup>2</sup> using the SNPs, by summing risk alleles either with weighting of the effect size of each allele or without weighting (PRS<sup>2</sup><sub>unweighted</sub>) [31]. Similarly, for PRS<sup>2</sup>, we carried out association meta-analyses of BMI using the 3 cohorts, and selected SNPs that were BMI-associated (meta-analysis,  $p < 0.01$ ). Consequently, 61

**Table 1.** Baseline characteristics of the 3 Korean cohorts

Characteristics	KARE	CAVAS	HEXA
Subjects, <i>n</i>	8,444	9,300	17,350
Males, <i>n</i> (%)	4,044 (47.90)	3,455 (37.15)	5,976 (34.44)
Age, years	52.16 (8.90)	62.16 (9.72)	53.81 (7.89)
BMI	24.60 (3.13)	24.38 (3.17)	23.81 (2.67)
Obesity, <i>n</i> (%)	4,312 (43.01)	3,764 (40.47)	5,170 (29.80)
Calorie intake, kcal	1,918.896 (681.336)	1,559.352 (493.118)	1,759.130 (537.348)
Protein intake, g	66.664 (30.043)	46.704 (19.990)	59.673 (24.990)
Fat intake, g	32.574 (21.120)	19.050 (14.102)	27.818 (17.116)
Carbohydrate intake, g	344.182 (118.714)	294.330 (84.956)	313.479 (88.348)

Data are presented as mean (SD), unless otherwise indicated.

SNPs were selected for the aPRS<sup>2</sup> in each cohort (online suppl. Table S3). Individual aPRS<sup>2</sup> were calculated in the same way as that described for PRS<sup>2</sup>. The average PRS<sup>2</sup> and aPRS<sup>2</sup> in each cohort are shown in online supplementary Table S3.

#### Measurements

Weight and height were measured via standard procedures. For each cohort, BMI was calculated as weight divided by height squared. For the association analysis of obesity, subjects were dichotomized into a normal (BMI <25) and an obese (BMI ≥25) group [33].

A previously validated [37, 38] food frequency questionnaire was used to obtain the total calorie, protein, carbohydrate, and fat intake. The fat intake value did not include the amount of oil used in cooking [38].

#### Statistical Analysis

Linear regression analysis was performed for the association between calorie intake and BMI, and logistic regression analysis was performed for obesity cases and control tests using SPSS (PASW Statistics v23.0). All regression analyses were adjusted for age, sex, recruitment site, and 10 principal components for the KARE cohort, and for age, sex, and 10 principal components for the CAVAS and HEXA cohorts. The 10 principal components were calculated using the *-pca* option in PLINK v1.90 to account for population stratification.

Associations between genetic factors (individual SNPs, PRS, and aPRS) and obesity were assessed by a linear regression analysis for BMI; a logistic regression analysis was used for obesity. For each analysis, age, sex, recruitment site, and 10 principal components were adjusted for the KARE cohort, and age, sex, and 10 principal components for the CAVAS and HEXA cohorts. We used PLINK v1.90 to conduct individual SNP association analysis to select SNPs for aPRS and calculate PRS and aPRS [39]. In addition, we used SPSS v25 for the association and interaction analyses of PRS and aPRS for each cohort. All data were reported as mean ± SD.  $p < 4.17 \times 10^{-4}$  (0.05/120) was considered statistically significant after multiple-correction analysis considering 4 scoring indices (PRS, PRS<sub>unweighted</sub>, aPRS, and aPRS<sub>unweighted</sub>), 5 analyses (1 association analysis and 4 interaction analyses with lifestyle factors), 2 outcomes (BMI and obesity), and 3 Korean cohorts.

## Results

### Association of Calorie Intake with BMI and Obesity

The characteristics of each cohort appear in Table 1 and online supplementary Table S4. For BMI analysis (Table 1), 8,444 participants (4,044 men) were selected from the KARE cohort, 9,300 (3,455 men) from the CAVAS cohort, and 17,350 (5,976 men) from the HEXA cohort. The mean BMI was  $24.60 \pm 3.13$  in KARE,  $24.38 \pm 3.17$  in CAVAS, and  $23.81 \pm 2.67$  in HEXA. The average total calorie intake, protein intake, fat intake, and carbohydrate intake values are shown in Table 1.

Total calorie intake (per 1-SD) was significantly associated with BMI in all 3 cohorts:  $\beta \pm SE = 0.162 \pm 0.34$ ,  $p = 2.00 \times 10^{-6}$  in KARE;  $\beta \pm SE = 0.249 \pm 0.035$ ,  $p = 6.84 \times 10^{-13}$  in CAVAS; and  $\beta \pm SE = 0.103 \pm 0.020$ ,  $p = 4.14 \times 10^{-7}$  in HEXA. Protein intake (per 1-SD) was also significantly associated with BMI in all 3 cohorts:  $\beta \pm SE = 0.151 \pm 0.034$  in KARE;  $\beta \pm SE = 0.217 \pm 0.035$  in CAVAS; and  $\beta \pm SE = 0.101 \pm 0.020$  in HEXA. Fat intake (per 1-SD) was significantly associated with BMI in HEXA, but not in KARE or CAVAS following multiple corrections considering the 4 lifestyle factors, 2 outcomes (BMI and obesity), and 3 Korean cohorts ( $p < 2.08 \times 10^{-3}$ ). Carbohydrate intake (per 1-SD) was significantly associated with BMI in all 3 cohorts:  $\beta \pm SE = 0.175 \pm 0.034$  in KARE;  $\beta \pm SE = 0.257 \pm 0.034$  in CAVAS; and  $\beta \pm SE = 0.093 \pm 0.020$  in HEXA. The associations of calorie and macronutrient intake with BMI are shown in Table 2.

Online supplementary Table S4 shows the basic characteristics of obesity cases and controls in each cohort. The KARE cohort comprised 3,632 cases (BMI ≥25, mean BMI  $27.43 \pm 2.09$ ) and 4,812 controls (BMI <25, mean BMI  $22.47 \pm 1.82$ ). The CAVAS cohort comprised 3,764



cases (mean BMI  $27.4 \pm 2.07$ ) and 5,536 controls (mean BMI  $22.32 \pm 1.88$ ). The HEXA cohort comprised 5,170 cases (mean BMI  $26.96 \pm 1.83$ ) and 12,180 controls (mean BMI  $22.48 \pm 1.66$ ).

Total calorie intake (per 1-SD) was significantly associated with obesity in all 3 cohorts: odds ratio (OR) 1.086 (95% confidence interval [CI] 1.040–1.135),  $p = 2.24 \times 10^{-4}$  in KARE; OR 1.148 (95% CI 1.098–1.201),  $p = 1.51 \times 10^{-9}$  in CAVAS; and OR 1.074 (95% CI 1.039–1.111),  $p = 2.30 \times 10^{-5}$  in HEXA (online suppl. Table S5). Protein intake (per 1-SD) was also significantly associated with obesity in all 3 cohorts: OR 1.087 (95% CI 1.040–1.136) in KARE; OR 1.137 (95% CI 1.087–1.190) in CAVAS; and OR 1.072 (95% CI 1.037–1.107) in HEXA. Fat intake (per 1-SD) was not significant in any of the 3 cohorts after multiple correction ( $p < 2.08 \times 10^{-3}$ ). Carbohydrate intake (per 1-SD) was significantly associated with obesity in all 3 cohorts: OR 1.089 (95% CI 1.042–1.137) in KARE; OR 1.148 (95% CI 1.099–1.200) in CAVAS; and OR 1.067 (95% CI 1.032–1.103) in HEXA.

#### Association of PRS and aPRS with BMI and Obesity

We determined the PRS on the basis of BMI-related GWAS SNPs by accounting for the effect weight of each SNP in the PRS computation. Starting from 347 GWAS SNPs, we used 193 SNPs for KARE, 152 for CAVAS, and 192 for HEXA, depending on the imputed genotype data of each cohort (online suppl. Table S2). Association analysis of the PRS was performed using linear regression for BMI and logistic regression for obesity. As shown in Table 3, the PRS was significantly associated with BMI ( $\beta \pm SE = 0.015 \pm 0.002$ ,  $p = 3.96 \times 10^{-22}$  in KARE;  $\beta \pm SE = 0.012 \pm 0.002$ ,  $p = 8.23 \times 10^{-12}$  in CAVAS; and  $\beta \pm SE = 0.013 \pm 0.001$ ,  $p = 6.73 \times 10^{-38}$  in HEXA). The associations of PRS with BMI in the 3 cohorts appear as scatter plots in online supplementary Figure S1. Online supplementary Table S6 shows that PRS was significantly associated with obesity (OR 1.008 [95% CI 1.006–1.010],  $p = 4.71 \times 10^{-14}$  in KARE; OR 1.006 [95% CI 1.004–1.009],  $p = 4.99 \times 10^{-8}$  in CAVAS; and OR 1.008 [95% CI 1.007–1.010],  $p = 1.15 \times 10^{-22}$  in HEXA).

We determined the unweighted PRS ( $PRS_{\text{unweighted}}$ ) using the same SNPs as those for PRS, without accounting for the effect weight of each SNP in the  $PRS_{\text{unweighted}}$  computation. Association analysis of the  $PRS_{\text{unweighted}}$  was performed and was also determined to be significantly associated with BMI and obesity in all 3 cohorts (Table 3; online suppl. Table S6).

In addition, we determined the aPRS on the basis of 62 BMI-related SNPs validated by the meta-analysis of the 3

**Table 2.** Association analyses of calorie and macronutrient intake with BMI

Study	Environmental effect (intake)	BMI	
		$\beta$ (SE)	<i>p</i> value
KARE	Total calories (1-SD)	0.162 (0.034)	<b>2.00E-06</b>
	Protein (1-SD)	0.151 (0.034)	<b>1.10E-05</b>
	Fat (1-SD)	0.072 (0.035)	4.05E-02
	Carbohydrates (1-SD)	0.175 (0.034)	<b>3.45E-07</b>
CAVAS	Total calories (1-SD)	0.249 (0.035)	<b>6.84E-13</b>
	Protein (1-SD)	0.217 (0.035)	<b>5.36E-10</b>
	Fat (1-SD)	0.089 (0.035)	1.14E-02
	Carbohydrates (1-SD)	0.257 (0.034)	<b>2.35E-14</b>
HEXA	Total calories (1-SD)	0.103 (0.020)	<b>4.14E-07</b>
	Protein (1-SD)	0.101 (0.020)	<b>5.29E-07</b>
	Fat (1-SD)	0.067 (0.020)	<b>1.05E-03</b>
	Carbohydrates (1-SD)	0.093 (0.020)	<b>4.00E-06</b>

The associations of calorie and macronutrient intakes (per 1-SD) with BMI were analyzed by linear regression model, adjusted for age, sex, and recruitment area in KARE, and for age and sex in CAVAS and HEXA. The significance threshold was  $p < 2.08E-03$  (0.05/24 after multiple correction). SE, standard error; BMI, body mass index.

cohorts ( $p < 0.01$ ). Similar to the PRS, the aPRS was calculated by accounting for the effect weight of each SNP. Association analysis of the aPRS was performed using linear regression for BMI and logistic regression for obesity. The aPRS was found to be significantly associated with BMI ( $\beta \pm SE = 0.020 \pm 0.003$ ,  $p = 1.46 \times 10^{-12}$  in KARE;  $\beta \pm SE = 0.019 \pm 0.003$ ,  $p = 2.00 \times 10^{-12}$  in CAVAS; and  $\beta \pm SE = 0.019 \pm 0.002$ ,  $p = 8.15 \times 10^{-29}$  in HEXA; Table 4) and obesity (OR 1.010 [95% CI 1.007–1.014],  $p = 3.60 \times 10^{-8}$  in KARE; OR 1.010 [95% CI 1.007–1.014],  $p = 1.59 \times 10^{-8}$  in CAVAS; and OR 1.012 [95% CI 1.009–1.015],  $p = 2.14 \times 10^{-17}$  in HEXA; online suppl. Table S7).

We also determined the  $aPRS_{\text{unweighted}}$  using the same 62 SNPs, without accounting for the effect weight of each SNP. Association analysis of the  $aPRS_{\text{unweighted}}$  was also significantly associated with BMI ( $\beta \pm SE = 0.076 \pm 0.007$ ,  $p = 2.34 \times 10^{-29}$  in KARE;  $\beta \pm SE = 0.069 \pm 0.006$ ,  $p = 8.07 \times 10^{-27}$  in CAVAS; and  $\beta \pm SE = 0.063 \pm 0.004$ ,  $p = 5.62 \times 10^{-56}$  in HEXA; Table 4) and obesity (OR 1.041 [95% CI 1.032–1.050],  $p = 4.15 \times 10^{-19}$  in KARE; OR 1.040 [95% CI 1.031–1.049],  $p = 9.67 \times 10^{-20}$  in CAVAS; and OR 1.056 [95% CI 1.044–1.069],  $p = 1.70 \times 10^{-20}$  in HEXA; online suppl. Table S7).

**Table 3.** Association and interaction analyses of PRS with BMI

Study	Test	BMI			
		$\beta$ (SE)	<i>p</i> value		
KARE	PRS	Genetic effect (G)	1.58E-02 (1.63E-03)	3.96E-22	
		Interaction effect (GxE)			
		Calorie intake (1-SD)	-1.65E-03 (1.65E-03)	0.319	
		Protein (1-SD)	1.10E-04 (1.68E-03)	0.948	
		Fat (1-SD)	4.73E-04 (1.60E-03)	0.768	
		Carbohydrate (1-SD)	-2.44E-03 (1.66E-03)	0.141	
	PRS <sub>unweighted</sub>	Genetic effect (G)	4.90E-02 (3.79E-03)	8.37E-38	
		Interaction effect (GxE)			
		Calorie intake (1-SD)	-2.43E-03 (3.74E-03)	0.517	
		Protein (1-SD)	-7.00E-05 (3.72E-03)	0.985	
		Fat (1-SD)	-8.80E-04 (3.68E-03)	0.811	
		Carbohydrate (1-SD)	-3.36E-03 (3.78E-03)	0.373	
	CAVAS	PRS	Genetic effect (G)	1.22E-02 (1.78E-03)	8.23E-12
			Interaction effect (GxE)		
Calorie intake (1-SD)			-9.00E-04 (1.77E-03)	0.611	
Protein (1-SD)			-2.14E-03 (1.79E-03)	0.232	
Fat (1-SD)			-2.26E-04 (1.76E-03)	0.898	
Carbohydrate (1-SD)			-9.76E-04 (1.78E-03)	0.583	
PRS <sub>unweighted</sub>		Genetic effect (G)	4.00E-02 (4.17E-03)	1.19E-21	
		Interaction effect (GxE)			
		Calorie intake (1-SD)	-3.22E-03 (4.15E-03)	0.438	
		Protein (1-SD)	-5.04E-03 (4.21E-03)	0.232	
		Fat (1-SD)	2.32E-04 (4.14E-03)	0.955	
		Carbohydrate (1-SD)	-3.99E-03 (4.16E-03)	0.337	
HEXA		PRS	Genetic effect (G)	1.25E-02 (9.72E-04)	6.73E-38
			Interaction effect (GxE)		
	Calorie intake (1-SD)		1.31E-03 (9.83E-04)	0.181	
	Protein (1-SD)		1.49E-03 (9.78E-04)	0.128	
	Fat (1-SD)		1.24E-03 (9.73E-04)	0.203	
	Carbohydrate (1-SD)		1.06E-03 (9.85E-04)	0.280	
	PRS <sub>unweighted</sub>	Genetic effect (G)	3.60E-02 (2.27E-03)	2.87E-56	
		Interaction effect (GxE)			
		Calorie intake (1-SD)	-1.74E-03 (2.31E-03)	0.451	
		Protein (1-SD)	-6.63E-04 (2.34E-03)	0.777	
		Fat (1-SD)	-3.87E-04 (2.30E-03)	0.867	
		Carbohydrate (1-SD)	-2.21E-03 (2.30E-03)	0.336	

The association between PRS and phenotype and the interaction of PRS with calorie intake were analyzed by linear regression for BMI, and adjusted for age, sex, recruitment area and 10 principal components for KARE, and for sex, age and 10 principal components for CAVAS and HEXA. The significance threshold was  $p < 4.17E-04$  (0.05/120 after multiple correction). PRS, polygenic risk score; SE, standard error.

#### *Interaction Analysis between PRS and aPRS with Calorie Intake in BMI and Obesity*

We conducted an interaction analysis of the PRS and total calorie intake in the 3 cohorts using linear regression for BMI and logistic regression for obesity. These results indicated that no significant interaction exists between

the PRS and total calorie intake for BMI (Table 3) or obesity (online suppl. Table S6). We conducted this analysis also on the intake of protein, fat, and carbohydrates and, again, did not observe any significant interaction with each of these after multiple correction ( $p < 4.17 \times 10^{-4}$ ; Table 3; online suppl. Table S6).

**Table 4.** Association and interaction analyses of aPRS with BMI

Study	Test	Obesity			
		OR (95% CI)	<i>p</i> value		
KARE	aPRS	Genetic effect (G)	1.97E-02 (2.79E-03)	1.46E-12	
		Interaction effect (GxE)			
		Calorie intake (1-SD)	9.64E-04 (2.83E-03)	0.733	
		Protein (1-SD)	2.47E-03 (2.88E-03)	0.391	
		Fat (1-SD)	3.19E-03 (2.76E-03)	0.249	
		Carbohydrate (1-SD)	-1.03E-03 (2.85E-03)	0.718	
	aPRS <sub>unweighted</sub>	Genetic effect (G)	7.59E-02 (6.72E-03)	2.34E-29	
		Interaction effect (GxE)			
		Calorie intake (1-SD)	-5.00E-05 (6.82E-03)	0.994	
		Protein (1-SD)	3.61E-03 (6.87E-03)	0.599	
		Fat (1-SD)	3.95E-03 (6.81E-03)	0.562	
		Carbohydrate (1-SD)	-4.45E-03 (6.74E-03)	0.510	
	CAVAS	aPRS	Genetic effect (G)	1.92E-02 (2.72E-03)	2.00E-12
			Interaction effect (GxE)		
Calorie intake (1-SD)			-7.50E-05 (2.72E-03)	0.978	
Protein (1-SD)			-1.34E-03 (2.75E-03)	0.625	
Fat (1-SD)			6.77E-04 (2.71E-03)	0.803	
Carbohydrate (1-SD)			-5.36E-07 (2.74E-03)	0.9998	
aPRS <sub>unweighted</sub>		Genetic effect (G)	6.91E-02 (6.43E-03)	8.07E-27	
		Interaction effect (GxE)			
		Calorie intake (1-SD)	-8.20E-04 (6.51E-03)	0.900	
		Protein (1-SD)	-2.83E-03 (6.60E-03)	0.668	
		Fat (1-SD)	2.09E-03 (6.56E-03)	0.750	
		Carbohydrate (1-SD)	8.69E-01 (6.52E-03)	0.869	
HEXA		aPRS	Genetic effect (G)	1.85E-02 (1.65E-03)	8.15E-29
			Interaction effect (GxE)		
	Calorie intake (1-SD)		2.07E-03 (1.64E-03)	0.208	
	Protein (1-SD)		2.01E-03 (1.63E-03)	0.219	
	Fat (1-SD)		1.60E-03 (1.63E-03)	0.326	
	Carbohydrate (1-SD)		1.80E-03 (1.65E-03)	0.276	
	aPRS <sub>unweighted</sub>	Genetic effect (G)	6.27E-02 (3.97E-03)	5.62E-56	
		Interaction effect (GxE)			
		Calorie intake (1-SD)	-1.89E-03 (3.99E-03)	0.635	
		Protein (1-SD)	-1.87E-04 (3.96E-03)	0.962	
		Fat (1-SD)	8.73E-04 (3.94E-03)	0.824	
		Carbohydrate (1-SD)	-3.12E-03 (4.01E-03)	0.437	

The association between aPRS and phenotype and the interaction of aPRS with calorie intake were analyzed by linear regression for BMI, adjusted for age, sex, recruitment area, and 10 principal components for KARE, and for sex, age and 10 principal components for CAVAS and HEXA. The significance threshold was  $p < 4.17E-04$  (0.05/120 after multiple correction). aPRS, association polygenic risk score; SE, standard error.

Next, we analyzed the interaction of calorie intake and PRS<sub>unweighted</sub> in both BMI and obesity. The results were similar to those for PRS, in that we did not identify any significant interaction between total calorie, protein, fat, or carbohydrate intake in any of the 3 cohorts (Table 3; online suppl. Table S6).

In addition, we conducted an interaction analysis of the aPRS that was calculated with potentially associated GWAS SNPs in these cohorts. The interactions between aPRS and total calorie intake in all 3 cohorts were performed using linear regression for BMI and logistic regression for obesity. Again, in all 3 cohorts, no interaction

was observed between aPRS and total calorie intake (Table 4; online suppl. Table S7). Furthermore, when the interactions of protein, fat, and carbohydrate intake were analyzed, there were similar negative results in all 3 cohorts for BMI and obesity (Table 4; online suppl. Table S7).

We also analyzed the interaction of calorie intake with the aPRS<sub>unweighted</sub> (Table 4; online suppl. Table S7). We did not observe any significant results for total calorie, protein, fat, or carbohydrate intake in all 3 cohorts.

Recently, a BMI GWAS discovered 941 independent SNPs using around 700,000 participants of European ancestry [15]. We generated another set of BMI PRS using these 941 SNPs (PRS<sup>2</sup> and PRS<sup>2</sup><sub>unweighted</sub> and aPRS<sup>2</sup> and aPRS<sup>2</sup><sub>unweighted</sub>). Using these, we analyzed the interactions with calorie and macronutrient intakes for BMI, and no significant interactions were observed (online suppl. Tables S8, S9).

## Discussion

In this study, we calculated the PRS on the basis of 347 BMI GWAS SNPs in 35,094 individuals in 3 Korean cohorts, and observed no significant interactions between the PRS and calorie intake for BMI or obesity, in any of the 3 cohorts. In addition, we selected 62 SNPs displaying potential associations with BMI and obesity in the Korean cohorts for the aPRS and, again, observed no interactions in the aPRS for calorie intake based on BMI and obesity in each cohort.

Several methods have been reported for the selection of PRS SNPs in accordance with the appropriate studies to be considered for the interaction: (1) whether all GWAS SNPs, or only ethnically related SNPs were included, (2) whether PRS were determined by being weighted for effect size of SNPs, or unweighted; (3) whether the PRS SNPs were selected by validation in the study samples. We attempted to test for the most likely associations, but no interaction between BMI PRSs and calorie intake were found.

Although previous studies have investigated the interaction between BMI PRS and diverse nutrients including sugar-sweetened beverages, fried foods, carbohydrates, animal protein and fat, and vegetable protein, fat, and fiber [28–31, 40], no study has yet investigated the direct interaction between BMI PRS and total calorie intake. However, Tyrrell et al. [31] analyzed the interactions of PRS with a calorie-dense “Western” diet along with diverse nutrients in the UK Biobank study, and also did not identify any interactions between them based on BMI. This calorie-dense “Western” diet is similar to the total calorie intake in terms of the high consumption of calories.

There are several limitations to this study. The first is the statistical power, which remains a major issue in gene-environment interaction studies [41–43]. To determine the effects of the interaction between these 2 factors, a sample size 4 times greater than that of the GWAS sample is required [41, 42, 44]. We determined the statistical power for this study using the Quanto program. We assumed the following conditions for power calculation: unmatched case-control, 1.5 control per case; risk allele frequency, 0.35; genetic model of log-additive inheritance model, OR for the marginal association between the genetic variant and obesity risk, 1.08; population prevalence for obesity, 42%; and OR for the marginal association between total calorie intake and obesity risk, 1.05. Approximately 4,000 obesity cases and 5,600 normal controls included here yielded a statistical power of 80% for the detection of a gene-environment interaction OR of between 1.19 ( $\alpha = 0.05$ ) and 1.29 ( $\alpha = 0.001$ ) for common risk alleles (frequency, 35%). Since there is no evidence to support that the OR for the gene-environment in obesity is as high as 1.19, the power calculation suggests that a cohort with a much larger sample size is required to detect the interaction for obesity. Therefore, interaction analyses with a much larger sample (at least >4-fold greater, at least, is needed to detect an OR <1.10) are needed for the interaction between PRS and calorie intake to be evident.

This study reports that the PRS conducted with BMI GWAS SNPs are not associated with calorie intake for both BMI and obesity, using data on 35,094 Korean participants from 3 population-based cohorts, and performed with weighted and unweighted PRS and weighted and unweighted aPRS.

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## Statement of Ethics

This study was conducted according to the guidelines established in the Declaration of Helsinki. All participants provided written informed consent to participate in the study. The protocol used for this project was approved by the Institutional Review Board (IRB) of Kyung Hee University (KHSIRB-19-387(EA)).



## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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## Author Contributions

W.-J.L. and J.E.L. conceived the original idea for the study, conducted the statistical analyses, and drafted the manuscript. B.O. and J.E.L. provided guidance on study design and statistical analyses. S.Y.R., M.K.K., and Y.-J.K. contributed to the analytical strategy and access to the KoGES consortium data. H.U.J., J.-O.K., T.P. and S.W. provided guidance on statistical analyses. All authors read and approved the final version.

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