

Ultra-processed food intake, genetic polymorphisms, and the risk of dyslipidemia in the adult Korean population

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Ethical Standards Disclosure: Data in this study were from the Korean Genome and Epidemiology Study (KoGES, 4851-302), National Research Institute of Health, Centers of Disease Control and Prevention, Ministry for Health and Welfare, Republic of Korea. The KoGES was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving the KoGES participants were approved the Institutional Review Board of all the participating hospitals or institutes. The written informed consent in the KoGES was signed by participants prior to their participation.

Abstract

Objective: This study aimed to examine the association between ultra-processed food intake and dyslipidemia risk, and whether this association varied by the polygenic score for dyslipidemia in the adult Korean population.

Design: Prospective cohort study

Setting: Ultra-processed foods were identified under the NOVA classification. Participants were categorized into <5, 5 to <10, 10 to <15, 15 to <20, and $\geq 20\%$ E/d of ultra-processed food intake. The polygenic scores for dyslipidemia were calculated from 53,950 single nucleotide polymorphisms. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using multivariate logistic regression models.

Participants: 20,044 Korean adults aged ≥ 40 years in the Health Examinees (HEXA) study, the Cardiovascular Disease Association Study (CAVAS), and the Korea Association Resource (KARE) study

Results: During median follow-ups of 4.09, 8.67, and 15.67 years in the HEXA, CAVAS, and KARE studies, respectively, there were a total of 7,331, 786, and 1,732 incident dyslipidemia events. Ultra-processed food intake was not significantly associated with dyslipidemia risk. Compared with <5%E/d, the pooled OR (95% CI) of $\geq 20\%$ E/d of ultra-processed food intake for dyslipidemia incidence was 1.01 (0.90, 1.13; p for trend=0.83). There was no interaction by dyslipidemia-related genetic variations; ORs (95% CIs) were 1.04 (0.89, 1.22; p for trend=0.91) and 0.98 (0.84, 1.15; p for trend=0.72) for individuals with high and low polygenic scores, respectively (p for interaction=0.90).

Conclusions: No significant association was observed between ultra-processed food intake and the overall risk of dyslipidemia, nor in subgroups of polygenic scores for dyslipidemia among Korean adults with low ultra-processed food intake.

Keywords: Ultra-processed food, dyslipidemia, polygenic score, single nucleotide polymorphism

Introduction

The Global Burden of Disease Study revealed a growing contribution of dyslipidemia to the global disease burden over the past decade. In 1990, elevated low-density lipoprotein cholesterol (LDL cholesterol) levels ranked as the fifteenth leading risk factor for death, rising to eleventh in 2007 and eighth in 2017⁽¹⁾. A recent meta-analysis of randomized clinical trials indicated that diets rich in unsaturated fatty acids and soluble fiber, while low in saturated and *trans* fatty acids, were associated with reduced LDL cholesterol levels⁽²⁾, suggesting that modifying dietary factors could potentially prevent the risk of dyslipidemia.

Ultra-processed foods have drawn attention for their relation to the risk of non-communicable diseases and the sustainability of food systems. The NOVA classification, introduced in 2010 to categorize foods based on the type, degree, and scope of industrial processes, defines ultra-processed foods as ready-to-heat or ready-to-eat products with food additives and minimal whole foods⁽³⁾. In contrast to processed foods, which are whole foods preserved by typical methods like pickling or canning, ultra-processed foods are predominantly composed of components isolated from foods, either altered or unaltered, often consisting of five or more ingredients. Due to significant alterations in the food matrix during processing, the extensively damaged physical composition of ultra-processed foods may impact absorption processes, appetite, glucose response, and the function and nature of the gut microbiota, possibly leading to health outcomes distinct from those of whole foods of comparable nutritional composition⁽⁴⁾. The increasing production and intake of ultra-processed foods are thus considered challenges that need to be addressed within the framework of the UN Sustainable Development Goals and the Decade of Nutrition⁽⁵⁾. Economic development has been linked to a steady rise in ultra-processed food intake, particularly in Korea. The Korea National Health and Nutrition Examination Survey (KNHANES) reported that the proportions of consuming sugar-sweetened beverages and Western-style fast foods, such as sandwiches, pizza, hamburgers, and chicken nuggets, doubled from 1998 to 2009⁽⁶⁾. Despite the growing prevalence of dyslipidemia and ultra-processed food intake in Korea, studies on the association between ultra-processed food intake and the risk of dyslipidemia among Koreans are limited.

A recent meta-analysis of observational studies has reported positive associations between ultra-processed food intake and low HDL cholesterol levels (OR 2.02) and cardiovascular disease risk (RR 1.29)⁽⁷⁾. Cross-sectional studies have also suggested associations between ultra-processed food intake and low levels of HDL cholesterol^(8,9). Ultra-processed foods may contribute to unfavorable lipid profiles, partly due to their high content of saturated and *trans* fatty acids, and free sugars, but low content of dietary fiber and micronutrients⁽¹⁰⁾. A high intake of added sugars and refined carbohydrates, and a low intake of unsaturated fatty acids and dietary fiber have been suggested as

contributing factors to the elevation in LDL and non-HDL cholesterol levels⁽¹¹⁾.

Genetic factors may contribute to the development of dyslipidemia. Genome-wide association studies (GWASs) have reported that genetic variants explain approximately 10 to 12% of the total variance in lipid traits⁽¹²⁾. Since interactions by genetic variants may partially explain the residual susceptibility to dyslipidemia, further research on these interactions is important⁽¹³⁾.

The objective of this study was to examine whether ultra-processed food intake was associated with the risk of dyslipidemia and whether this association varied by genetic susceptibility to dyslipidemia in >20,000 Korean adults aged 40 years or older.

Methods

Study population

The participants were drawn from three prospective cohorts within the Korean Genome and Epidemiology Study (KoGES), a nationwide initiative aimed at investigating the etiological factors of complex diseases⁽¹⁴⁾: the Health Examinees (HEXA) study, the Cardiovascular Disease Association Study (CAVAS), and the Korea Association Resource (KARE) study. These cohorts comprised community-dwellers and individuals recruited from the national health examinee registry, all aged 40 years or older at baseline. Recruitment took place from 2004 to 2013 for the HEXA study, from 2005 to 2011 for the CAVAS, and from 2001 to 2002 for the KARE study.

Follow-up examinations were conducted once between 2012 and 2016 for the HEXA study, with a median (interquartile range [IQR]) follow-up duration of 4.09 (3.84, 5.84) years. In the CAVAS, a total of four follow-ups were carried out between 2007 and 2016 at intervals of one to three years, resulting in a median (IQR) follow-up of 8.67 (7.58, 8.92) years. The KARE study included a total of eight follow-ups conducted between 2003 and 2018 at two-year intervals, with a median (IQR) follow-up of 15.67 (15.17, 15.92) years. For the HEXA study, participants who completed the follow-up surveys were included, while for the CAVAS and KARE studies, the inclusion criteria encompassed anyone who participated in at least one of the last two follow-up periods.

In our analysis of the association between ultra-processed food intake and dyslipidemia risk, there were a total of 211,562 participants at baseline (n=173,195 for the HEXA study, n=28,337 for the CAVAS, and n=10,030 for the KARE study). Participants with the following characteristics were excluded: those who did not participate in a follow-up examination (n=131,095) (n=107,587 for the HEXA study, n=22,627 for the CAVAS, and n=881 for the KARE study); those who did not have genetic information (n=13,184) (n=12,948 for the HEXA study, n=0 for the CAVAS, and n=236 for the KARE study); those who had a history of dyslipidemia, myocardial infarction, coronary heart disease, heart failure, stroke, or cancer at baseline (n=45,955) (n=35,458 for the HEXA study, n=4,446 for the CAVAS, and n=6,051 for the KARE study); those who did not provide food frequency questionnaires (FFQs) at baseline (n=262) (n=170 for the HEXA study, n=3 for the

CAVAS, and n=89 for the KARE study); those who had implausible total energy intake at baseline (± 3 standard deviations (SDs) from the mean of log-transformed total energy intake) (n=182) (n=141 for the HEXA study, n=11 for the CAVAS, and n=30 for the KARE study); or those who did not have information on total cholesterol level, LDL cholesterol level, HDL cholesterol level, triacylglycerol level, self-reported diagnosis of dyslipidemia, or use of dyslipidemia medication (n=840) (n=2 for the HEXA study, n=0 for the CAVAS, and n=838 for the KARE study) (Figure S1). A total of 20,044 participants (n=16,889 for the HEXA study, n=1,250 for the CAVAS, and n=1,905 for the KARE study) were included in this study.

Ascertainment of dyslipidemia

As part of the KoGES conducted by the Korea Centers of Disease Control and Prevention, blood samples were collected after an overnight fast, and levels of total cholesterol, HDL cholesterol, and triacylglycerol were measured through biochemical assays at a central laboratory (Seoul Clinical Laboratories, Seoul, Korea). LDL cholesterol levels were calculated using the Friedewald equation for participants with triacylglycerol levels < 400 mg/dl⁽¹⁵⁾. We adopted four lipid parameters from the 2022 Korean Guidelines for the Management of Dyslipidemia and considered levels above the normal or optimal range as cutoff values. Dyslipidemia was defined as the presence of any one of the following criteria⁽¹⁶⁾: 1) total cholesterol ≥ 200 mg/dl, 2) LDL cholesterol ≥ 130 mg/dl, 3) triacylglycerol ≥ 150 mg/dl, or 4) HDL cholesterol < 40 mg/dl. Additionally, a history of diagnosed dyslipidemia or current use of dyslipidemia medication was also considered as dyslipidemia. Incident events were identified as those who did not have dyslipidemia at baseline and met any of the aforementioned criteria during the follow-up period.

Assessment of ultra-processed food intake

Ultra-processed food intake was evaluated using a 106-item semi-quantitative FFQ in the HEXA study and the CAVAS, and a 103-item semi-quantitative FFQ in the KARE study, which were developed based on the same protocols. A description of the validity and reproducibility of the FFQs can be found elsewhere^(17, 18). In the KoGES, participants were required to choose from nine categories indicating the frequency of ultra-processed food intake over the preceding year, ranging from almost never to three times or more per day. For coffee, the intake frequency of coffee additives, cream and sugar, was also collected. Portion sizes were categorized as half, equal to, or one and a half or twice the standard serving size.

We classified food items based on the NOVA classification⁽³⁾ and previous publications^(5, 19, 20). In cases of aggregated food groups or mixed meals containing food items with varying processing degrees, we segmented them and applied weights using information from Korean food recipes. These weights represented the percentage of weight supplied by an ultra-processed food item within the food group or mixed meal. Consequently, the ultra-processed food items in this study included

instant noodle (*ramen*), cereal/corn flakes, loaf bread/sandwich/toast, red bean bread/steamed bun/*pulppang*, other breads, bread spread (jam/butter/margarine), cake/*chocopie*, cookie/cracker/snack, candy/chocolate, pizza/hamburger, vegetable juice, tomato juice/tomato ketchup, carrot juice, orange juice, apple juice, grape juice, ham/sausage, fish cake/crab stick, processed milk, yogurt/*yoplait*, ice cream, processed cheese, soybean milk, carbonated drink, other drinks, and coffee cream (Table S1). We computed the percentage of total energy intake from ultra-processed foods in the total energy intake (percentage of total energy intake from ultra-processed foods = total energy of ultra-processed foods [kcal/d]×100/total energy intake [kcal/d]). Ultra-processed food intake was categorized into five groups: <5%E, 5 to <10%E, 10 to <15%E, 15 to <20%E, and ≥20%E per day. As most participants had low ultra-processed food intake (Figure S2) and to ensure a decent number of participants in each category, the top category of ultra-processed food intake was set as ≥20%E/d.

Assessment of other risk factors

The following demographic and lifestyle factors were assessed by trained interviewers for each cohort study: education level, smoking status (never, past, and current), the number of years spent smoking, the number of cigarettes smoked daily, alcohol drinking status (never, past, and current), alcohol drinking frequency, alcohol serving size, and the frequency of vigorous physical activity. In the KARE study, the frequency and duration of eight types of physical activities (aerobics, jogging, swimming, tennis, golf, bowling, walking, and climbing) were also assessed. We then determined metabolic equivalent minutes per week (MET-min/week) by multiplying the minutes per week spent on each physical activity by the metabolic cost of each activity in METs⁽²¹⁾. We calculated pack-years of smoking by dividing the number of cigarettes smoked daily by 20 and multiplying this result by the number of years smoked. We calculated total alcohol intake as grams of ethanol per day and body mass index (BMI) as the weight in kilograms divided by the square of the height in meters.

Genotyping and polygenic score calculation

Genotyping of participant genomic DNA (gDNA) was performed by the National Research Institute of Health, Centers for Disease Control and Prevention, Ministry for Health and Welfare, Republic of Korea. Blood samples were collected at baseline and each follow-up, placed in a serum separator tube and two EDTA tubes⁽¹⁴⁾. Additional details regarding the study design have been discussed elsewhere⁽¹⁴⁾. Among the 211,562 KoGES participants, gDNA samples from a total of 82,459 participants were genotyped (n=61,562 for the HEXA study, n=12,057 for the CAVAS, and n=8,840 for the KARE study). In the HEXA study, gDNA samples from peripheral blood were genotyped by the Affymetrix Genome-Wide Human SNP Array 6.0, and genotypes were determined using the birdseed genotyping algorithm⁽²²⁾. Some CAVAS participants were genotyped using the same

technique, while others were genotyped by the Illumina Omni1-Quad bead microarrays^(22, 23). Participants in the KARE study were genotyped by the Affymetrix Genome-Wide Human SNP Array 5.0, and genotypes were determined by the Bayesian robust linear model with the Mahalanobis distance genotyping algorithm⁽²⁴⁾. Missing or non-typed genotypes were imputed using IMPUTE v2 with 1000 Genomes Project data⁽²⁵⁾. Additionally, some participants in each cohort were genotyped by the Korea Biobank Array, referred to as KoreanChip, a customized Korean genome structure-based array⁽²⁵⁾. Genotyping by Affymetrix 5.0, Affymetrix 6.0, Illumina Omni1-Quad, and KoreanChip, along with the quality control methods, has been reported earlier⁽²²⁻²⁵⁾.

We computed an individual polygenic score of dyslipidemia using single nucleotide polymorphisms (SNPs) related to dyslipidemia, obtained from the PGS Catalog (<https://www.pgscatalog.org>). The SNPs, included in the polygenic score (PGS002029) of abnormal circulating lipid concentration, were selected from the publication by Privé et al. (2022), which included East Asian ancestry data in the GWAS or polygenic score evaluation stage⁽²⁶⁾. As a result, a total of 764,390 genetic variants were extracted based on evidence from the PGS Catalog, and 53,950 genetic variants with a missing call rate of <0.2 were available from genotyping within the HEXA, CAVAS, and KARE studies.

Statistical analysis

We calculated polygenic scores of dyslipidemia using the allelic scoring command of PLINK version 1.9 (www.cog-genomics.org/plink/1.9)^(27, 28). Whether dyslipidemia incidence occurred during the follow-up period was used as a binary outcome variable in the scoring model. Each SNP related to dyslipidemia was assigned a value of 0, 1, or 2 based on the number of minor alleles and then weighted by its relative effect size (β coefficient obtained from the GWAS). The polygenic score was the sum of the weighted values for each candidate genetic variant, calculated using the formula: polygenic score = $i \times (\beta_1 \times \text{SNP}_1 + \beta_2 \times \text{SNP}_2 + \dots + \beta_i \times \text{SNP}_i) / (\beta_1 + \beta_2 + \dots + \beta_i)$ (<https://www.cog-genomics.org/plink/1.9/score>)⁽²⁹⁾. To assess whether the polygenic score of dyslipidemia served as an interaction variable in the association between ultra-processed food intake and dyslipidemia risk, it was categorized as either high or low based on the median value.

Multivariate logistic regression models were utilized to explore the associations between ultra-processed food intake and the risk of dyslipidemia. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated based on categories of ultra-processed food intake and per 5%E/d continuous increment. All multivariable analyses included age (years, continuous) and sex (men and women). We further adjusted for BMI (<18.5, 18.5 to <23, 23 to <25, ≥ 25 kg/m² for HEXA, <23, 23 to <25, ≥ 25 kg/m² for CAVAS and KARE), smoking status (never, <10, 10 to <20, 20 to <30, ≥ 30 pack-years for men; never, <5, 5 to <10, ≥ 10 pack-years for women for HEXA, never, past, current for men; never, ever for women for CAVAS, never, <10, 10 to <20, 20 to <30, ≥ 30 pack-years for men;

non-current, current for women for KARE), alcohol drinking (never, ethanol <10, 10 to <20, 20 to <30, 30 to <40, 40 to <50, 50 to <60, ≥ 60 g/d for men; never, ethanol <10, 10 to <20, ≥ 20 g/d for women for HEXA, non-current, current for CAVAS, never, ethanol <10, 10 to <20, 20 to <30, ≥ 30 g/d for men; non-current, current for women for KARE), education level (elementary school or below, middle school, high school or above), regular exercise (none, vigorous physical activity frequency 1 to 2, 3 to 4, 5 to 6, every day per week for HEXA, none, vigorous physical activity frequency 1 to 2, 3 to 6, every day per week for CAVAS, quartiles in MET-min/week for KARE), total energy intake (kcal/d, continuous), and total fat intake (g/d, continuous) in our final model. To analyze the interaction by polygenic scores, we included a cross-product term of ultra-processed food intake and polygenic scores in the model and assessed the interaction using a likelihood ratio test (LRT) in each cohort study and a Wald test on the cross-product term for pooled analysis.

To examine linear trends across categories of ultra-processed food intake, we modeled the median intake of each category as a continuous variable. Pooled ORs were estimated using a random-effects model in the presence of heterogeneity or a fixed-effects model in its absence⁽³⁰⁾. Heterogeneity across the studies was assessed using Q statistics⁽³⁰⁾. The potential variation in the association between ultra-processed food intake and dyslipidemia risk based on polygenic scores (high or low) was explored. Additionally, we performed subgroup analyses to investigate whether age (<50 or ≥ 50 years), sex (men or women), BMI (<25 or ≥ 25 kg/m²), or alcohol drinking (non-current or current drinker) modified the association between ultra-processed food intake and dyslipidemia risk. All statistical tests were two-sided, and *p* values less than 0.05 were considered statistically significant. All analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina).

We conducted sensitivity analyses to evaluate the robustness of our findings. First, to minimize reverse causation, we excluded participants who developed dyslipidemia at the first follow-up in the CAVAS and KARE studies. Second, participants were categorized into tertiles based on polygenic scores instead of two categories. Third, we generated genetic risk scores specific to our study participants, using fourteen dyslipidemia-related SNPs that were genome-wide significant ($p < 5 \times 10^{-8}$) in the study population. To calculate the genetic risk scores, we examined whether the selected genetic variants were associated with dyslipidemia in our study population. Among the genetic variants associated with dyslipidemia with suggestive significance ($p < 1 \times 10^{-6}$) extracted from the GWAS Catalog (<https://www.ebi.ac.uk/gwas>), we selected those reported from GWASs that included $\geq 100,000$ individuals of East Asian descent only. We performed a GWAS in our study population, adjusting for age (years, continuous) and sex (men and women). As a result, fourteen dyslipidemia-related SNPs were identified as genome-wide significant ($p < 5 \times 10^{-8}$) through GWAS, and these SNPs were incorporated into the genetic risk scores. The genetic risk score was calculated

as the sum of the weighted number of each candidate genetic variant using the equation: genetic risk score = $14 \times (\beta_1 \times \text{SNP}_1 + \beta_2 \times \text{SNP}_2 + \dots + \beta_{14} \times \text{SNP}_{14}) / (\beta_1 + \beta_2 + \dots + \beta_{14})$. Table S2 provides details of the SNPs included in the genetic risk score calculation. In a sensitivity analysis, participants were categorized into high or low genetic risk score groups based on the median. Additionally, we aggregated the three cohort studies to examine the association between ultra-processed food intake and dyslipidemia risk with a higher cutoff for the top category of ultra-processed food intake ($\geq 30\% \text{E/d}$).

Results

During the follow-up period across the three studies, a total of 9,849 (49.14%) incident dyslipidemia events were identified among 20,044 participants. The median follow-up durations for the HEXA study, the CAVAS, and the KARE study were 4.09, 8.67, and 15.67 years, respectively.

The general characteristics of participants from the three cohort studies according to ultra-processed food intake are presented in Table 1. Generally, participants with higher ultra-processed food intake were younger, exhibited higher total energy intake, and had higher education levels than those with lower intake.

Table 2 presents the ORs and 95% CIs for dyslipidemia incidence according to ultra-processed food intake. There was no significant association between ultra-processed food intake and the risk of dyslipidemia. Compared to $< 5\% \text{E/d}$ of ultra-processed food intake, the pooled ORs (95% CIs) were 1.02 (0.94, 1.11) for 5 to $< 10\% \text{E/d}$, 1.09 (0.99, 1.19) for 10 to $< 15\% \text{E/d}$, 0.97 (0.87, 1.08) for 15 to $< 20\% \text{E/d}$, and 1.01 (0.90, 1.13) for $\geq 20\% \text{E/d}$ of ultra-processed food intake (p for trend=0.83; p for heterogeneity across the three cohort studies=0.60) (Table 2). An increment of $5\% \text{E/d}$ in ultra-processed food intake did not show a significant association with the risk of dyslipidemia (pooled OR 1.00; 95% CI 0.98, 1.02). No significant associations were found in each cohort study. When compared to $< 5\% \text{E/d}$ of ultra-processed food intake, the ORs (95% CIs) for $\geq 20\% \text{E/d}$ of ultra-processed food intake were 1.00 (0.89, 1.12; p for trend=0.69) in the HEXA study, 1.28 (0.79, 2.06; p for trend=0.44) in the CAVAS, and 0.98 (0.55, 1.73; p for trend=0.88) in the KARE study.

We investigated whether the association between ultra-processed food intake and dyslipidemia risk was modified by genetic susceptibility to dyslipidemia (Table 3). The non-significant associations were consistent across dichotomous polygenic score categories of dyslipidemia (pooled p for interaction=0.90). No statistically significant interactions were observed in each cohort study (p for interaction=0.61, 0.13, and 0.99 in the HEXA study, the CAVAS, and the KARE study, respectively) (Table S3).

Subgroup analyses according to age, sex, BMI, and alcohol drinking revealed no significant association between ultra-processed food intake and dyslipidemia risk (Table S4). Compared to $< 5\% \text{E/d}$ of ultra-processed food intake, the pooled ORs (95% CIs) for $\geq 20\% \text{E/d}$ of ultra-processed

food intake were 0.89 (0.74, 1.06; p for trend=0.16) for age <50 years, 1.09 (0.94, 1.27; p for trend=0.21) for age \geq 50 years, 0.93 (0.76, 1.15; p for trend=0.63) for men, 1.06 (0.93, 1.21; p for trend=0.86) for women, 1.07 (0.94, 1.21; p for trend=0.43) for BMI <25kg/m², 0.83 (0.66, 1.05; p for trend=0.05) for BMI \geq 25kg/m², 1.10 (0.94, 1.28; p for trend=0.46) for non-current drinkers, and 0.90 (0.76, 1.06; p for trend=0.20) for current drinkers. The lack of a significant association did not vary by sex, BMI, or alcohol drinking (p for interaction=0.17, 0.12, and 0.46, respectively). Although the pooled ORs were slightly higher in those aged \geq 50 years compared to those aged <50 years overall (p for interaction=0.01), the associations within each age group were not statistically significant.

In sensitivity analyses, the association between ultra-processed food intake and dyslipidemia risk remained non-significant, even after excluding participants who had dyslipidemia at the first follow-up in the CAVAS and KARE studies (Table S5). When polygenic scores were categorized into tertiles (high, medium, and low polygenic scores), no significant interaction was observed (p for interaction=0.74) (Table S6). Similar results were found in sensitivity analyses using genetic risk scores instead of polygenic scores (p for interaction=0.70) (Table S7). Additionally, when we aggregated the three cohort studies, no significant association between ultra-processed food intake and dyslipidemia risk was observed in the higher top category (\geq 30%E/d) (Table S8).

Discussion

In this pooled analysis of 20,044 participants from three Korean prospective studies, we found no significant association between ultra-processed food intake and the risk of dyslipidemia. The association between ultra-processed food intake and the risk of dyslipidemia did not vary by genetic variants related to dyslipidemia. Since our study participants were Korean adults aged 40 years or older, who had low ultra-processed food intake, future studies involving younger populations with higher ultra-processed food intake demand ongoing attention and careful consideration.

In contrast to our findings, a number of explanations have been proposed to elucidate the potential unfavorable effects of ultra-processed food on dyslipidemia risk. Ultra-processed foods are characterized by a high content of *trans* and saturated fatty acids, which are assumed to elevate dyslipidemia risk and negatively influence lipid profiles, and a low content of polyunsaturated fatty acids^(31, 32). Ultra-processed foods may result in low dietary intakes of fiber, micronutrients, and other naturally occurring bioactive substances present in whole foods, but high intakes of sugars, refined carbohydrates, and sodium⁽³³⁾. The combination of elevated blood glucose and pressure, resulted from such dietary patterns, has been suggested to synergistically accelerate atherosclerosis through mechanisms like insulin resistance, endothelial dysfunction, and oxidative stress⁽³⁴⁾.

A prospective cohort study on Spanish adults aged 60 years or older revealed an association between high ultra-processed food intake and incident dyslipidemia⁽³⁵⁾. In that study, a high intake

of ultra-processed foods was associated with a higher risk of hypertriglyceridemia (OR 2.66; 95% CI 1.20, 5.90; p for trend=0.01) and low HDL cholesterol levels (OR 2.23; 95% CI 1.22, 4.05; p for trend=0.01). However, there was no association between ultra-processed food intake and high LDL cholesterol levels (OR 1.03; 95% CI 0.43, 2.47) or changes in HDL and LDL cholesterol levels. A cross-sectional study of young adults in Canada showed an association of ultra-processed food intake with a higher prevalence of reduced HDL cholesterol levels (OR 2.05; 1.25, 3.38 [Q5 vs. Q1]; p for trend=0.02), but not with hypertriglyceridemia (OR 0.93; 95% CI 0.57, 1.52 [Q5 vs. Q1]; p for trend=0.71)⁽⁸⁾. Among Brazilian adolescents aged 11.3 ± 1.3 years, ultra-processed food intake was not correlated with baseline levels of total cholesterol ($\rho = -0.16$, $p = 0.07$), LDL cholesterol ($\rho = -0.16$, $p = 0.07$), HDL cholesterol ($\rho = -0.04$, $p = 0.67$), or triacylglycerol ($\rho = -0.07$, $p = 0.44$), nor with levels of total cholesterol ($\rho = 0.05$, $p = 0.43$), LDL cholesterol ($\rho = 0.06$, $p = 0.38$), HDL cholesterol ($\rho = 0.06$, $p = 0.37$), or triacylglycerol ($\rho = 0.001$, $p = 0.99$) after a 4-year follow-up⁽³⁶⁾. These mixed outcomes from previous studies may not provide strong evidence for a clear association between ultra-processed food intake and the risk of dyslipidemia. The heterogeneity in the populations studied, differences in dietary assessment methods, various intake levels of ultra-processed foods, and the diverse composition of ultra-processed foods could explain the discrepancies.

Moreover, Asian studies remained limited and exhibited inconsistent results. Among Iranian adults aged 20 to 50 years, high ultra-processed food intake was associated with a higher risk of triacylglycerol and HDL cholesterol abnormalities (OR 3.69; 95% CI 1.67, 8.16; p for trend=0.001 [Q3 vs. Q1] and OR 3.38; 95% CI 1.42, 8.07; p for trend=0.01 [Q3 vs. Q1], respectively)⁽³⁷⁾. However, no associations were observed between ultra-processed food intake and total or LDL cholesterol levels in that study. In another cross-sectional study from Lebanon, medium or high adherence to a dietary pattern rich in ultra-processed foods, compared with low adherence, was not associated with high triacylglycerol levels (OR 1.08; 95% CI 0.28, 4.11) or low HDL cholesterol levels (OR 1.82, 95% CI 0.52, 6.42)⁽³⁸⁾.

It is noteworthy that ultra-processed food intake is higher in Western populations than in our study population. The contribution of ultra-processed foods to total energy intake in Korea is 25.1%⁽³⁹⁾, considerably lower than in the United States (57.9%)⁽⁹⁾, the United Kingdom (56.8%)⁽³³⁾, Canada (45%)⁽⁴⁰⁾, and France (29%)⁽⁴¹⁾. Korean dietary patterns, although gradually, are becoming closer to Western dietary patterns. Predictions indicate that ultra-processed food sales in Asian countries will approach those in high-income countries by 2035⁽⁵⁾. Our study included participants aged 40 years or older, who likely had a lower intake of ultra-processed foods than young adults. Therefore, further prospective studies focusing on young Asian adults are warranted.

We did not observe significant interactions of polygenic scores in the association between ultra-processed food intake and dyslipidemia risk. Nonetheless, recent studies have presented evidence

supporting interactions by genetic variants for components in ultra-processed foods and lipid profiles. Several epidemiological studies in Western countries have reported potential interactions between saturated and unsaturated fats and *CETP* gene polymorphisms⁽⁴²⁾, dietary sucrose and *APOE* gene polymorphisms⁽⁴³⁾, and sodium and *AGT* gene polymorphisms⁽⁴⁴⁾. While investigations involving diverse ethnic groups are necessary to explore population-specific associations, develop effective nutrition strategies, and generalize study results, the current evidence is mostly from Caucasian populations. The KARE study found that a dietary pattern rich in whole grains and soybean products was inversely associated with hypercholesterolemia risk (HR 0.74; 95% CI 0.59, 0.93 [Q4 vs. Q1]; p for trend=0.01; p for interaction=0.08) among Korean adults with higher genetic risk scores related to dyslipidemia⁽⁴⁵⁾. In Chinese Han young adults, changes in levels of LDL and HDL cholesterol after a high-carbohydrate low-fat diet were different according to the genotypes of *LEPR* gene polymorphisms⁽⁴⁶⁾. However, Asian studies on gene-diet interactions for ultra-processed food intake and lipid profiles or cardiovascular diseases are limited.

The present pooled analysis has several limitations. First, the potential for residual confounding could persist; however, we adjusted for possible confounding factors, and the associations remained largely unchanged after adjustment. Second, dietary information was collected only at baseline and lacked repeatedly measured exposures. Additionally, FFQs may introduce measurement error and challenges in accurate portion quantification compared to prospective approaches relying on weighing and recording foods consumed. Third, our questionnaire was not specifically designed to assess ultra-processed food intake as defined by the NOVA classification. Fourth, even though the NOVA classification is widely acknowledged, it may not be universally applicable because of diverse dietary and cultural habits, as well as variations in food processing. Finally, our study population had a low intake of ultra-processed foods, and there was a small proportion with $\geq 30\%$ E/d of ultra-processed food intake. Given the increasing intake of ultra-processed foods, notably among younger populations, further studies in younger populations are required. Nonetheless, this study possesses some strengths. First, we included prospective cohort studies with data collected in a temporal sequence, enabling the distinction of a temporal relationship⁽⁴⁷⁾. Second, the study involved an Asian population with a relatively large sample size, addressing Asian gene-diet interaction studies on ultra-processed food intake and the risk of dyslipidemia.

In conclusion, we found no significant association between ultra-processed food intake and the risk of dyslipidemia in an adult Korean population aged 40 years or older. This lack of association did not differ by polygenic scores and genetic risk scores. Further epidemiological and intervention studies including younger Asian populations with higher intake of ultra-processed foods are needed to clarify the effects of dyslipidemia-related genetic variation and high ultra-processed food intake on cardiometabolic disease risk.

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Table 1. Baseline characteristics of participants according to ultra-processed food intake

	Ultra-processed food intake (%E/d)					
	Total	<5	5 to <10	10 to <15	15 to <20	≥20
HEXA						
No. of participants	16,889	3,284	5,042	3,877	2,198	2,488
Age (years)	51.8 (8.2)	55.2 (7.8)	52.7 (8.1)	50.7 (7.8)	49.8 (7.8)	49.0 (7.7)
Sex						
Men	5,167 (30.59)	1,062 (32.34)	1,642 (32.57)	1,160 (29.92)	644 (29.30)	659 (26.49)
Women	11,722 (69.41)	2,222 (67.66)	3,400 (67.43)	2,717 (70.08)	1,554 (70.70)	1,829 (73.51)
BMI (kg/m ²)*	23.1 (2.7)	23.3 (2.7)	23.3 (2.7)	23.1 (2.7)	22.9 (2.7)	23.0 (2.8)
Smoking status (pack-years)*	4.4 (10.9)	4.9 (11.7)	4.6 (11.0)	4.4 (11.3)	4.2 (10.4)	3.7 (9.5)
Alcohol drinking (ethanol g/d)*	6.3 (26.1)	7.7 (49.2)	5.9 (15.0)	6.2 (18.0)	6.2 (15.5)	5.4 (15.9)
Total energy intake (kcal/d)	1,750.0 (504.5)	1,543.3 (380.3)	1,683.9 (421.1)	1,771.7 (477.1)	1,860.5 (543.6)	2,025.4 (640.1)
Education level*						
High school or above	12,225 (72.38)	1,934 (58.89)	3,489 (69.20)	2,987 (77.04)	1,760 (80.07)	2,055 (82.60)
CAVAS						
No. of participants	1,250	404	392	210	121	123
Age (years)	56.8 (9.2)	59.0 (8.2)	56.6 (9.2)	55.2 (9.3)	54.9 (9.8)	54.8 (9.9)
Sex						
Men	477 (38.16)	137 (33.91)	161 (41.07)	84 (40.00)	41 (33.88)	54 (43.90)
Women	773 (61.84)	267 (66.09)	231 (58.93)	126 (60.00)	80 (66.12)	69 (56.10)
BMI (kg/m ²)	23.5 (2.9)	23.4 (3.0)	23.4 (2.9)	23.8 (3.0)	23.4 (2.9)	23.5 (2.9)
Smoking status (pack-years)	7.3 (15.5)	6.3 (14.3)	7.9 (15.7)	7.6 (15.5)	6.2 (15.0)	9.7 (19.1)

Alcohol drinking (ethanol g/d)*	9.6 (25.4)	8.8 (24.4)	11.8 (31.5)	9.8 (23.0)	5.8 (15.0)	8.7 (16.5)
Total energy intake (kcal/d)	1,672.9 (479.6)	1,514.8 (420.9)	1,628.4 (381.5)	1,752.3 (479.2)	1,833.8 (516.3)	2,040.8 (620.9)
Education level*						
High school or above	339 (27.12)	64 (15.84)	106 (27.04)	74 (35.24)	51 (42.15)	44 (35.77)
KARE						
No. of participants	1,905	472	492	400	279	262
Age (years)	50.8 (8.9)	55.4 (9.2)	51.2 (8.5)	49.0 (8.3)	48.4 (8.1)	46.9 (6.9)
Sex						
Men	739 (38.79)	182 (38.56)	203 (41.26)	157 (39.25)	99 (35.48)	98 (37.40)
Women	1,166 (61.21)	290 (61.44)	289 (58.74)	243 (60.75)	180 (64.52)	164 (62.60)
BMI (kg/m ²)*	23.4 (3.1)	23.4 (3.3)	23.5 (3.0)	23.5 (3.0)	23.3 (2.7)	23.3 (3.1)
Smoking status (pack-years)*	7.5 (14.8)	9.3 (16.3)	8.6 (16.1)	6.5 (14.2)	4.9 (10.1)	6.9 (14.2)
Alcohol drinking (ethanol g/d)*	8.4 (19.8)	9.5 (19.9)	9.9 (23.5)	6.0 (14.8)	6.7 (18.4)	9.0 (20.2)
Total energy intake (kcal/d)	1,947.7 (630.2)	1,784.5 (610.0)	1,889.0 (570.7)	1,961.9 (589.8)	2,113.6 (648.7)	2,153.7 (711.3)
Education level*						
High school or above	822 (43.15)	107 (22.67)	185 (37.60)	210 (52.50)	165 (59.14)	155 (59.16)

Abbreviations: HEXA, the Health Examinees; BMI, body mass index; CAVAS, Cardiovascular Disease Association Study; KARE, the Korea Association Resource.

Continuous variables are reported as mean (standard deviation), and categorical variables are reported as no. (%).

*The total number of participants was not equal because of missing values.

Table 2. Multivariate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the risk of dyslipidemia according to ultra-processed food intake

	per 5%E/d	Ultra-processed food intake (%E/d)					<i>p</i> for trend
		<5	5 to <10	10 to <15	15 to <20	≥20	
Pooled							
Case/total no.	9,849/20,044	2,119/4,160	2,885/5,926	2,236/4,487	1,242/2,598	1,367/2,873	
Age, sex adjusted model	0.99 (0.97, 1.01)	Reference	1.00 (0.92, 1.09)	1.06 (0.97, 1.16)	0.93 (0.84, 1.03)	0.96 (0.87, 1.07)*	0.21
Multivariate adjusted model	1.00 (0.98, 1.02)	Reference	1.02 (0.94, 1.11)	1.09 (0.99, 1.19)	0.97 (0.87, 1.08)	1.01 (0.90, 1.13)*	0.83
HEXA							
Case/total no.	7,331/16,889	1,432/3,284	2,196/5,042	1,738/3,877	916/2,198	1,049/2,488	
Age, sex adjusted model	0.99 (0.97, 1.01)	Reference	1.01 (0.92, 1.10)	1.06 (0.96, 1.17)	0.93 (0.83, 1.04)	0.95 (0.85, 1.05)	0.14
Multivariate adjusted model	1.00 (0.98, 1.02)	Reference	1.02 (0.94, 1.12)	1.09 (0.99, 1.20)	0.97 (0.86, 1.09)	1.00 (0.89, 1.12)	0.69
CAVAS							
Case/total no.	786/1,250	257/404	238/392	134/210	72/121	85/123	
Age, sex adjusted model	1.03 (0.95, 1.11)	Reference	0.91 (0.68, 1.21)	1.03 (0.72, 1.46)	0.83 (0.54, 1.27)	1.33 (0.86, 2.07)	0.33
Multivariate adjusted model	1.02 (0.94, 1.11)	Reference	0.91 (0.68, 1.23)	1.03 (0.72, 1.50)	0.85 (0.54, 1.32)	1.28 (0.79, 2.06)	0.44

KARE

Case/total no.	1,732/1,905	430/472	451/492	364/400	254/279	233/262	
Age, sex adjusted model	1.00 (0.91, 1.11)	Reference	1.18 (0.74, 1.86)	1.12 (0.69, 1.82)	1.12 (0.66, 1.92)	0.92 (0.54, 1.55)	0.68
Multivariate adjusted model	1.02 (0.91, 1.14)	Reference	1.21 (0.76, 1.93)	1.17 (0.71, 1.95)	1.21 (0.69, 2.15)	0.98 (0.55, 1.73)	0.88

Abbreviations: HEXA, the Health Examinees; CAVAS, Cardiovascular Disease Association Study; KARE, the Korea Association Resource.

Fixed-effects model was used for pooled meta-analysis.

Multivariate adjusted model was adjusted for age (years, continuous), sex (men, women), body mass index (BMI, <18.5, 18.5 to <23, 23 to <25, ≥ 25 kg/m² for HEXA, <23, 23 to <25, ≥ 25 kg/m² for CAVAS and KARE), smoking status (never, <10, 10 to <20, 20 to <30, ≥ 30 pack-years for men; never, <5, 5 to <10, ≥ 10 pack-years for women for HEXA, never, past, current for men; never, ever for women for CAVAS, never, <10, 10 to <20, 20 to <30, ≥ 30 pack-years for men; non-current, current for women for KARE), alcohol drinking (never, ethanol <10, 10 to <20, 20 to <30, 30 to <40, 40 to <50, 50 to <60, ≥ 60 g/d for men; never, ethanol <10, 10 to <20, ≥ 20 g/d for women for HEXA, non-current, current for CAVAS, never, ethanol <10, 10 to <20, 20 to <30, ≥ 30 g/d for men; non-current, current for women for KARE), education level (elementary school or below, middle school, high school or above), regular exercise (none, vigorous physical activity frequency 1 to 2, 3 to 4, 5 to 6, every day per week for HEXA, none, vigorous physical activity frequency 1 to 2, 3 to 6, every day per week for CAVAS, quartiles in MET-min/week for KARE), total energy intake (kcal/d, continuous), and total fat intake (g/d, continuous).

**P* for heterogeneity across the three cohort studies >0.10.

Table 3. Pooled multivariate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the risk of dyslipidemia by polygenic scores according to ultra-processed food intake

Polygenic scores*	per 5%E/d	Ultra-processed food intake (%E/d)					<i>p</i> for trend	<i>p</i> for interaction
		<5	5 to <10	10 to <15	15 to <20	≥20		
Low polygenic scores								0.90†
Case/total no.	4,659/10,021	998/2,062	1,382/3,004	1,076/2,278	565/1,268	638/1,409		
Age, sex adjusted model	0.99 (0.97, 1.02)	Reference	1.02 (0.91, 1.15)	1.07 (0.94, 1.22)	0.91 (0.78, 1.06)	0.98 (0.85, 1.14)	0.37	
Multivariate adjusted model	1.01 (0.98, 1.03)	Reference	1.04 (0.92, 1.17)	1.10 (0.97, 1.26)	0.96 (0.81, 1.12)	1.04 (0.89, 1.22)	0.91	
High polygenic scores								
Case/total no.	5,190/10,023	1,121/2,098	1,503/2,922	1,160/2,209	677/1,330	729/1,461		
Age, sex adjusted model	0.99 (0.97, 1.02)	Reference	0.99 (0.88, 1.12)	1.06 (0.93, 1.20)	0.95 (0.82, 1.10)	0.94 (0.81, 1.09)	0.29	
Multivariate adjusted model	1.00 (0.97, 1.03)	Reference	1.00 (0.89, 1.13)	1.09 (0.95, 1.24)	0.98 (0.84, 1.14)	0.98 (0.84, 1.15)	0.72	

Fixed-effects model was used for pooled meta-analysis.

Multivariate adjusted model was adjusted for age (years, continuous), sex (men, women), body mass index (BMI, <18.5, 18.5 to <23, 23 to <25, ≥25 kg/m² for HEXA, <23, 23 to <25, ≥25 kg/m² for CAVAS and KARE), smoking status (never, <10, 10 to <20, 20 to <30, ≥30 pack-years for men; never, <5, 5 to <10, ≥10 pack-years for women for HEXA, never, past, current for men; never, ever for women for CAVAS, never, <10, 10 to <20, 20 to <30, ≥30 pack-years for men; non-current, current for women for KARE), alcohol drinking (never, ethanol <10, 10 to <20, 20 to <30, 30 to <40, 40

to <50, 50 to <60, ≥ 60 g/d for men; never, ethanol <10, 10 to <20, ≥ 20 g/d for women for HEXA, non-current, current for CAVAS, never, ethanol <10, 10 to <20, 20 to <30, ≥ 30 g/d for men; non-current, current for women for KARE), education level (elementary school or below, middle school, high school or above), regular exercise (none, vigorous physical activity frequency 1 to 2, 3 to 4, 5 to 6, every day per week for HEXA, none, vigorous physical activity frequency 1 to 2, 3 to 6, every day per week for CAVAS, quartiles in MET-min/week for KARE), total energy intake (kcal/d, continuous), and total fat intake (g/d, continuous).

*Polygenic scores were calculated using 53,950 SNPs related to dyslipidemia weighted by relative effect (β coefficient).

†*P* value was obtained using the multivariate adjusted model.