THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Apolipoprotein E Genotype and Coronary Heart Disease in a Mongolian Cohort: An Exploratory Case–Control Study

ABSTRACT

Background: To investigate the association between apolipoprotein E (*APOE*) gene polymorphisms and coronary heart disease (CHD) risk within a localized Mongolian clinical cohort.

Methods: This hospital-based case–control study recruited 63 patients with angiographically confirmed CHD and 61 sex-matched healthy controls. Anthropometric measurements and lipid profiles and pathways for *APOE* genotypes were strictly assessed. This exploratory hospital-based case–control study was not designed as a nationally representative population-based survey, and participant recruitment was limited to a single tertiary referral center in Mongolia.

Results: High-density lipoprotein cholesterol levels were significantly higher in the case group than in the control group (1.56 ± 0.14 vs. 1.33 ± 0.18 mmol/L, $P < .001$), while total cholesterol was significantly lower in cases than in controls (3.91 ± 0.60 vs. 5.34 ± 0.80 mmol/L, $P < .001$). The distribution of *APOE* genotypes (ε2/ε3, ε3/ε3, ε3/ε4, and ε4/ε4) differed significantly between the case and control groups ($P = .009$). Both systolic and diastolic blood pressure significantly correlated with waist circumference ($P = .026$). Multivariable logistic regression revealed that the ε2/ε3 genotype was associated with significantly lower odds of disease (odds ratio [OR] = 0.29, $P = .007$, 95% CI: 0.12-0.71), whereas ε4-related findings were highly imprecise due to sparse genotype counts and lacked statistical significance (OR = 1.07, $P = .930$, 95% CI: 0.23-5.02).

Conclusion: This study showed a significant association between the *APOE* genotype and CHD in a Mongolian population. These findings highlight the importance of considering qualitative aspects of lipid metabolism, rather than total cholesterol alone, and suggest that genetic factors, including *APOE* polymorphisms, may contribute to CHD risk independently of absolute cholesterol levels, underscoring the need for population-specific cardiovascular risk assessment.

Keywords: Apolipoprotein E, case–control study, coronary heart disease, genotype

INTRODUCTION

The coronary heart disease (CHD) is a growing health concern worldwide, with its prevalence steadily increasing across developed and developing nations.[1] Genetic factors play a crucial role in determining an individual's susceptibility to coronary artery disease, especially the apolipoprotein E (*APOE)* gene, which is a well-studied genetic marker.[2] The *APOE* gene is essential in regulating cholesterol metabolism, and its polymorphisms have been associated with varying risks of CHD across different populations.[3,4]

Located on chromosome 19q13.2, the *APOE* gene contains key single-nucleotide polymorphisms (SNPs), notably rs429358 and rs7412, which give rise to 3 primary allelic variants: ε2, ε3, and ε4.[5] These variants (ε2, ε3, and ε4) code for isoforms of apolipoprotein E that differ in their amino acid sequence, particularly at residues 112 and 158, leading to differential binding affinities for lipoprotein receptors and diverse physiological effects on lipid transport and degradation.[6] The 3 common alleles, designated ε2, ε3, and ε4, form 6 distinct genotypes (ε2/ε2, ε2/ε3, ε3/ε3, ε2/ε4, ε3/ε4, and ε4/ε4), each conferring a unique biochemical profile and

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Received: February 5, 2026
Accepted: June 19, 2026
Available Online Date: August 3, 2026

Cite this article as: Dogsom O, Punsaldulam A, Dogsom O, et al. Apolipoprotein E genotype and coronary heart disease in a Mongolian cohort: An exploratory case–control study. *Anatol J Cardiol.* 2026;XX(X):X-X.

DOI: 10.14744/AnatolJCardiol.2026.6198

influencing an individual's predisposition to dyslipidemia and cardiovascular disease (CVD).[7] For instance, the ε4 allele is consistently associated with an increased risk of coronary artery disease, whereas the ε2 allele is recognized for its protective role.[8]

In Mongolia, a country experiencing rapid lifestyle changes and increasing CVD rates, it is essential to understand the relationship between *APOE* gene variants and CHD risk factors.[9] Notably, CHD manifests approximately 8-9 years earlier among Mongolians than in more developed countries.[9,10] Previous studies have shown genetic variations in *APOE* as significant contributors to the development of coronary artery disease.[3,5]

APOE polymorphisms have substantially influenced lipid metabolism, a key determinant of cardiovascular health. The *APOE* genotype is therefore of considerable interest, as it has been associated with various cardiovascular conditions, including CHD.[4,11] Although numerous studies have examined the association between *APOE* polymorphisms and CVD risk across diverse populations, evidence specific to the Mongolian ethnic group is limited, with existing literature focusing primarily on other Asian groups.[9,12,13]

The present study addresses a critical evidence gap by examining the association between *APOE* genotype polymorphisms and CHD in a population significantly underrepresented in genetic cardiovascular epidemiology literature. The vast majority of *APOE*-CHD association studies have focused on populations of European descent, with some representation of African American, Chinese, and Latino cohorts; however, Central Asian populations such as Mongolians remain poorly characterized.[13-17] This geographic and ethnic underrepresentation is concerning because population-specific variation in allele frequencies, genetic backgrounds, and environmental exposure can substantially modify the strength and direction of genetic associations with complex diseases such as CHD.[18-20]

By elucidating *APOE* genotype distributions and their relationship with CHD risk in the Mongolian population—shaped by unique genetic ancestry, dietary patterns, and environmental exposures—this study contributes to greater diversity in global genetic epidemiology literature and provides population-specific insights relevant to prevention and management strategies. This approach is crucial, given that the impact of specific allelic variations on CHD risk can significantly depend on varying genetic and environmental contexts among populations. It is especially relevant to the Mongolian population, where cardiovascular health patterns are influenced by socioeconomic determinants such as income, education, and access to health insurance, highlighting the need for tailored public health strategies.[9,21-24] Therefore, a deeper understanding of the genetic architecture of CHD in this specific demographic is paramount for the development of effective, culturally sensitive interventions. Therefore, achieving a comprehensive understanding of the genetic underpinnings of CHD in this population is essential for developing targeted and effective interventions. Accordingly, this study investigates the association between *APOE* polymorphisms and CHD susceptibility among Mongolians, elucidating the genetic and environmental factors contributing to this major public health challenge.

HIGHLIGHTS

- The *APOE* ε4 allele was significantly associated with increased coronary heart disease risk in a Mongolian population.
- Coronary heart disease cases exhibited altered lipid fraction distribution despite lower total cholesterol levels.
- ε4 carriers showed unfavorable cardiometabolic profiles, including higher body mass index and blood pressure.
- Findings underscore the importance of qualitative lipid assessment and population-specific genetic risk evaluation.

METHODS

Participants and Study Design

Cases and controls were recruited using a non-random hospital-based sampling strategy, and the findings should therefore be interpreted as exploratory rather than population representative.

This hospital-based case–control study was conducted at the Third State Central Hospital in Mongolia, in collaboration with the Mongolian National University of Medical Sciences. A total of 124 participants were enrolled, including 63 patients diagnosed with CHD and 61 healthy controls exhibiting no evidence of coronary artery disease, who served as the reference group. Participants in both the control and case groups were sex-matched and recruited from individuals visiting state and central hospitals across various provinces for routine health check-ups. Lifestyle and medical history information were obtained using a questionnaire-based interview.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of the participating institution (Approval MEC No. 2018/3-09). Written informed consent was obtained from all participants, who were informed of their right to withdraw at any time.

Coronary Heart Disease Diagnosis and Severity Assessment

Coronary heart disease was diagnosed based on angiographic findings, which represent the gold standard for the detection of coronary artery disease. Coronary angiography was performed using standard techniques, and all angiograms were reviewed by experienced interventional cardiologists. The severity of CHD was assessed according to established criteria from the Coronary Artery Surgery Study.[25] The number of diseased vessels was determined based on the presence of ≥70% stenosis in the proximal, mid, or distal segments of the 3 major coronary arteries: the right coronary artery, left anterior descending artery, and left circumflex artery.[25] Patients were classified as having

single-vessel disease, double-vessel disease, or triple-vessel disease according to the number of major coronary arteries with significant stenosis.[26] In cases involving the left main coronary artery, disease severity was classified as equivalent to 2-vessel disease in right dominant circulation or 3-vessel disease in left dominant circulation.[25] This angiographic classification system has been widely validated and provides a standardized measure of disease burden that correlates with cardiovascular outcomes.[27]

All study participants, including both control and case groups, were sex-matched and recruited from individuals visiting Third State Central Hospital in Mongolia across various provinces for routine health check-ups.

Lifestyle and Medical History Assessment

Comprehensive lifestyle and medical history data were collected using standardized questionnaire-based interviews administered by trained research personnel. The following variables were assessed using operational definitions:

Smoking Status

Smoking was categorized as never, former, or current smoker. Never smokers were defined as participants who had not smoked regularly (i.e., less than 100 cigarettes in their lifetime). Current smokers were those participants who reported smoking at least 1 cigarette per day during the past year. Former smokers were those with a history of regular smoking who had quit for at least 1 year.[28,29] For current and former smokers, cumulative exposure was measured in pack-years, calculated as the average number of cigarettes smoked per day divided by 20 (1 pack), multiplied by the number of years smoked.[28,30]

Alcohol Consumption

Alcohol consumption was assessed through self-report. Participants who reported no alcohol intake in the past year were classified as non-consumers. Among consumers, alcohol intake was quantified in grams of ethanol per day based on reported drinking frequency and typical consumption amounts.[31]

Dietary Patterns

Dietary assessment was based on a food frequency questionnaire designed to capture habitual intake patterns over the past year. Intake of key food groups—including fruits, vegetables, whole grains, fish, and sources of saturated and unsaturated fats—was evaluated.[31] A diet quality index ranging from 0 to 6 was developed, with higher scores indicating greater adherence to heart-healthy dietary patterns characterized by higher intake of fruits, vegetables, fish, and polyunsaturated fats, and lower consumption of saturated fats and refined sugars.[32]

Physical Activity

Physical activity (referred to as "training" in the original questionnaire) was assessed using a validated questionnaire that captured the frequency, duration, and intensity of activities across multiple domains, including occupational, transportation, household, and leisure-time activities.[33,34] Activity intensity was classified as light (<4 metabolic equivalents [METs]), moderate (4-7 METs), or vigorous (>7 METs), where 1 MET represents the energy expenditure at rest (approximately 3.5 mL O_2/kg/min or 1 kcal/kg/hour).[33,35] Participants were asked to report the type of activities performed (e.g., walking, running, swimming, ball games, gymnastics), along with the frequency (times per week) and duration (minutes per session).[34] Total physical activity was quantified as MET-hours per week, calculated by multiplying the MET value of each activity by its frequency and duration.[35,36] This methodology aligns with World Health Organization guidelines for physical activity assessment and has been validated in large cardiovascular cohort studies.[37]

Biometric Measurements

A registered nurse or an attending physician interviewed the participants to gather medical history and measure their height and weight. Height was measured without shoes using a stadiometer, and weight was measured in light clothing using a calibrated scale. Body mass index (BMI) was calculated as the ratio of the participant's weight in kilograms to the square of their height in meters (kg/m^2).[38,39] Blood pressure was measured following standard protocols with participants at rest in a seated position for at least 5 minutes prior to measurement. Three consecutive readings were taken, and the average of the last 2 measurements was recorded as the systolic and diastolic blood pressure values.

Lipoprotein Measurements

Fasting venous blood samples were collected from participants after an overnight fast. Biochemical and lipid profiles were analyzed, including total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), using standard laboratory techniques. The analyses were conducted with automated biochemical analyzers (BA-400 and A-25), using photometric and turbidimetric methods with reagents from Biosystems (Applied Biosystems, Foster City, CA, USA). Triglyceride levels were measured photometrically using a glycerol-3-phosphate oxidase–based diagnostic kit, per the manufacturer's instructions.

Sample Collection and Processing

After overnight fasting, participants rested in a supine position for 30 minutes before blood collection. Approximately 5-8 mL of blood was drawn into tubes containing acid citrate dextrose as an anticoagulant. A portion of the sample (2-3 mL) was transferred to another vial and allowed to clot to obtain serum for biochemical parameter estimation. The remaining sample was centrifuged at 1500 rpm for 10 minutes at 4°C for plasma extraction, which was also used for biochemical parameter analyses.[40] Peripheral blood leukocytes were isolated and utilized for DNA extraction.

Determination of APOE Genotypes

Genomic DNA was extracted from leukocytes using a standard protocol and stored at 4°C. *APOE* genotypes were initially identified using an agarose gel-based method, as described by Reymer et al.[41] Briefly, polymerase chain reaction (PCR) was used to amplify the *APOE* allelic variants, which were subsequently digested using the restriction enzyme HhaI.[42] The resulting fragments were separated by agarose gel electrophoresis and visualized under ultraviolet

light to determine the participants' *APOE* genotypes. The participants' *APOE* genotypes were determined using the SNaPshot fluorescent single-base extension assay to genotype the rs429358 and rs7412. A 352 bp region of the *APOE* gene containing these SNPs was amplified by PCR using forward (5′- CTA CAA ATC GGA ACT GGA GG-3′) and reverse (5′- CAC GCG GCC CTG TTC CAC GAG-3′) primers. Each 20 µL reaction mixture contained 50 ng of DNA, 3 pmol of each primer, 1× buffer, 0.33 U of Taq DNA polymerase, and 0.2 mM deoxynucleotide triphosphates.

Polymerase chain reaction cycling conditions were as follows: initial denaturation at 95°C for 5 minutes; 38 cycles of denaturation at 95°C for 40 seconds, annealing at 56°C for 30 seconds, and extension at 72°C for 45 seconds; followed by a final extension at 72°C for 10 minutes. Polymerase chain reaction products were purified using polyethylene glycol and subsequently genotyped using the SNaPshot multiplex kit.[43]

Statistical Analysis

Normality was assessed using the Shapiro–Wilk test. Independent samples *t*-test or Mann–Whitney *U*-test were applied according to distributional assumptions, while categorical variables were compared using Pearson chi-square or Fisher's exact tests as appropriate.

Prior to group comparisons, the normality of continuous variables was assessed using the Shapiro–Wilk test, given the moderate sample size ($n < 100$ per group). Continuous variables that conformed to a normal distribution are presented as mean ± SD whereas non-normally distributed variables are reported as median with interquartile range. Group comparisons for normally distributed continuous variables were performed using 1-way ANOVA.[44] This approach was selected to allow simultaneous comparison of means across the defined subgroups (e.g., *APOE* genotype strata), thereby preserving the overall type 1 error rate relative to multiple pairwise *t*-tests. Post hoc pairwise comparisons were performed using Bonferroni correction to control the family-wise error rate across multiple comparisons. For non-normally distributed variables, the Kruskal–Wallis test was used, followed by Dunn's post hoc procedure with Bonferroni adjustment.[45] Categorical variables are expressed as frequencies and percentages. Between-group differences were evaluated using Pearson's chi-square test or Fisher's exact test, as appropriate. *APOE* allele frequencies and genotype distributions were assessed for compliance with Hardy–Weinberg equilibrium[46] using a chi-square goodness-of-fit test, performed separately for each group.

Binary logistic regression was used to estimate odds ratios (ORs) and 95% CIs for the association between *APOE* genotype and CHD risk, with the E3/E3 genotype serving as the reference category. Model 1 (unadjusted) included *APOE* genotype only. Model 2 (adjusted) additionally included age, sex, BMI, smoking status, systolic blood pressure, total cholesterol, LDL-C, HDL-C, triglycerides, family history of CVD, and physical activity as covariates. These variables were selected a priori based on established cardiovascular risk factors and those that differed significantly between groups at baseline. Odds ratios (ORs) are reported with corresponding 95% confidence intervals (CIs) and *P* values.[47]

Given the number of statistical tests performed, a Bonferroni-corrected significance threshold of $P < .003$ was applied for genotype–phenotype correlation analyses. A 2-sided *P*-value <.05 was retained as the primary threshold for prespecified comparisons. All analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Clinical Characteristics

A total of 124 participants were included in the study, comprising a case group and a control group. Among these, 63 individuals had CVD, while 61 did not. In the case group, 54% (34/63) were female, and 46% (29/63) were male. In the control group, 48% (29/61) were female, and 52% (32/61) were male. Statistical analysis revealed no significant difference in sex distribution between the 2 groups ($P = .400$).

The mean age of participants in the case and control groups was 52 ± 7 years and 53 ± 8 years, respectively ($P = .600$), indicating no statistically significant difference; however, other clinical parameters differed significantly. Body mass index was significantly higher in the case group (28.3 ± 3.0 kg/m^2) than in the control group (23.0 ± 3.0 kg/m^2; $P < .001$). Table 1 shows the clinical characteristics of the study participants.

Age distribution was consistent across study groups and genotypes. However, BMI was significantly higher among ε4/ε4 genotype carriers, particularly in the case group, indicating an association with increased metabolic risk. Individuals carrying the ε4 allele, especially those with the ε4/ε4 genotype, exhibited elevated diastolic blood pressure, suggesting a potential association with hypertension. Similarly, cases with the ε4/ε4 genotype showed higher systolic blood pressure, indicating increased cardiovascular risk. Total cholesterol levels varied significantly by genotype, with ε4 allele carriers in the case group exhibiting higher levels, consistent with the established role of the *APOE* ε4 allele in lipid metabolism disorders. Triglyceride levels were also significantly elevated among ε4/ε4 carriers in the case group, further highlighting the metabolic impact of this allele. High-density lipoprotein cholesterol levels showed only marginal variation, while LDL-C levels did not differ significantly across genotypes.

Biochemical Analysis

Table 1 summarizes the biochemical markers studied. Serum triglyceride levels were significantly lower in the case group than in the control group (1.00 ± 0.30 vs. 1.56 ± 0.74 mmol/L, $P < .001$). Serum HDL-C levels were higher in the case group than in the control group (1.56 ± 0.14 vs. 1.33 ± 0.18 mmol/L, $P < .001$). Serum LDL-C levels were also higher in the case group than in the control group (3.39 ± 0.60 vs. 2.62 ± 0.76 mmol/L, $P = .027$). Total cholesterol levels differed significantly between the 2 groups and were lower in the case group than in the control group (3.91 ± 0.60 vs. 5.34 ± 0.80 mmol/L, $P < .001$).

Table 1. Clinical Characteristics of Studied Participants

Parameters	Study Group: Case n = 63 (51%)[a]	Study Group: Control n = 61 (49%)[a]	*P* value[b]
Sex, n (%)			.400
Female	34 (54)	29 (48)	
Male	29 (46)	32 (52)	
Clinical characteristics			
Age (years)	52 ± 7 (40, 64)	53 ± 8 (40, 71)	.600
BMI (kg/m^2)	28 ± 3 (23, 37)	23 ± 3 (19, 35)	<.001
Systolic BP (mm Hg)	115.87 ± 3.6	137.27 ± 15.4	<.001
Diastolic BP (mm Hg)	77.17 ± 3.9	84.97 ± 7.8	<.001
Waist circumference (cm)	74.97 ± 6.5	92.8 ± 8.9	<.001
Lipids			
Cholesterol (mmol/L)	3.912 ± 0.6	5.34 ± 0.8	<.001
Triglycerides (mmol/L)	1.00 ± 0.3	1.56 ± 0.74	<.001
HDL (mmol/L)	1.56 ± 0.14	1.33 ± 0.18	<.001
LDL (mmol/L)	3.39 ± 0.6	2.62 ± 0.76	.027
Lifestyle/history, n (%)			
Family history of CVD			.001
Yes	24 (38)	5 (8.2)	
No	39 (62)	56 (92)	
Smoking status			.003
Yes	28 (44)	12 (20)	
No	35 (56)	49 (80)	
Alcohol consumption			.200
Yes	4 (6.3)	8 (13)	
No	59 (94)	53 (87)	
Stress			.800
Yes	15 (28)	14 (25)	
No	39 (72)	41 (75)	
Physical activity			.001
Yes	5 (7.9)	21 (34)	
No	58 (92)	40 (66)	
Dietary patterns			.090
Yes	14 (22)	22 (36)	
No	49 (78)	39 (64)	

BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]n (%): The percentage of individuals in that category relative to the total sample size.
[b]Pearson's chi-squared test; Wilcoxon rank sum test; Fisher's exact test.

The overall distribution of *APOE* genotypes differed significantly between the case and control groups ($\chi^2 = 9.08$, df = 3, $P = .009$; Table 2). Descriptively, the ε4/ε4 genotype was more frequent among cases than controls (15.9% vs 4.9%), whereas the ε2/ε3 genotype was less frequent among cases (12.7% vs 36.1%) (Table 2).

Genetical Analysis

APOE genotyping was performed on samples from 61 healthy participants and 63 patients with CHD. The identified genotypes in both groups were ε2/ε3, ε3/ε3, ε3/ε4, and ε4/ε4.

Table 2. ApoE Genotypes in Control and Case Groups

Genotype	Control n	Control n (%)	Case n	Case n (%)	χ^2	*P*
ε2/ε3	22	36.1	8	12.7		
ε3/ε3	33	54.1	41	65.1		
ε3/ε4	3	4.9	4	6.3		
ε4/ε4	3	4.9	10	15.9		
Total	61	100	63	100	9.08	.009

Genotype distributions were compared between groups using the chi-square (χ^2) test with 3 *df*.

Analysis of genotype frequencies for the *APOE* gene polymorphisms rs429358 and rs7412, in 124 individuals, showed that the control group had the following frequencies: ε2/ε3 (36.1%), ε3/ε3 (54.1%), and ε3/ε4 (4.9%). In the case group, the frequencies were as follows: ε2/ε3 (12.7%), ε3/ε3 (65.1%), ε3/ε4 (6.3%), and ε4/ε4 (15.9%). The distribution of APOE genotypes differed significantly between the case and control groups ($\chi^2 = 9.08$, $P = .009$) (Table 3).

Logistic regression analysis was conducted to evaluate the association between APOE genotypes and CHD risk. Using the ε3/ε3 genotype as the reference category, the ε2/ε3 genotype was associated with significantly lower odds of CHD (OR = 0.29, $P = .007$, 95% CI: 0.12-0.71), indicating a protective association. In contrast, no statistically significant associations were observed for the ε3/ε4 genotype (OR = 1.07, $P = .930$, 95% CI: 0.23-5.02) or the ε4/ε4 genotype (OR = 2.68, $P = .160$, 95% CI: 0.68-10.55). The wide CIs for the ε3/ε4 and ε4/ε4 genotypes reflect limited statistical precision due to the small number of carriers, particularly ε4/ε4 homozygotes.

No significant correlations were observed between *APOE* polymorphisms and demographic variables, including age ($r = -0.192$, $P = .090$) and sex ($r = 0.000$, $P = 1.000$), as shown in Table 4, suggesting that these factors did not confound the genotype–phenotype associations observed in this cohort.

Correlation Among Biomarkers

Serum cholesterol levels showed a significant positive correlation with waist circumference ($r = 0.348$, $P = .002$) and triglyceride levels ($r = 0.322$, $P = .004$). Triglycerides were also significantly associated with BMI ($r = 0.297$, $P = .008$), smoking status ($r = 0.288$, $P = .010$), and alcohol consumption ($r =$

Table 3. Frequency of *ApoE* Genotypes in Control (n = 61) and Case (n = 63) Groups and Calculated Odds Ratio

ApoE Genotype	Study Group: Control (%)	Study Group: Case	OR (95% CI)	*P*
ε3/ε3	33 (54.1)	41 (65.1)	Reference	–
ε2/ε3	22 (36.1)	8 (12.7)	0.29 (0.12-0.71)	.007
ε3/ε4	3 (4.9)	4 (6.3)	1.07 (0.23-5.02)	.930
ε4/ε4	3 (4.9)	10 (15.9)	2.68 (0.68-10.55)	.160

Odds ratios calculated using logistic regression with ε3/ε3 as the reference genotype.
OR, odds ratio.

Table 4. Correlation Analysis Among Biomarkers and Coronary Heart Disease Risk Factors

Variable 1	Variable 2	Correlation (*r*)	Adjusted *P*
Serum cholesterol	Waist circumference	0.348	.002
Serum cholesterol	Triglycerides	0.322	.004
Serum cholesterol	HDL	−0.360	.001
Triglycerides	BMI	0.297	.008
Triglycerides	Smoking status	0.288	.010
Triglycerides	Alcohol consumption	0.285	.011
BMI	Waist circumference	0.712	<.001
BMI	Smoking status	0.236	.036
LDL	Alcohol consumption	−0.245	.029
Alcohol consumption	Smoking status	0.317	.004
Alcohol consumption	Sex	0.236	.037
SBP/DBP	Waist circumference	0.250	.026
APOE genotype	Age	−0.192	.090
APOE genotype	Sex	0.000	1.000

r represents Spearman's rank correlation coefficient. All negative values are adjusted for multiple comparisons using the false discovery rate method.
BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

0.285, $P = .011$). A strong positive correlation was observed between BMI and waist circumference ($r = 0.712$, $P < .001$). In addition, both systolic and diastolic blood pressure showed a significant association with waist circumference ($r = 0.250$, $P = .026$) (Table 4).

Further analysis demonstrated that LDL-C was significantly associated with alcohol consumption ($r = -0.245$, $P = .029$), while HDL-C showed a significant correlation with total serum cholesterol ($r = -0.360$, $P < .001$).

Body mass index was also significantly correlated with smoking status ($r = 0.236$, $P = .036$) and waist circumference ($r = 0.712$, $P < .001$). Alcohol consumption showed a statistically significant association with smoking ($r = 0.317$, $P = .004$), sex ($r = 0.236$, $P = .037$), and triglyceride levels ($r = -0.285$, $P = .011$).

Regarding genetic factors, no significant correlations were observed between *APOE* genotype and demographic variables, including age ($r = -0.192$, $P = .090$) and sex ($r = 0.000$, $P = 1.000$), suggesting that these factors did not confound the observed genetic associations in this cohort (Table 4).

Finally, the observed age distribution did not differ significantly between the case and control groups across *APOE* genotypes, suggesting that age is not a significant confounding variable in this analysis (Table 5).

APOE Genotype–Related Differences in Metabolic and Cardiovascular Traits

Carriers of the ε4/ε4 genotype in the case group displayed significantly higher systolic and diastolic blood pressure, suggesting a strong association between this genotype and increased hypertensive risk. Overall group comparisons (Figure 1C and 1D) showed that both systolic and diastolic blood pressure were significantly elevated in cases compared with controls ($P < .001$), regardless of genotype, highlighting the elevated baseline cardiovascular risk in the CHD population.

Total Cholesterol

Total cholesterol levels varied significantly by genotype. In particular, ε4 allele carriers in the case group exhibited higher cholesterol levels than ε2 or ε3 carriers. However, at the group level (Figure 1E), total cholesterol was significantly lower in cases than in controls ($P < .001$), reflecting the influence of lipid-lowering therapy among patients.

Triglycerides

As illustrated in Figure 1F, triglyceride levels showed highly significant differences between groups ($P < .001$). The ε4/ε4 genotype was strongly associated with the highest triglyceride concentrations in the CHD group.

Lipoproteins

A statistically significant, albeit small, difference in HDL-C levels was observed between groups based on genotype and disease status (Figure 1G, $P < .005$). In contrast, LDL-C levels showed no significant difference between cases and controls ($P = .400$), irrespective of *APOE* genotype (Figure 1H).

Collectively, these findings indicate that while BMI and blood pressure are the primary distinguishing factors between CHD cases and controls, the ε4 allele—particularly in its homozygous (ε4/ε4) form—significantly exacerbates the metabolic and cardiovascular risk within the Mongolian CHD population (Figure 1B).

DISCUSSION

The current study aimed to investigate the associations between *APOE* genotypes, lipid profiles, and CHD risk factors in a Mongolian population. This work builds upon prior research characterizing *APOE* gene polymorphism in the Mongolian population, which reported an ε4 allele frequency of 1.9%,[9] and extends these findings by examining specific correlations with CVD markers.[8,48] The current findings indicate that carriers of the *APOE* ε3/4 and ε4/4 genotypes may exhibit an increased risk of CHD compared with ε3/3 carriers, consistent with findings from meta-analyses across diverse populations.[3] Specifically, the ε4 allele—especially in the homozygous ε4/ε4 state—is associated with elevated serum LDL-C levels, further solidifying its role in dyslipidemia and increased cardiovascular risk.[49]

In contrast, this study observed paradoxically lower total cholesterol levels in CHD cases compared with controls. This finding is likely attributable to the high prevalence of lipid-lowering therapy among patients with established coronary artery disease, reflecting adherence to secondary

Table 5. Correlation Analysis Between Biomarkers in the Healthy Control and Case Group

Variables	Age (Years)	Cholesterol	Sex	TGs	BMI	Smoking Status	Alcohol Consumption	SBP	DBP	Dietary Patterns	Waist Circumference	*ApoE* Genotype	Physical Activity	HDL	LDL
Age (years)	–														
Cholesterol	$r=-0.12$	–													
	$P=.290$														
Sex	$r=0.075$	$r=-0.078$	–												
	$P=.512$	$P=.497$													
TGs	$r=-0.184$	$r=0.322$	$r=-0.193$	–											
	$P=.102$	**$P=.004$**	$P=.089$												
BMI	$r=-0.082$	$r=0.307$	$r=-0.122$	$r=0.297$	–										
	$P=.472$	**$P=.006$**	$P=.286$	**$P=.008$**											
Smoking status	$r=0.219$	$r=-0.255$	$r=0.389$	$r=-0.288$	$r=-0.236$	–									
	$P=.053$	**$P=.023$**	**$P=0.001$**	**$P=.010$**	**$P=.036$**										
Alcohol consumption	$r=0.122$	$r=-0.054$	$r=0.236$	$r=-0.285$	$r=-0.006$	$r=0.317$	–								
	$P=.283$	$P=.636$	**$P=.037$**	$P=.011$	$P=.957$	**$P=.004$**									
SBP	$r=-0.039$	$r=-0.034$	$r=0.009$	$r=-0.13$	$r=0.084$	$r=0.034$	$r=0.075$	–							
	$P=.736$	$P=.763$	$P=.937$	$P=.252$	$P=.464$	$P=.763$	$P=.511$								
DBP	$r=0.226$	$r=0.068$	$r=0.09$	$r=0.092$	$r=0.121$	$r=0.183$	$r=0.047$	$r=0.247$	–						
	$P=.045$	$P=.550$	$P=.429$	$P=.419$	$P=.289$	$P=.107$	$P=.678$	**$P=.028$**							
Dietary patterns	$r=-0.002$	$r=-0.05$	$r=0.215$	$r=0.194$	$r=0.176$	$r=-0.135$	$r=-0.139$	$r=0.027$	$r=0.085$	–					
	$P=.984$	$P=.661$	$P=.057$	$P=.086$	$P=.121$	$P=.236$	$P=.221$	$P=.813$	$P=.455$						
Waist circumference	$r=-0.13$	$r=0.348$	$r=-0.381$	$r=0.203$	$r=0.712$	$r=-0.231$	$r=-0.075$	$r=0.25$	$r=0.02$	$r=0.001$	–				
	$P=.253$	**$P=.002$**	**$P=.001$**	$P=.072$	**$P<.001$**	**$P=.041$**	$P=.512$	**$P=.026$**	$P=.858$	$P=.990$					
ApoE genotype	$r=-0.192$	$r=0.177$	$r=0$	$r=0.076$	$r=-0.141$	$r=-0.251$	$r=-0.036$	$r=-0.076$	$r=-0.16$	$r=-0.025$	$r=-0.107$	–			
	$P=.090$	$P=.119$	$P=1.000$	$P=.507$	$P=.215$	**$P=.026$**	$P=.750$	$P=.508$	$P=.158$	$P=.828$	$P=.347$				
Physical activity	$r=-0.043$	$r=0.095$	$r=0.087$	$r=-0.12$	$r=0.094$	$r=-0.094$	$r=0.191$	$r=0.03$	$r=-0.01$	$r=0.061$	$r=0.099$	$r=-0.161$	–		
	$P=.707$	$P=.405$	$P=.446$	$P=.294$	$P=.410$	$P=.408$	$P=.091$	$P=.792$	$P=.928$	$P=.595$	$P=.384$	$P=.156$			
HDL	$r=-0.009$	$r=-0.36$	$r=0.126$	$r=-0.187$	$r=0.028$	$r=0.215$	$r=0.365$	$r=0.157$	$r=0.043$	$r=-0.002$	$r=0.044$	$r=-0.192$	$r=-0.017$	–	
	$P=.940$	**$P=.001$**	$P=.270$	$P=.098$	$P=.807$	$P=.057$	**$P=.001$**	$P=.167$	$P=.705$	$P=.988$	$P=.698$	$P=.089$	$P=.883$		
LDL	$r=-0.243$	$r=0.194$	$r=0.153$	$r=0.076$	$r=-0.043$	$r=-0.029$	$r=-0.245$	$r=0.037$	$r=-0.073$	$r=0.121$	$r=-0.113$	$r=0.083$	$r=0.116$	$r=-0.003$	–
	$P=.031$	$P=.086$	$P=.177$	$P=.506$	$P=.708$	$P=.799$	$P=.029$	$P=.747$	$P=.525$	$P=.290$	$P=.323$	$P=.465$	$P=.309$	$P=.976$	

Values are Pearson correlation coefficients (r) with P-values in parentheses. Significant correlations ($P < .05$) are shown in bold. Only the lower triangle is presented.
ApoE, apolipoprotein E; BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; TGs, triglycerides.

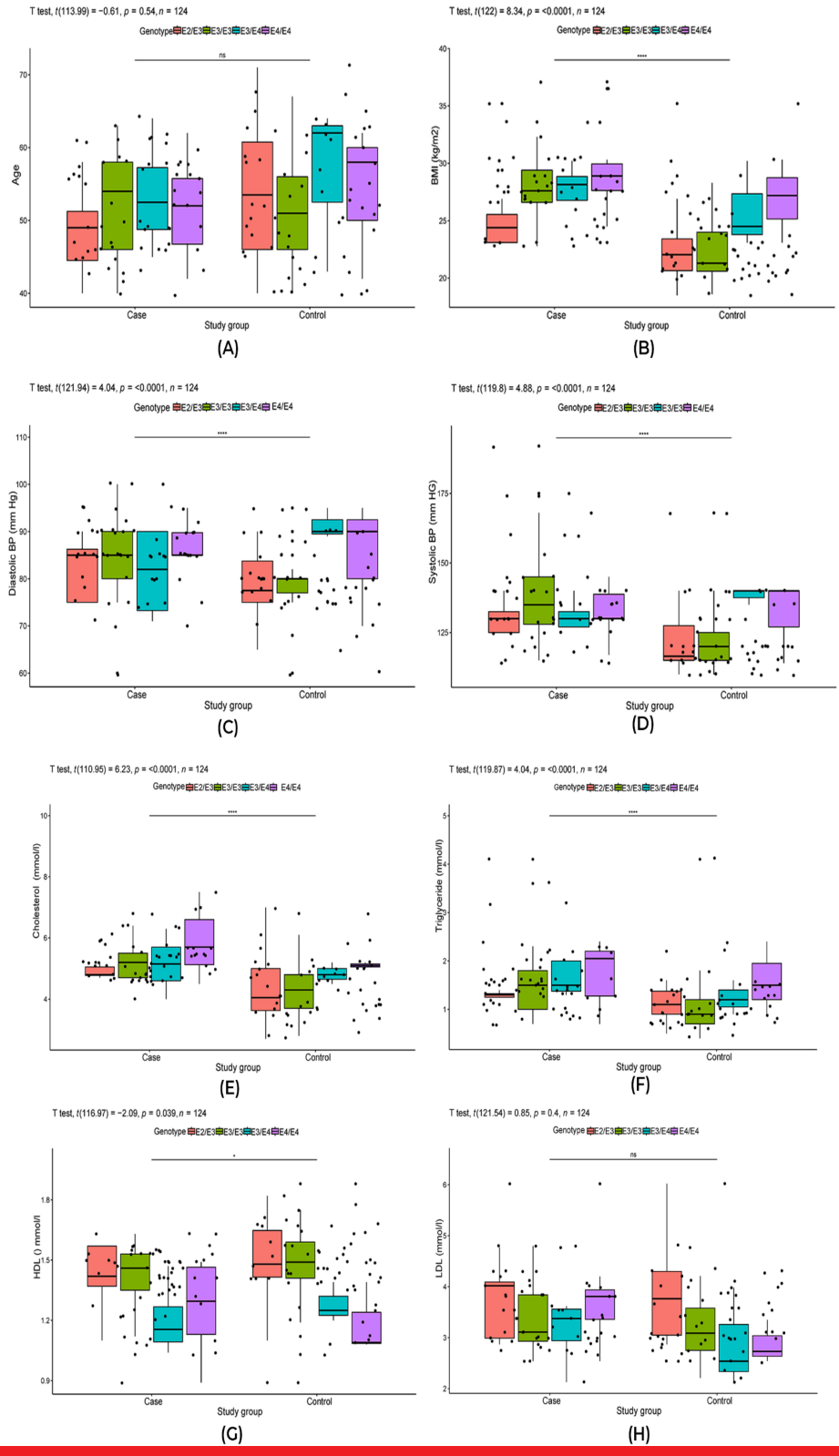

Figure 1. Distribution of clinical and biochemical parameters across study groups and *APOE* genotypes. The figure illustrates the distribution and comparison of metrics between CHD cases (63) and healthy controls (61): (A) Age (years). (B) BMI (kg/m²). (C) Diastolic blood pressure (mmHg). (D) Systolic blood pressure (mmHg). (E) Total cholesterol (mmol/L). (F) Triglycerides (mmol/L). (G) HDL cholesterol (mmol/L). (H) LDL cholesterol (mmol/L). The asterisk indicates a significant *P*-value when the case group was compared with healthy controls. All *P*-values were reformatted according to journal style requirements (*P* = .xxx or *P* < .001). BMI, body mass index; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

prevention targets in clinical practice.[37] Such pharmacological interventions often mask the underlying metabolic phenotype associated with high-risk genotypes.[27] Nevertheless, the significant association between the ε4 allele and CHD remains evident, suggesting that genetic risk factors contribute to disease susceptibility, regardless of subsequent therapeutic lipid reduction.[28,50]

The distribution of *APOE* alleles in the Mongolian population demonstrates significant variation when compared to other ethnic groups. In this study, a notably higher ε4 allele frequency was observed in CHD cases (15.9% for the ε4/ε4 genotype alone) compared with controls. This finding is consistent with that of previous research in the Mongolian population that reported an overall ε4 frequency of 15.5%, noting it as one of the highest frequencies recorded in Asia.[9]

Across Asian populations, the Mongolian ε4 allele frequency follows a prominent south to north geographic gradient. For example, southern Chinese populations (e.g., in Kunming) report relatively low ε4 frequencies (4.9%), whereas northern cohorts (e.g., in Harbin) demonstrate substantially higher prevalence (17.5%).[51] The frequency observed in this Mongolian cohort is consistent with the northern distribution pattern. Furthermore, the overall ε4 frequency in general Han Chinese populations is typically lower, approximately 7%-8.5%, compared to the levels found in the Mongolian cohort.[51,52] Japanese populations show a comparatively wide range of ε4 allele frequencies (between 11.7% and 27.8%), placing the risk profile of the Mongolian subjects within a similar range to these high-risk Japanese groups.[52,53]

Despite these observations, the current analysis did not demonstrate a statistically significant association between ε4 allele and CHD risk ($P < .945$).

While the isoform is a well-documented risk factor for atherosclerosis and neurodegeneration globally, its notable presence in the Mongolian cohort—specifically with 15.9% of the case group identified as homozygotes—provides evidence for its significant role in CHD susceptibility within this specific population.[9,54] Consequently, this interpretation has been revised to classify these ε4 findings as preliminary, emphasizing that larger multi-center studies are required to achieve the statistical power necessary to evaluate rare genetic variants in Central Asian ancestries.[55]

The findings demonstrate a robust protective association between the ε2/ε3 genotype and CHD risk (OR = 0.29), suggesting that ε2 carriers in the Mongolian population may benefit from inherently lower pro-atherogenic lipid profiles. This protective effect is biologically plausible, as the APOE2 isoform exhibits reduced binding affinity for the LDL receptor, which typically results in lower plasma LDL-C levels. These findings contrast with the ε4 allele, which, although not statistically significant in this study (OR = 1.07 for ε3/ε4), is widely recognized as a potent risk factor for atherosclerosis and late-onset Alzheimer's disease.[56,57,58]

While the ε3 isoform remains the most common "normal" variant, the differential effects of the ε2 and ε4 alleles highlight the pleiotropic nature of the *APOE* gene.[57] Although the ε2 allele is generally considered protective against CHD, it has occasionally been associated with dysbetalipoproteinemia; however, this phenotypic expression typically requires additional environmental or genetic factors.[58,59] Future studies in the Mongolian population should further explore these associations alongside neurocognitive assessments to determine whether the protective effect of ε2 extends to dementia risk within this specific ancestry.

Analysis of metabolic and cardiovascular phenotypes across *APOE* genotypes revealed significant variations, particularly among carriers of the ε4 allele. Individuals with the ε4/ε4 genotype in the CHD case group exhibited the highest metabolic risk profile, characterized by significantly elevated BMI compared with other genotypes. This pattern was consistent across the cohort, as the current results indicate that BMI was significantly higher in the CHD group than in the healthy control group ($P < .0001$), independent of specific *APOE* polymorphisms.[60]

Cardiovascular markers also demonstrated genotype-specific associations.[61,62] Specifically, the ε4 allele has been previously linked to elevated total cholesterol and LDL-C levels, as well as an increased risk of CVD and Alzheimer's disease.[63,64] However, the current analysis indicates that individuals carrying the ε2/ε3 and ε2/ε4 genotypes tend to exhibit more favorable lipid profiles, characterized by enhanced triglyceride metabolism and reduced LDL-C accumulation, suggesting a protective effect against CVD.[48] Conversely, the ε4 allele, particularly in the homozygous ε4/ε4 state, is associated with elevated very-low-density lipoprotein cholesterol and triglyceride levels, along with decreased HDL-C.[65] These findings are consistent with previous studies indicating that the ε4 allele contributes to elevated total cholesterol and LDL-C levels, whereas the ε2 allele correlates with lower triglyceride and LDL-C concentrations.[66]

Compared with European and Caucasian populations, the ε4 allele frequency observed in this study is slightly lower than the range of 14.7%-36.7% reported in various Western cohorts.[52,53] However, meta-analyses suggest that the impact of the ε4 allele on CHD risk may be more pronounced in Mongolian populations than in Caucasians, indicating that the genetic background of this population may confer increased sensitivity to the lipid-elevating effects of the allele.[3] In Turkish populations, findings have been inconsistent; while some studies report no significant association with CHD, others demonstrate that ε4 carriers exhibit significantly higher LDL-C and total cholesterol levels, mirroring the metabolic associations observed in this study.[67,68]

These findings emphasize that although the ε4 allele is a global risk factor, its prevalence and phenotypic expression in the Mongolian population appear to be distinct and may contribute significantly to the regional burden of CVD.[9]

Limitations

The modest sample size and single-center recruitment design limited statistical power and reduced the generalizability of the findings to the broader Mongolian population, including rural and nomadic communities.

This study has several limitations that require a cautious interpretation of the findings. First, the modest sample size (63 cases and 61 controls) limits the statistical power to detect associations involving less common genotypes, such as the ε2/ε4 or ε4/ε4 variants.[55,60] Second, as the study was conducted only at the Third State Central Hospital in Mongolia, its single-center, urban setting may limit the generalizability of the findings to rural or nomadic populations, which may have distinct environmental exposures and dietary patterns.[9,19] Furthermore, the case–control design prevents the determination of causal relationships; thus, longitudinal research is needed to clarify temporal associations between *APOE* genotypes and CHD in this population.[69] Finally, the current analysis was restricted to 2 canonical SNPs (rs429358 and rs7412), potentially overlooking other genetic variants or epigenetic factors that may influence CHD susceptibility in Central Asian populations.[19,70]

Future multi-regional studies are essential to validate these findings across the diverse Mongolian population. Such comprehensive investigations would facilitate a more comprehensive understanding of how genetic predisposition, environmental factors, and lifestyle choices interact to influence CVD risk. Moreover, expanding the scope of genetic markers beyond *APOE*, such as those related to lipid metabolism and inflammation, would provide a more holistic understanding of CHD susceptibility in this distinct ethnic group. Further molecular studies examining genetic polymorphisms—particularly those related to lipid processing and inflammation—are warranted to elucidate the complete genetic architecture underlying CHD risk in Mongolian populations.

CONCLUSION

Accordingly, these findings should be interpreted as preliminary and hypothesis-generating until validated in larger, multi-center Mongolian cohorts with formal power calculations and broader geographic representation. This exploratory case–control study provides the first systematic evidence linking *APOE* genotype polymorphisms to CHD risk in a Mongolian cohort, a population critically underrepresented in cardiovascular genetics research. The principal statistically supported finding is a robust protective association of the ε2/ε3 genotype against CHD, consistent with the known cardioprotective effects of the *APOE* ε2 allele, including enhanced receptor-mediated LDL clearance and favorable effects of lipoprotein metabolism. The overall *APOE* genotype distribution differed significantly between cases and controls, with the ε4/ε4 genotype more prevalent among cases; although, this difference did not reach statistical significance in logistic regression analyses, likely reflecting the limited statistical power associated with the modest sample size. A notable feature of this cohort was the paradoxically lower total cholesterol observed in CHD cases compared with controls, which is likely attributable to guideline-directed lipid-lowering therapy in patients with established disease. This finding underscores the inherent limitation of total cholesterol as a sole cardiovascular biomarker and supports the value of comprehensive lipoprotein fraction profiling, particularly in the context of *APOE* genotyping, for accurate risk stratification. Given the single-center, urban design of this study, the findings should be interpreted as exploratory and are not nationally representative of the Mongolian population.

Nevertheless, this study establishes an important evidence base for *APOE*-related cardiovascular susceptibility in Central Asian populations and identifies key priorities for future research. Multi-center, longitudinal studies involving larger and more geographically diverse Mongolian cohorts, incorporating detailed medication data and extended phenotyping characterization, are essential to validate these findings and to support the development of population-specific, genotype-informed strategies for CVD prevention.

Ethics Committee Approval: This study was approved by the Ethics Committee of Mongolian National University of Medical Sciences (Approval No.: 2025/06/1093; Date: April 22, 2025).

Informed Consent: Written informed consent was obtained from all participants before their enrollment in the study.

Peer-review: Externally peer-reviewed.

Acknowledgments: The authors are grateful to the staff of the Mongolian National University of Medical Sciences, National Center Mental Health of Mongolia, and The Third Clinical Hospital for their cooperation and assistance during the research.

Author Contributions: Concept – Ye.Ch, O.D., N.M.; Design – Ye.Ch, N.M.; Supervision – Ye.Ch.; Resources – O.D., A.P., O.D., Ts.Z.; Materials – O.D., A.P., O.D., Ts.Z., G.Z., U.G., O.N.; Data Collection and/or Processing – O.D., A.P, O.D., Ts.Z., G.Z., U.G., O.N.; Analysis and/or Interpretation – O.D., B.U., N.M., Ye.Ch.; Literature Search – O.D., A.P., O.D., Ts.Z., G.Z., U.G., O.N.; Writing – O.D., N.M., Ye.Ch; Critical Review – O.D., N.M., Ye.Ch.

Declaration of Interests: The authors declare no competing interests.

Funding: The authors declare that this study received no financial support.

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