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# Association between the *APOB* rs1469513 polymorphism and obesity is modified by dietary fat intake in Koreans

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ABSTRACT

*Objective:* The apolipoprotein B (*APOB*) gene has been reported to be a candidate gene for individual susceptibility to dyslipidemia and obesity. The aim of this study was to investigate the effect of the *APOB* rs1469513 polymorphism on plasma lipid profiles and obesity-related phenotypes, together with their modulation by dietary intake in Korean individuals.
*Methods:* We analyzed the plasma lipid profiles, obesity-related phenotypes, and dietary intake of 6470 Korean aged 40 to 59 y from the KoGES (Korean Genome Epidemiology Study) database. The effects of *APOB* rs1469513 on traits, the interaction of *APOB* rs1469513 and dietary intake on traits were analyzed.
*Results:* Plasma levels of total cholesterol ($P = 0.001$) and low-density lipoprotein cholesterol ($P = 0.010$), body weight ($P = 0.048$), and body mass index ($P = 0.029$) were significantly different in carriers of the A allele and minor G allele of *APOB* rs1469513. Among individuals whose fat intake was above the median, the difference for the body mass index across genotypes is 1.14% (AA 24.66 kg/m$^2$ versus AG+GG 24.94 kg/m$^2$, $P = 0.004$) and carriers of the minor G allele had increased odds of being obese (Odds ratios, 1.31; 95% confidence interval, 1.09–1.57; $P = 0.004$) compared with homozygotes for the A allele.
*Conclusions:* Our findings support a significant association between the *APOB* rs1469513 variant, plasma lipid profiles, and obesity-related phenotypes. This association has the potential to be modified by dietary fat intake. These results may offer proof that the differences between normal weight and overweight/obese individuals might partly result from different SNPs.


## Introduction

Dyslipidemias, such as hypercholesterolemia, hyper-low-density lipoprotein (LDL) and hypo-high-density lipoprotein cholesterolemia, and obesity are problems that pose a considerable burden to public health worldwide [1,2]. Dyslipidemia and obesity have been associated strongly with an increased risk for cardiovascular disease, diabetes, metabolic syndrome, and other health problems [3]. Therefore, early detection of dyslipidemia and obesity is important for the appropriate prevention and treatment of these diseases.

Apolipoprotein B (*APOB*) plays an important role in lipid metabolism as the main apolipoprotein of chylomicrons and LDL and serves as the ligand for the recognition and catabolism of LDL by the LDL receptor [4]. The plasma lipid profiles and body weight of an individual are affected by interactions between dietary and genetic factors. The *APOB* gene has been reported to be a candidate gene for individual susceptibility to dyslipidemia and obesity [5–7].

The association of single nucleotide polymorphisms (SNPs) within the *APOB* gene with dyslipidemia has been observed in many different populations [8–10]. Additionally, *APOB* SNPs have been reported to be associated with obesity in Chinese children [6], American youths [11] and Canadian adults [12]. However, one study reported that *APOB* SNPs did not appear to influence dyslipidemia and obesity in Asian Indians [13]. These

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inconsistent results might be explained by differences in *APOB* that result from genetic variations among ethnic groups; some of these variations might correspond to functionally important mutations, but those found in other ethnic group might not. Furthermore, the interaction between genetic variation and environmental factors, such as dietary intake, might modulate the phenotype, which might create inconsistent and confusing study results.

A positive association between high energy intake and dyslipidemia or obesity is well established [14,15]. Additionally, different compositions of dietary macronutrients can affect dyslipidemia and obesity [16,17]. High dietary fat intake has been shown to worsen dyslipidemia and increase the risk for obesity [16]. In contrast, a decrease in carbohydrate intake and an increase in protein intake improved the blood lipid profile and were associated negatively with obesity [17]. Recent studies have reported that interactions between genetic variations and dietary macronutrient intake modify dyslipidemia or obesity [18,19].

We hypothesized that the differences between normal weight and overweight/obese individuals might partly result from different SNPs of the gene to influence serum lipid levels. Therefore, we aimed to evaluate the association of the *APOB* SNP (rs1469513) with plasma lipid profiles and obesity-related phenotypes in middle-aged Koreans who participated in KoGES (Korean Genome Epidemiology Study). We also elucidated the interaction between the *APOB* allele and dietary intake in relation to the plasma levels of total cholesterol (TC) and LDL cholesterol (LDL-C), and body mass index (BMI).

## Methods

### *Participants*

The KoGES was performed as a cohort study to investigate chronic disease (diabetes, hypertension, osteoporosis, obesity, and metabolic syndrome) in adults aged 40 to 69 y [20]. Among the 10 038 participants participating in the KoGES, 6470 (3164 men and 3306 women) were selected. The age of the participants ranged from 40 to 59 y. Participants who completed dietary records were selected. Men with daily energy intake of $\leq$800 kcal or $\geq$4000 kcal and women with intakes of $\leq$500 kcal or $\geq$3,500 kcal were excluded. Finally, individuals were also excluded due to lack of data on their anthropometric variables. This study protocol was approved by the Institutional Review Board of Ewha Womans University, Seoul, Korea.

### *Anthropometric variables and blood pressure*

Body weight, height, and waist circumference (WC) were measured using a standardized procedure. Body composition (lean body mass, fat body mass, and waist-to-hip ratio) was analyzed using an In-body 3.0 (Biospace Co., Ltd, Seoul, Korea), an eight-polar bioelectrical impedance analysis system. BMI was calculated by dividing the weight in kg by the height in $m^2$. Obesity was defined as a BMI $\geq$25 kg/$m^2$, which is the World Health Organization's Asia-Pacific Area criterion for obesity [21].

Systolic and diastolic blood pressures (BPs) were measured with the individuals in a prone position, after 5 min of rest. An average of three BP readings, which were conducted at intervals of 30 sec, was used for the analysis.

### *Blood biochemical measurements*

Venous blood was collected after an overnight fast, and all plasma samples were subjected to biochemical measurements. Fasting glucose, fasting insulin, TC, HDL-C, and triacylglycerols (TGs) were measured using a Hitachi 7600 Automatic Analyzer (Hitachi, Tokyo, Japan). The homeostatic model assessment-insulin resistance index (HOMA-IR) was calculated as fasting insulin (μIU/mL) × fasting glucose (mmol/L)/22.5 [22]. The level of LDL-C was calculated using the following equation, described previously, for individuals with plasma TG levels <400 mg/dL [23]: LDL-C = [TC−{HDL-C−(TGs/5)}].

### *Dietary analysis*

Dietary intake was estimated using a semi-quantitative food frequency questionnaire that had been developed and validated for the KoGES [24]. It consisted of questions on 103 food items, which were combined into the 23 nutrients used in the Korean food composition table. The data were analyzed to give the average daily dietary intake using the Computer Aided Nutritional Analysis Program Pro 3.0., a nutrient database developed by the Korean Nutrition Society [25]. Intakes of protein, fat, and carbohydrate were given as percentages of the total daily energy intake.

### *Genotyping and SNP selection*

Genomic DNA was extracted from whole blood and genotyped on an Affymetrix Genome-Wide Human SNP array 5.0. The genotype quality control processes were described in the previous GWAS (Genome-Wide Association Study) [20]. Briefly, the Bayesian Robust Linear Modeling using the Mahalanobis Distance genotyping algorithm was used for genotype calling. Samples with a high missing call rate ($\geq$4%), high heterozygosity (>30%), sex inconsistencies, and any kinds of tumor were excluded from subsequent analyses, along with related or identical individuals whose computed identity-by-state value was high (>0.80). Four SNPs in and around *APOB* (rs693, rs1271395, rs570877, and rs1469513) were initially found, as part of the entire SNPs of the KoGES. The *APOB* rs1271395 polymorphism was deviated from Hardy–Weinberg equilibrium ($P > 0.05$) and the minor allele frequency (MAF) of *APOB* rs570877 polymorphism was <0.05. Additionally, the inequality of variance between different genotypes was found in the *APOB* rs693. Therefore, these SNPs were not considered in our association analysis, and *APOB* rs1469513, which presented the significant associations with plasma lipid profiles and obesity-related phenotypes, was studied.

### *Statistical analysis*

All statistical analyses were performed using SPSS for Windows software (version 17.0; SPSS Inc, Chicago, IL, USA) and R (version 2.14.0). Continuous variables were examined for normal distribution before statistical testing, and logarithmic transformation was performed on skewed variables. Data were presented as mean values ± SEM. Log-transformations were applied to TGs, glucose, insulin and HOMA-IR; data were presented as back-transformed geometric mean and 95% confidence intervals (CIs). The *APOB* rs1469513 polymorphism was in Hardy–Weinberg equilibrium ($P > 0.657$) according to the $\chi^2$ test. The effect of rs1469513 on traits was analyzed with generalized linear models, and sex and age were also considered as covariates to prevent their confounding effect. To determine the interaction between the *APOB* rs1469513 genotype and intake of macronutrients, TC, LDL-C, and BMI of the participants were compared according to their levels of total energy intake and the percentage of energy they obtained from protein, fat, and carbohydrate with the median levels for these parameters (energy: 1983.7 kcal, protein: 15.7%, fat: 19.9%, carbohydrate: 64.9%, respectively). TC, LDL-C, and BMI were dichotomized, and the interaction between the *APOB* rs1469513 genotype and dietary macronutrient intake was detected with the logistic regression. Sex and age were also considered as covariates in the logistic regression. With the coefficients of the interaction term, the odds ratios (ORs) of being obese and 95% CIs were estimated. Multiple testing was adjusted with the false discovery rate (FDR) using R software. The FDR suggested previously [26] indicated the expected proportion of false positives among all significant hypotheses. In our analysis, the correlations between response variables of interest were found to be high and therefore the distributions of test statistics were calculated with permutation. The FDRs were estimated by previously [27].

## Results

### *General characteristics*

The anthropometric and biochemical characteristics of the 6470 participants classified by sex are listed in Table 1. Significant differences in height, weight, BMI, waist-to-hip ratio, lean body mass, fat body mass, and BPs were observed between men and women (Table 1). The plasma levels of TC, LDL-C, and TGs were significantly higher in men than in women. The intake of dietary energy and fat was higher in men than in women, but dietary carbohydrate intake was higher in women than in men.

The MAF of *APOB* rs1469513 was 0.10 in all of the participants, and the genotype distributions did not deviate from Hardy–Weinberg equilibrium ($P > 0.05$). The MAF of *APOB* rs1469513 did

**Table 1**
General characteristics of Korean participants

| | Men (n = 3164) | Women (n = 3306) |
|---|---|---|
| Age (y) | 47.74 ± 0.10 | 47.94 ± 0.01 |
| Height (cm) | 167.81 ± 0.10* | 154.85 ± 0.09 |
| Weight (kg) | 69.22 ± 0.17* | 59.68 ± 0.15 |
| BMI (kg/m$^2$) | 24.52 ± 0.06* | 24.88 ± 0.05 |
| Waist-to-hip ratio† | 0.89 ± 0.001* | 0.85 ± 0.001 |
| Lean body mass (kg)† | 54.14 ± 0.12* | 40.62 ± 0.09 |
| Fat body mass (kg)† | 15.38 ± 0.09* | 18.93 ± 0.10 |
| Blood pressure (mm Hg) | | |
| Systolic | 115.61 ± 0.29* | 113.54 ± 0.32 |
| Diastolic | 76.21 ± 0.22* | 72.17 ± 0.22 |
| Total cholesterol (mg/dL) | 194.46 ± 0.64* | 188.28 ± 0.61 |
| HDL-cholesterol (mg/dL) | 43.16 ± 0.17* | 46.09 ± 0.18 |
| LDL-cholesterol (mg/dL)‡ | 117.14 ± 0.60§ | 114.68 ± 0.54 |
| Triacylglycerols (mg/dL) | 183.04 ± 2.25* | 140.34 ± 1.41 |
| Fasting glucose (mg/dL) | 89.74 ± 0.47* | 83.19 ± 0.40 |
| Fasting insulin (μIU/mL) | 7.17 ± 0.09* | 7.74 ± 0.09 |
| HOMA-IR (arbitrary units) | 17.65 ± 0.11* | 15.38 ± .11 |
| Dietary intake | | |
| Energy intake (kcal) | 2142* | 1970 |
| Protein (%energy) | 16 | 16 |
| Fat (%energy) | 20* | 19 |
| Carbohydrate (%energy) | 64* | 65 |
| *APOB* rs1469513 A>G (MAF/HWE) | 0.10/0.13 | 0.10/0.38 |

*APOB*, apolipoprotein B; BMI, body mass index; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment-insulin resistance; HWE, Hardy–Weinberg equilibrium; LDL, low-density lipoprotein; MAF, minor allele frequency

Data represent mean ± SEM

* *P*-values obtained in the independent *t* test or $\chi^2$ test for differences between men and women ($P < 0.001$).

† Waist-to-hip ratio, lean body mass, and fat body mass were measured in 2655 men and 2664 women.

‡ LDL-cholesterol was measured in 2999 men and 3169 women. Dietary fat intake was measured in 3028 men and 3038 women, and if triacylglycerols were <400 mg/dL, LDL-cholesterol = [total cholesterol − {HDL-cholesterol + (triacylglycerol/5)}].

§ *P*-values obtained in the independent *t* test or $\chi^2$ test for differences between men and women ($P < 0.005$)

**Table 2**
Association of *APOB* rs1469513 genotype with anthropometric variables and biochemical profiles in Korean participants

| | AA (n = 5203) | AG+GG (n = 1232) | *P*-value* |
|---|---|---|---|
| Height (cm) | 161.20 ± 0.07 | 161.18 ± 0.15 | 0.912 |
| Weight (kg) | 64.23 ± 0.12 | 64.79 ± 0.25 | 0.048 |
| BMI (kg/m$^2$) | 24.66 ± 0.04 | 24.70 ± 0.09 | 0.029 |
| Waist-to-hip ratio† | 0.87 ± 0.001 | 0.87 ± 0.002 | 0.073 |
| Lean body mass (kg)† | 47.34 ± 0.08 | 47.50 ± 0.16 | 0.397 |
| Fat body mass (kg)† | 17.08 ± 0.08 | 17.42 ± 0.16 | 0.056 |
| Total cholesterol (mg/dL) | 190.59 ± 0.49 | 194.23 ± 1.01 | 0.001 |
| HDL-cholesterol (mg/dL) | 44.64 ± 0.14 | 44.71 ± 0.29 | 0.832 |
| LDL-cholesterol (mg/dL)‡ | 115.35 ± 0.45 | 117.98 ± 0.92 | 0.010 |
| Triacylglycerols (mg/dL)§ | 139.11 (137.22–140.89) | 142.47 (138.44–146.63) | 0.173 |
| Glucose (mg/dL)§ | 85.79 (85.36–86.22) | 86.57 (85.64–87.50) | 0.209 |
| Insulin (μIU/mL)§ | 6.51 (6.40–6.62) | 6.66 (6.44–6.88) | 0.190 |
| HOMA-IR (arbitrary units)§ | 16.26 (16.16–16.35) | 16.45 (16.25–16.65) | 0.200 |

*APOB*, apolipoprotein B; BMI, body mass index; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment-insulin resistance; LDL, low-density lipoprotein

* Data represents mean ± SEM and *P*-values obtained in the generalized linear model with adjustment for sex and age.

† Waist-to-hip ratio, lean body mass, and fat body mass were measured in 4266 individuals of the AA genotype and 1023 of the AG+GG genotype.

‡ LDL-cholesterol was measured in 5047 individuals with the AA genotype and 1191 with the AG+GG genotype, and if triacylglycerols were <400 mg/dL, LDL-cholesterol = [Total cholesterol − {HDL-cholesterol + (triacylglycerol/5)}].

§ Values are geometric mean (95% CI).

not differ between men and women (Table 1). No significant interaction between *APOB* rs1469513 genotype and sex for the biochemical profiles and anthropometric variables was observed. Therefore, we carried out sex-adjusted analysis in all participants combined.

### APOB *rs1469513 genotype, anthropometric variables, and biochemical profiles*

Table 2 shows anthropometric and biochemical variables depending on the *APOB* 1469513 polymorphism. The percent of participants with the minor homozygous genotypes of *APOB* rs1469513 was small (1.1%, n = 69) and the genotypes with at least one minor G allele were pooled into one category and compared with homozygotes A allele. The difference for plasma levels of TC and LDL-C in carriers of the A allele and minor G allele of *APOB* rs1469513 was 1.87% (AA 190.59 ± 0.49 mg/dL versus AG+GG 194.23 ± 1.01 mg/dL; $P = 0.001$) and 2.23% (AA 115.35 ± 0.45 mg/dL versus AG+GG 117.98 ± 0.92 mg/dL; $P = 0.010$), respectively. And for body weight, the difference in carriers of the A allele and minor G allele of *APOB* rs1469513 was 0.86%. Body weight showed borderline significant association with the *APOB* rs1469513 ($P = 0.048$). The *APOB* rs169513 SNP showed a significant association with BMI in the dominant model, after adjustment for age and sex, although the difference was small at 0.16% (AA 24.66 ± 0.04 kg/m$^2$ versus AG+GG 24.70 ± 0.09 kg/m$^2$; $P = 0.029$) (Table 2). After adjustment for multiple testing using the FDR method, participants with G allele carrier still showed significantly higher plasma level of TC ($P = 0.006$). However, the significant difference of LDL-C (FDR = 0.090), body weight (FDR = 0.343), and BMI (FDR = 0.227) across genotypes disappeared after adjustment for multiple testing.

### *Interaction of the* APOB *rs1469513 genotype and dietary intakes in relation to dyslipidemia and BMI*

We analyzed whether the interaction between the *APOB* rs1469513 genotype and dietary macronutrient intake affected the levels of plasma TC and LDL-C or BMI because those variables were significantly associated with *APOB* rs1469513 genotype in a dominant model (Table 3). We classified each individual by comparing his or her total energy intake and the percentage of energy they obtained from protein, fat, and carbohydrate with the respective medians for these parameters (1983.7 kcal, 15.7%, 19.9%, and 64.9%, respectively). Only in the participants who consumed high levels of energy, did we find significant difference for plasma levels of TC and LDL-C across genotype of *APOB* rs1469513, although the differences were small at 2.42% (AA 190.83 ± 0.70 mg/dL versus AG+GG 195.56 ± 0.14 mg/dL; $P = 0.005$) and 1.96% (AA 116.77 ± 1.32 mg/dL versus AG+GG 119.10 ± 1.28 mg/dL; $P = 0.017$), respectively. Among participants who consumed low levels of energy, the levels of TC ($P = 0.102$) and LDL-C ($P = 0.265$) were not significantly different between homozygotes for the A allele and carriers of the G allele. Among participants with high fat intake, the difference for TC between carriers of the A allele and minor G allele of *APOB* rs1469513 was 2.04% (AA 192.51 ± 1.47 mg/dL versus AG+GG 196.51 ± 1.45 mg/dL; $P = 0.041$), whereas the two genotype groups were not

**Table 3**
Effects of interaction between *APOB* rs1469513 genotype and dietary intake on plasma lipid profiles and BMI in Korean participants

| | Total cholesterol (mg/dL) | | | | LDL-cholesterol (mg/dL) | | | | BMI (kg/m$^2$) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | AA (n = 4939) | AG+GG (n = 1167) | *P*-value* | *P*-value† | AA (n = 4793) | AG+GG (n = 1126) | *P*-value* | *P*-value† | AA (n = 4939) | AG+GG (n = 1167) | *P*-value* | *P*-value† |
| Energy, kcal | | | | 0.113 | | | | 0.309 | | | | 0.025 |
| <1983.7 | 190.19 ± 0.70 | 192.83 ± 1.45 | 0.102 | | 115.12 ± 0.63 | 115.57 ± 0.64 | 0.265 | | 24.51 ± 0.06 | 24.65 ± 0.13 | 0.323 | |
| ≥1983.7 | 190.83 ± 0.70 | 195.56 ± 0.14 | 0.005 | | 116.77 ± 1.32 | 119.10 ± 1.28 | 0.017 | | 24.80 ± 0.06 | 25.10 ± 0.12 | 0.029 | |
| Protein, % energy | | | | 0.788 | | | | 0.775 | | | | 0.018 |
| <15.7 | 188.67 ± 0.73 | 192.88 ± 0.70 | 0.004 | | 114.03 ± 0.66 | 117.09 ± 0.63 | 0.043 | | 24.59 ± 0.06 | 24.74 ± 0.13 | 0.289 | |
| ≥15.7 | 193.40 ± 1.46 | 195.68 ± 1.46 | 0.091 | | 117.05 ± 1.33 | 119.29 ± 1.33 | 0.137 | | 24.70 ± 0.06 | 25.05 ± 0.13 | 0.013 | |
| Fat, % energy | | | | 0.291 | | | | 0.323 | | | | 0.035 |
| <19.9 | 188.12 ± 0.72 | 193.51 ± 0.71 | 0.016 | | 113.37 ± 0.65 | 117.79 ± 0.64 | 0.131 | | 24.64 ± 0.07 | 24.84 ± 0.13 | 0.940 | |
| ≥19.9 | 192.51 ± 1.47 | 196.90 ± 1.45 | 0.041 | | 115.68 ± 1.34 | 120.56 ± 1.31 | 0.063 | | 24.66 ± 0.06 | 24.94 ± 0.13 | 0.004 | |
| Carbohydrate, % energy | | | | 0.189 | | | | 0.437 | | | | 0.012 |
| <64.9 | 193.76 ± 0.71 | 187.94 ± 0.71 | 0.133 | | 118.05 ± 0.65 | 113.17 ± 0.65 | 0.255 | | 24.67 ± 0.06 | 24.99 ± 0.13 | 0.021 | |
| ≥64.9 | 196.29 ± 1.46 | 192.80 ± 1.46 | 0.003 | | 119.80 ± 1.33 | 116.54 ± 1.33 | 0.023 | | 24.63 ± 0.06 | 24.81 ± 0.13 | 0.223 | |

* Data represent mean ± SEM and *P*-values obtained in the multivariable interaction model after adjustment for sex and age (within genotype).
† Data represent mean ± SEM and *P*-values obtained in the multivariable interaction model after adjustment for sex and age (within gene–diet interaction).

significantly different with respect to the level of LDL-C ($P$ = 0.063). On the other hand, among participants with high carbohydrate intake, the differences for levels of TC and LDL-C across genotype of *APOB* rs146951 were 1.81% ($P$ = 0.003) and 2.80% ($P$ = 0.023), whereas those were not significantly different in two genotype groups that consumed low levels of carbohydrate.

Although no direct interaction between *APOB* rs1469513 genotypes and dietary macronutrient intake was found with respect to plasma lipid levels, the genetic effect of *APOB* rs1469513 on BMI was influenced by dietary macronutrient intake (Table 3). Interactions between *APOB* rs1469513 and all dietary macronutrient intakes with respect to BMI showed significant level ($P$ for the interaction terms for energy, protein, fat, and carbohydrate were 0.025, 0.018, 0.035, and 0.012, respectively; Table 3). However, the interactions between *APOB* rs1469513 and dietary macronutrient intake did not reach statistically significant value (FDRs for the interaction terms for energy, protein, fat, and carbohydrate were 0.065, 0.093, 0,060, and 0,058, respectively) after correction of multiple testing. The difference for BMI between carriers of the A allele and minor G allele of *APOB* rs1469513 was 1.20% in those who consumed high levels of energy (AA 24.80 ± 0.06 kg/m$^2$ versus AG+GG 25.10 ± 0.12 kg/m$^2$; $P$ = 0.029), 1.40% in protein (AA 24.70 ± 0.06 kg/m$^2$ versus AG+GG 25.05± 0.13 kg/m$^2$; $P$ = 0.013) or 1.12% in fat (AA 24.66 ± 0.06 kg/m$^2$ versus AG+GG 24.94 ± 0.13 kg/m$^2$; $P$ = 0.004), whereas those were not significantly different in two genotype groups who consumed low levels of energy ($P$ = 0.323), protein ($P$ = 0.289), or fat ($P$ = 0.940). In the low-carbohydrate intake group, the significant difference for BMI across genotype of *APOB* rs1469513 was 1.28% (AA 24.67 ± 0.06 kg/m$^2$ versus AG+GG 24.99 ± 0.13 kg/m$^2$; $P$ = 0.021); on the other hand, BMI was not significantly different in participants with high carbohydrate intake ($P$ = 0.223).

### *Interaction between the* APOB *rs1469513 genotype and dietary intake with respect to the odds of being obese*

We used logistic regression to test the effects of the *APOB* rs1469513 genotypes and dietary macronutrients intake on the odds of being obese, after adjustment for age and sex (Fig. 1). Among the effects of the *APOB* rs1469513 genotypes and intake of dietary macronutrients on the odds of being obese, we found a significant interaction between *APOB* rs1469513 genotype and

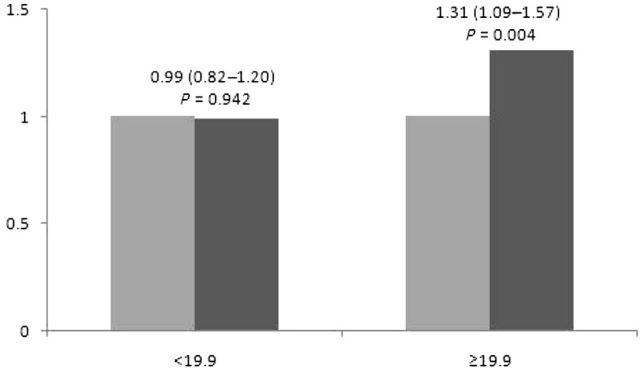


**Fig. 1.** Association of *APOB* rs1469513 genotype and dietary fat intake with obesity in Korean participants. ■: AA, ■: AG+GG. Odds ratios (95% CI) and corresponding *P*-values were calculated by logistic regression analysis, after adjustment for age and sex in 6066 Korean participants.

dietary fat intake in relation to the odds of being obese (*P*-interaction = 0.015). At low levels of dietary fat intake, there was no significant difference with respect to odds of being obese between the *APOB* rs169513 genotypes (ORs, 0.99; 95% CI, 0.82–1.20; $P = 0.942$). Conversely, at high levels of dietary fat intake, participants with the minor G allele of *APOB* rs1469513 showed a significantly increasing trend in odds of being obese when compared with homozygous carriers of the A allele (ORs, 1.31; 95% CI, 1.09–1.57; $P = 0.004$).

## Discussion

The rs1469513 polymorphism is the consequence of an A to G transversion at nucleotide 7256 in intron 5 of the *APOB* gene, which does not result in an amino acid change. The MAF for the rs1469513 in the Korean population was found to be ~10% in the present study. This MAF differed from that in a European population (40.8%), however, it was similar to those in other Asian (Japanese: 11.1%, China: 5.6%) populations and in an African (17.5%) population, which was obtained from HapMap data.

Our study reported significant interactions between the rs1469513 polymorphism and dietary macronutrient intake affecting BMI. To analyze the possibility of the false positive among our significant results, the multiple testing problems were adjusted with an FDR method. Significance of interactions between the rs1469513 and dietary intake on BMI disappeared after adjustment for multiple testing. One study [18] reported the interaction between ADIPOQ-11391 G>A and monounsaturated fatty acid intake reached statistical significance in an unadjusted model, however, the observed interaction was not significant after FDR adjustment [18]. The study results suggested no general consensus on how to best account for multiple comparisons [18,28]. The insufficient sample size might be a main reason for nonsignificance results, although there is still some possibility that our finding is of false-positive significance. The sample size at the 0.05 significance level required more than those of this study, adjusted with Bonferroni correction.

Similar results of our study were obtained in previous studies of other *APOB* polymorphisms [6,11,12]. For example, the 7367 C>T variant of *APOB* was associated with significantly higher plasma levels of TC or LDL-C in three different populations, but no significant associations were observed for plasma levels of HDL-C or TGs. Studies that applied systematic meta-analysis have reported that *APOB* polymorphisms are associated with altered lipid levels [29,30].

Moreover, the results of our study showed that the rs1469513 polymorphism was associated with a significantly greater incidence of obesity-related phenotypes. One study reported that, among Chinese children, those with the XbaI X(+) allele of the *APOB* gene exhibited significantly higher values of BMI than those with the X(−) allele [6]. Our results provide a new perspective in studying associations between genetic variations of rs1469513, and dyslipidemia and obesity among the Korean population.

Recent studies have reported that the interaction between dietary fat intake and genetic variation has the potential to modulate the risk for dyslipidemia and obesity [31,32]. The minor allele carrier (G) of other *APOB* SNP (rs512535) has been associated with obesity-related phenotypes (BMI, WC). Interestingly, among the habitual high-fat consumers (>35% of energy), the *APOB* rs512535 GG homozygotes have been shown to have higher BMI than A allele carriers, however, BMI is not significantly different in low-fat consumers (<35% of energy) [31]. Also, XbaI polymorphism of the *APOB* locus has been shown to influence dyslipidemia, which appeared to be modulated dietary fat intake [32]. In our study, a strong positive association between consumption of high fat (>19.9% of energy) and odds of obesity was shown in participants with the minor allele variant of rs1469513. Although the intake of dietary fat in this study was considerably lower than that in previous studies [31,32], it was in agreement with national Korean data (average fat intake 19.6% for 2011 Korean National Health and Nutrition Examination Survey [KNHANES]) [33] compared with Americans (33.5% for the 2007–2008 U.S. NHANES) [34].

Our study has several limitations that should be considered and interpreted with caution. First, its cross-sectional design could not explicate evidence for the reasons of gene–diet interaction and its mechanistic basis. Second, the dietary intake was estimated by semi-quantitative food frequency questionnaire and thus may be inaccurate measures of real consumption amounts. Third, the dietary fat intake was generally low in Korean population, which may not be generalized to other populations, especially, Western populations with high fat intake. Therefore, future replication studies are needed to confirm those interactions in different populations.

## Conclusion

This population-based study of middle-aged Korean individuals demonstrated that a small difference in participants across rs1469513 showed for BMI and odds of obesity with respect to the intake of high levels of dietary fat. These results may offer proof that the differences between normal weight and overweight/obese individuals might partly result from different SNPs.

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