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Association between APOE Gene Polymorphisms and Hyperuricemia in a County Population of Guangxi, China

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Abstract: *This study aims to explore the relationship between apolipoprotein E (APOE) gene polymorphisms and the risk of hyperuricemia (HUA), to provide a theoretical basis for further investigations into the genetic mechanisms and prevention and treatment of this disease. This study included 362 subjects in the hyperuricemic and 362 subjects in the healthy control group, testing for APOE gene polymorphisms (rs429358, rs7259620 and rs405509). Logistic regression was used to analyze the relationships between APOE gene SNPs and other risk factors and hyperuricemia. The distributions of the APOE gene alleles rs429358, rs7259620, and rs405509 were significantly different between the hyperuricemic group and the healthy control group ($P<0.05$). In terms of genotype distribution, only the rs7259620 locus was significantly different ($P<0.05$). Logistic regression analysis using codominant, recessive, dominant and overdominant models did not reveal a significant association between APOE gene polymorphism and hyperuricemia. No significant multiplicative or additive interaction effects between SNP loci and environmental factors were observed in the occurrence of hyperuricemia. BMI (23-27.5 kg/m^2) and triglyceride (TG) may be protective factors against HUA, whereas smoking, diastolic blood pressure (DBP), and low-density lipoprotein cholesterol (LDL-C) may be risk factors for HUA. The polymorphisms of the APOE genes rs429358, rs7259620, and rs405509 are not directly associated with susceptibility to hyperuricemia, and gene-environment interaction analysis did not reveal a significant effect on the risk of developing hyperuricemia.*

Keywords: *Hyperuricemia; APOE; Polymorphism; Allele; Influencing Factor*

1. Introduction

Hyperuricemia (HUA) is a condition characterized by elevated levels of uric acid in the blood, typically resulting from excessive production, reduced excretion, or a combination of both. HUA can lead to gout, and HUA significantly influences the onset and progression of gout[1]. In China, the prevalence of gout increased markedly from 1990 to 2019, with an average annual growth rate of 0.9%. By 2019, approximately 16.2 million people were affected by gout[2]. The prevalence of gout in China is increasing at an alarming rate. Because HUA is a precursor to gout, an increase in the prevalence of HUA indirectly indicates an increase in the prevalence of gout. Research statistics show that by 2016, the global prevalence of HUA had reached 21%, with a prevalence of 14.6–20% in the United States[3,4]. Among the Chinese population with HUA, the prevalence among adults rose from 11.1% in 2015–16 to 14.0% in 2018–19, with a higher prevalence in males than in females[5]. The prevalence of hyperuricemia is increasing, and hyperuricemia has become a global public health issue[6]. HUA is also

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strongly associated with diseases such as obesity, diabetes, kidney disease, and cardiovascular diseases[7-10], and has significant clinical relevance to hypertension[11]. Therefore, effectively managing HUA can reduce the health burden on individuals.

Studies have shown that a BMI ≥24 kg/m², abdominal obesity, and dyslipidemia are risk factors for hyperuricemia. Obesity-induced lipid metabolism disorders and vascular dysfunction can lead to elevated uric acid levels[12,13]. The APOE gene (Apolipoprotein E gene), encoding apolipoprotein E (APOE), plays a significant role in lipid metabolism and cholesterol transport and is highly enriched in human tissues, particularly in the brain[14-16]. Studies have shown that APOE can disrupt cholesterol transport and esterification as well as the expression of cholesterol-related metabolic genes[17], leading to lipid metabolism disorders.

Research has confirmed[18,19] that there is a certain association between APOE polymorphisms and hyperuricemia in different populations. However, despite the increase in prevalence of hyperuricemia few recent studies have investigated the relationships between APOE-related genes and HUA. The subjects selected for this study were mainly from Gongcheng Yao Autonomous County in Guangxi, predominantly consisting of the Yao ethnic minority. The local inhabitants have unique dietary habits, such as the consumption of oil tea. Guangxi oil tea (especially Yao oil tea from the Guilin and Gongcheng areas) is a local specialty beverage made from tea leaves, ginger, garlic, and other ingredients through pounding and boiling. It has a rich, spicy, and aromatic flavor, providing refreshing, warming, and dehumidifying effects. Currently, there is no research on the association between APOE gene polymorphisms and HUA in Gongcheng County. Therefore, the aim of this study is to explore the associations among personal behavioral factors, APOE gene polymorphisms, and HUA and to analyze the interactions between genes and various factors in the onset of HUA, providing a reference for reducing the incidence of HUA in the local population.

2. Materials and Methods

2.1 Study Population

The study population was drawn from a rural population that participated in a health survey from 2018–2019 in Gongcheng Yao Autonomous County, Guangxi, China.

The inclusion criteria were as follows: (1) Case group: male serum uric acid (SUA) > 416 mmol/L or female SUA > 357 mmol/L; (2) control group: matched by sex and age (± 2 years) at a 1:1 ratio; (3) willing to undergo a complete physical examination and questionnaire survey; and (4) signed written informed consent. The ***exclusion*** criteria were as follows: (1) known to have cancer, lung disease, liver disease, kidney disease, gastrointestinal disease, etc., or (2) taking any medication known to affect carbohydrate and lipid metabolism.

This study is a case–control study. The study adheres to the Declaration of Helsinki, and the research protocol was approved by the Ethics Committee of Guilin Medical University (No. 20180702-3). A total of 724 residents aged 26–91 years were included, with 362 in the case group (male, n=200; female, n=162) and 362 in the control group (male, n=200; female, n=162). Genetic analysis was conducted on the study population.

2.2 Epidemiological Survey and Biochemical Measurements

Following the principle of informed consent, a standardized and unified questionnaire survey was conducted. The questionnaire covered basic information, medical history, socioeconomic status, lifestyle, and cognitive function status. Height (accurate to 0.1 cm), weight (accurate to 0.1 kg), and waist circumference were measured as part of the physical examination. Body mass index (BMI) = weight (kg)/height² (m²).

Blood samples were collected from fasting venous blood by medical staff and transported the same day via cold chain to the laboratory department of Gongcheng Yao Autonomous County People's Hospital for testing. A routine blood analyzer (Sysmex CS-1600, Shanghai, China) was used to test fasting plasma glucose (FPG), and a blood biochemical analyzer (Hitachi 7600-020, Kyoto, Japan) was used to detect indicators such as glycated hemoglobin (HbA1C), uric acid (UA), serum total cholesterol (TC), blood creatinine (CERA), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and serum triglyceride (TG).

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2.3 Single Nucleotide Polymorphism (SNP) Selection and Genotyping

The SNP screening strategy was as follows: (1) Functional region SNP screening: We searched for the APOE gene, including regions such as the APOE gene promoter (upstream variant 2KB), 5'UTR, exons (missense, synonymous), and 3'UTR, on the NCBI-SNP1 website. The literature was reviewed, and the results were annotated with information on disease susceptibility. (2) Validated and hotspot SNP screening: Google Scholar was used to search for SNP loci with susceptibility and perform functional predictions using the NIH website. Linkage disequilibrium (LD) analysis was conducted on the SNP loci selected in the first step using the screened SNP loci, and completely linked loci with R = 1 were annotated. Finally, the SNP loci of APOE were optimized by discarding loci with R = 1 and retaining loci in the promoter region with R > 0.8.

The loci rs429358, rs7259620, and rs405509 of the APOE gene were selected for genotyping. DNA was extracted using a blood DNA kit (Tiangen, Beijing, China). The primers used for genotyping were designed and synthesized by Bio Miao Biological Technology Co., Ltd. (Beijing, China) using the Sequenom MassARRAY matrix-assisted laser desorption ionization time-of-flight mass spectrometry platform (Sequenom Inc, San Diego, California, USA).

2.4 Statistical Methods

The data were analyzed statistically using SPSS 28.0 software. Quantitative data with a normal distribution are expressed as the mean ± standard deviation, and comparisons between groups were performed using the independent t-test. Qualitative data are presented as percentages and were analyzed using the chi-square test or Fisher's exact test for control and case groups. LINK 1.90 software was used for Hardy–Weinberg equilibrium (HWE) (samples are representative when $p > 0.05$) and MAF statistical data. Haploview (MIT and Harvard University, USA, version 4.2) was used to analyze pairwise LD and haplotype frequencies in SNPs, and to analyze haplotypes containing strongly associated SNP loci and hyperuricemia. $P < 0.05$ was considered statistically significant.

Logistic regression was conducted to estimate the effects of genotype and gene–environment multiplicative interactions on SUA levels and odds ratio (OR), with 95% confidence intervals (95% CI) calculated, and a significance level of $\alpha=0.05$. However, logistic regression is limited to estimating multiplicative interactions. Therefore, the relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP), the synergy index (SI), and their 95% confidence intervals (CI) were calculated. When the 95% CI of the RERI and AP do not include 0 and the 95% CI of the SI does not include 1.18, the additive interaction is considered statistically significant. Additionally, the calculations of RERI, AP, and SI were completed using R software version 4.0.2 and the "epiR" package.

3. Results

3.1 Comparison of General Data

A total of 724 subjects were included in this study, with 362 in the case group and 362 in the control group. There were no statistically significant differences ($P>0.05$) between the two groups in terms of the composition ratios of education level, occupation, monthly household income per capita, smoking, and drinking, as well as in age, systolic blood pressure (SBP), and fasting plasma glucose (FPG).

There were statistically significant differences in the composition ratios of body mass index (BMI) ($\chi^2=65.713$, $P<0.001$), diastolic blood pressure (DBP; $t=-2.95$, $P=0.004$), creatinine (CREA; $t=-8.59$, $P<0.001$), urea ($t=-2.12$, $P=0.034$), glycated hemoglobin (HbA1c; $t=-2.09$, $P=0.037$), total cholesterol (TC; $t=-2.16$, $P=0.031$), low-density lipoprotein cholesterol (LDL-C; $t=-2.44$, $P=0.015$), triglyceride (TG; $t=-8.11$, $P<0.001$), high-density lipoprotein cholesterol (HDL-C; $t=6.91$, $P<0.001$), and the waist/hip ratio ($t=-6.58$, $P<0.001$). (Table 1)

Table 1 Demographic and behavioral characteristics of the study population. [n (%)]

Parameter	Total	Control	Case group	t/χ^2	*P*
Number	724	362	362		
Education					

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Uneducated	108 (14.9)	58 (16.0)	50 (13.8)		
Elementary Education	341 (47.1)	169 (46.7)	172 (47.5)	0.71	0.701
High School and above	275 (38.0)	135 (37.3)	140 (38.7)		
Work					
Farmer	86(11.9)	42 (11.6)	44 (12.2)	0.053	0.818
Other	638(88.1)	320 (88.4)	318 (87.8)		
Income					
<5000	223 (30.8)	120 (33.1)	103 (28.5)	1.873	0.171
>5000	501 (69.2)	242 (66.9)	259 (71.5)		
Smoking					
No	535 (73.9)	268 (74.0)	267 (73.8)	0.007	0.933
Yes	189 (26.1)	94 (26.0)	95 (26.2)		
Drinking					
No	437 (60.4)	231 (63.8)	206 (56.9)	3.608	0.058
Yes	287 (39.6)	131 (36.2)	156 (43.1)		
BMI					
<23.0	373 (51.5)	238 (65.7)	135 (37.3)		
23--27.5	277 (38.3)	108 (29.8)	169 (46.7)	65.713	<0.001*
≥27.5	74 (10.2)	16 (4.4)	58 (16.0)		
SBP[a]	137.06±26.09	135.19±25.57	138.94±26.51	-1.94	0.053
DBP[a]	82.26±14.68	80.66±14.33	83.86±14.87	-2.95	0.004*
Age[a]	62.42±12.66	62.84±12.07	62.01±13.23	0.88	0.381
CREA[a]	80.13±26.57	72.04±17.30	88.22±31.36	-8.59	<0.001*
Urea[a]	5.97±1.79	5.83±1.65	6.11±1.93	-2.12	0.034*
FPG[a]	5.05±1.24	5.02±1.34	5.08±1.13	-0.67	0.506
HbA1C[a]	5.90±0.87	5.83±0.96	5.97±0.77	-2.09	0.037*
TC[a]	5.63±1.16	5.54±1.07	5.72±1.23	-2.16	0.031*
LDL-C[a]	3.55±1.02	3.46±0.99	3.64±1.04	-2.44	0.015*
TG[a]	1.63±1.54	1.18±0.82	2.07±1.91	-8.11	<0.001*
HDL-C[a]	1.73±0.44	1.84±0.46	1.62±0.39	6.91	<0.001*
Waist/hip ratio[a]	0.89±0.07	0.87±0.07	0.91±0.08	-6.58	<0.001*

SD: standard deviation.
a: Mean ± SD; *p < 0.05 was considered statistically significant.

3.2 Multivariate Logistic Regression Analysis of General Characteristics and Hyperuricemia

Multivariate logistic regression analysis revealed significant associations (P<0.05) between smoking, BMI (23–27.5), DBP, LDL-C, TG, and hyperuricemia (HUA). Among them, BMI (23–27.5 kg/m^2) and triglyceride (TG) may be protective factors against HUA (OR=0.034, 95% CI: 0.209–0.939; OR=0.351, 95% CI: 0.176–0.698); smoking, diastolic blood pressure (DBP), and low-density lipoprotein cholesterol (LDL-C) may be risk factors for HUA, with OR values of 1.931 (95% CI: 1.251–2.982), 1.033 (95% CI: 1.023–1.044), and 1.660 (95% CI: 1.318–2.089), respectively. The other indicators were not significantly associated with hyperuricemia in this analysis(P>0.05). (Table 2)

Table 2 Logistic regression analysis between general characteristics and hyperuricemia.

Parameter	B	S.E,	Wald	*P* value	OR	95% CI
Education						
Uneducated						1.00
Elementary Education	0.184	0.297	0.383	0.536	1.202	0.671-2.151

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High School and above	0.128	0.201	0.405	0.524	1.137	0.766-1.687
Work						
Farmer						1.00
Other	-0.033	0.277	0.015	0.904	0.967	0.562-1.665
Income						
<5000						1.00
>5000	-0.154	0.197	0.608	0.436	0.857	0.582-1.262
Smoking						
No						1.00
Yes	0.658	0.222	8.816	0.003*	1.931	1.251-2.982
Drinking						
No						1.00
Yes	-0.338	0.190	3.179	0.075	0.713	0.492-1.034
BMI						
<23.0						1.00
23--27.5	-0.814	0.383	4.511	0.034*	0.443	0.209 -0.939
≥27.5	-0.375	0.359	1.091	0.296	0.687	0.340-1.389
SBP	0.012	0.009	1.867	0.172	1.012	0.995-1.030
DBP	0.033	0.005	39.114	0.000*	1.033	1.023-1.044
Age	-0.004	0.009	0.192	0.661	0.996	0.978-1.014
CREA	0.098	0.063	2.418	0.120	1.103	0.975-1.247
Urea	-0.017	0.104	0.028	0.866	0.983	0.802-1.205
FPG	-0.021	0.143	0.021	0.886	0.980	0.740-1.297
HbA1C	0.174	0.222	0.610	0.435	1.190	0.770-1.839
TC	-0.052	0.211	0.062	0.804	0.949	0.627-1.436
LDL-C	0.507	0.117	18.592	0.000*	1.660	1.318-2.089
TG	-1.047	0.351	8.908	0.003*	0.351	0.176-0.698
HDL-C	0.984	1.482	0.441	0.507	2.675	0.147-48.808
Constant	-3.957	1.633	5.869	0.015*	0.019	

*p < 0.05 was considered statistically significant.

3.3 Comparison of Genotype Types and Allele Distributions between the Two Groups

In both the control group and the HUA group, the genotyping success rate for three SNP loci (rs429358, rs7259620, and rs405509) was greater than 95%.The distribution of alleles in both groups was statistically significant (P<0.05); among the genotypes, only the genotypic distribution at the rs7259620 locus was statistically significant (P<0.05). In the HWE test, the control group and the HUA group for the three SNP loci showed no statistical significance (P>0.05), conforming to the HWE law, indicating that the sample in this study was derived from a genetically balanced population and has good sample representativeness. (Table 3)

Table 3 Genotype and allele frequencies of APOE SNPs in control and hyperuricemic groups[n (%)].

SNP	Genotype(allele)	Total	Control	Hyperuricemia	χ^2	*P*
	Sequencing success count	715(98.8)	358(98.9)	357(98.6)		
rs429358	C	142(9.9)	76(10.6)	66(9.2)	466.679	**<0.001**
T>C	T	1288(90.1)	640(89.4)	648(90.8)		
	CC	9(1.3)	5(1.4)	4(1.1)	0.848	0.838
	CT	124(17.3)	66(18.4)	58(16.3)		

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	TT	582(81.4)	287(80.2)	295(82.6)		
	MAF					0.099
	PHWE	**0.401**	**0.575**	**0.524**		
	Sequencing success count	719(99.3)	360(99.4)	359(99.2)		
	G	955(66.4)	485(67.4)	470(65.5)	78.333	**<0.001**
rs7259620 G>A	A	483(33.6)	235(32.6)	248(34.5)		
	GG	315(43.8)	165(45.8)	150(41.8)		
	GA	325(45.2)	155(43.1)	170(47.3)	158.884	**<0.001**
	AA	79(11.0)	40(11.1)	39(10.9)		
	MAF					0.336
	PHWE	**0.802**	**0.719**	**0.415**		
	Sequencing success count	719(99.3)	361(99.7)	358(98.9)		
	T	953(66.3)	480(66.5)	473(66.1)	74.631	**<0.001**
	G	485(33.7)	242(33.5)	243(33.9)		
rs405509 T>G	TT	315(43.8)	160(44.3)	155(43.3)		
	TG	323(44.9)	160(44.3)	163(45.5)	0.107	0.948
	GG	81(11.3)	41(11.4)	40(11.2)		
	MAF					0.337
	PHWE	**0.934**	**0.906**	**0.815**		

Qualitative data were assessed using the chi-square test; $P < 0.05$ indicated a statistically significant difference; PHWE > 0.05indicated genotype frequency conforms to Hardy-Weinberg Equilibrium.

3.4 Logistic Regression Model Analysis of APOE SNPs and Hyperuricemia

In this study, the presence or absence of hyperuricemia was used as the dependent variable, and logistic regression analysis was conducted using the codominant model, dominant model, recessive model, and overdominant model, respectively. The analysis results are shown in Table 4. The associations between each gene locus and hyperuricemia in the codominant model, dominant model, recessive model, and overdominant model were not significant (P>0.05).

Table 4 Logistic regression analysis between APOE polymorphisms and hyperuricemia.

SNP	Model	B	S.E,	Wald	*P* value	OR	95% CI
	Co-dominant			0.639	0.727		
		-0.146	0.199	0.543	0.461	0.864	0.585-1.275
rs429358		-0.235	0.676	0.121	0.729	0.791	0.211-2.977
T>C	Recessive	-208	0.675	0.095	0.758	0.812	0.216-3.051
	Dominant	-0.152	0.193	0.622	0.431	0.859	0.588-1.254
	Overdominant	0.143	0.198	0.518	0.472	1.123	0.782-1.701
	Co-dominant			1.333	0.513		
		0.182	0.159	1.323	0.251	1.2	0.879-1.638
rs7259620		0.068	0.252	0.074	0.786	1.01	0.654-1.754
G>A	Recessive	-0.024	0.239	0.01	0.919	0.956	0.613-1.558
	Dominant	0.16	0.151	1.127	0.289	1.174	0.873-1.577
	Overdominant	-0.169	0.15	10260	0.262	0.845	0.629-1.134
	Co-dominant			0.085	0.958		
rs405509		0.045	0.159	0.079	0.778	1.046	0.766-1.427
T>G		0.005	0.249	0.001	0.985	1.005	0.616-1.638

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Recessive	-0.018	0.236	0.006	0.941	0.982	0.618-1.561
Dominant	0.037	0.151	0.059	0.808	1.037	0.772-1.393
Overdominant	-0.043	0.15	0.085	0.771	0.957	0.713-1.285

95% CI: 95% confidence interval; OR: odds ratio.

3.5 Risk Relationship between APOE Gene Haplotypes and Hyperuricemia

The linkage disequilibrium analysis (LD analysis) results of the selected APOE gene SNP loci revealed (Figure 1) that among the tested loci in the study population, there was strong linkage disequilibrium between rs7259620 and rs405509 in both the control group and the hyperuricemic group ($D'=0.93>0.8$, $r^2=0.86>0.8$). As shown in Table 5, the main haplotypes are rs7259620A-rs405509G (sample >30%) and rs7259620G-rs405509T (sample >60%). However, the haplotype frequencies of rs7259620A-rs405509G (OR=1.049, 95%CI=0.839-1.312) and rs7259620G-rs405509T (OR=0.953, 95%CI=0.762-1.193) were not significantly different between the control group and the hyperuricemia group (P>0.05).

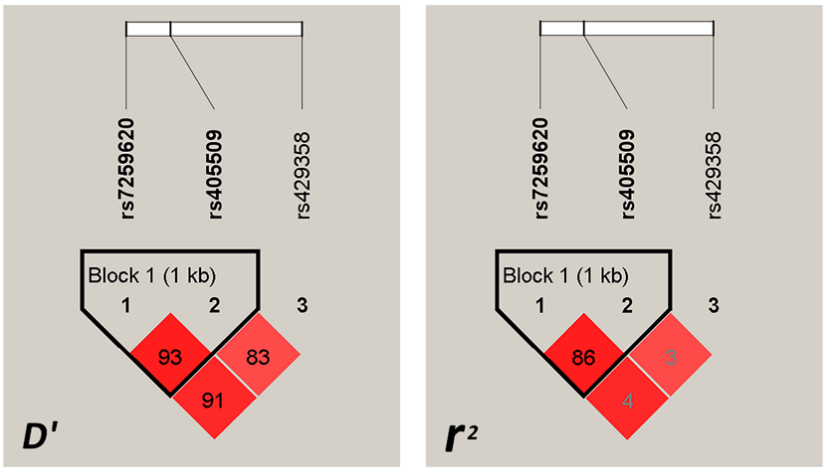

Figure 1: Chain imbalance analysis

Table 5 Prevalence of haplotype frequencies in the hyperuricemic and control groups[n (frequency)]

Haplotype	Control (N = 724)	Case group (N = 724)	χ^2	P	OR (95% CI)
A G	225.82 (0.312)	231.84 (0.320)	0.175	0.676	1.049 (0.839,1.312)
G T	468.82 (0.648)	458.84 (0.634)	0.175	0.676	0.953 (0.762,1.193)

Haplotypes were combined with APOE rs7259620-rs405509. Rare Hap in both groups (frequency <3%) was omitted from the analysis; OR is the dominance ratio; CI is the confidence interval; P<0.05 indicates a statistically significant difference; n=total number with the haplotype.

3.6 Analysis of the Association between APOE Gene-Environment Interaction and Hyperuricemia

To further analyze the relationship between APOE gene polymorphisms and environmental interactions with hyperuricemia, in this study multiplicative and additive models were employed to examine the gene–environment interactions of three genetic loci with diastolic and systolic blood pressure, triglycerides, smoking, drinking, and BMI. The analysis results are shown in Table 6. The results indicated that in the multiplicative interaction model, the interactions between the dominant and recessive models of the three genetic loci rs429358, rs7259620, and rs405509, and each environmental factor were not significantly associated with the occurrence of hyperuricemia (P>0.05). In the additive interaction model, the RERI and AP 95% confidence intervals of the interactions between rs429358, rs7259620, and rs405509, and each environmental factor all included 0, and the SI 95% confidence intervals all included 1, indicating that the additive interactions between these three loci and each

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environmental factor had no significant association with the occurrence of hyperuricemia.

Table 6 Results of gene-environment ploidy and additive interactions (only the statistically significant parts are shown)

Gene-environment interaction		Multiplication interactions			Additive interactions		
		β	*p* value	*OR* (95%*CI*)	RERI (95%*CI*)	AP (95%*CI*)	SI (95%*CI*)
rs429358	RM*DBP	-0.049	0.279	0.950 (0.870,1.040)	-0.744 (-130,11.500)	-0.019 (-0.324,0.285)	0.980 (0.722,1.330)
	RM*TG	-0.580	0.143	0.560 (0.260,1.220)	0.763 (-3.510,5.030)	0.217 (-0.521,0.955)	1.440 (0.475,4.340)
	DM*SBP	-0.007	0.323	0.993 (0.978,1.007)	-0.101 (-0.817,0.615)	-0.044 (-0.355,0.268)	0.928 (0.540,1.600)
	DM*DBP	-0.007	0.578	0.993 (0.967,1.019)	-0.050 (-0.517 ,0.416)	-0.032 (-0.342,0.277)	0.9170 (0.359,2.340)
rs7259620	RM*Smoking	-0.296	0.600	0.740 (0.240,2.270)	0.038 (-0.380, 0.455)	0.033 (-0.309,0.375)	1.340 (0.105,17.100)
	DM*SBP	-0.005	0.438	0.995 (0.984,1.007)	-0.0362 (-0.691 0.619)	-0.017 (-0.319,0.286)	0.971 (0.561,1.680)
	DM*DBP	-0.004	0.750	0.997 (0.976,1.018)	-0.013 (-0.473 ,0.448)	-0.008 (-0.308,0.292)	0.978 (0.419,2.280)
	DM*TG	0.094	0.624	1.100 (0.750,1.600)	0.058 (-0.813,0.929)	0.029 (-0.384,0.442)	1.060 (0.462,2.440)
	DM*Smoking	-0.028	0.940	0.970 (0.500,1.900)	0.054 (-0.457,0.566)	0.042 (-0.324,0.409)	1.230 (0.267,5.670)
	DM*Drinking	0.096	0.760	1.100 (0.600,2.020)	0.280 (-0.451,1.010)	0.159 (-0.140,0.457)	1.580 (0.780,3.190)
	DM*BMI	-0.123	0.625	0.880 (0.540,1.450)	0.556 (-1.070,2.190)	0.151 (-0.193,0.495)	1.260 (0.739 ,2.150)
rs405509	RM*SBP	0.008	0.405	1.008 (0.989,1.027)	-0.023 (-0.130,0.084)	-0.072 (-0.395,0.251)	1.030 (0.863,1.240)
	RM*Smoking	-0.301	0.600	0.740 (0.240,2.250)	-0.011 (-0.394,0.373)	-0.010 (-0.367,0.348)	0.896 (0.009,93.600)
	RM*BMI	0.076	0.858	1.080 (0.470,2.470)	0.044 (-1.340,1.430)	0.016 (-0.468,0.500)	1.030 (0.478,2.200)
	DM*SBP	-0.004	0.550	0.996	-0.103	-0.063	0.860

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				(0.984,1.008)	(-0.617,0.411)	(-0.379,0.253)	(0.367,2.020)
	DM*Smoking	-0.088	0.800	0.92 (0.470,1.790)	-0.007 (-0.407,0.392)	-0.007 (-0.366, 0.353)	0.945 (0.033,26.900)
	DM*BMI	0.061	0.810	1.060 (0.650,1.740)	-0.003 (-1.050,1.050)	-0.001 (-0.399,0.397)	0.998 (0.526,1.890)

Note: DM: dominant model; RM: recessive model; 95% CI: 95% confidence interval; OR: odds ratio; SI: synergy index; RERI: relative excess risk due to interaction. *p < 0.05 and **p< 0.001 were considered as statistically significant.

4. Discussion

The results of the multivariate logistic regression analysis indicated that smoking, diastolic blood pressure (DBP), and low-density lipoprotein cholesterol (LDL-C) may be risk factors for the occurrence of hyperuricemia (HUA), whereas BMI (23–27.5 kg/m^2) and triglyceride (TG) levels may have a protective effect against HUA. Yicheng Fang found that increases in SBP and DBP significantly increase the risk of hyperuricemia. Elevated blood pressure may affect uric acid metabolism by causing kidney damage, inducing endocrine disorders, and exacerbating inflammation and oxidative stress[20]. In this study, DBP (OR=1.033, P<0.001) may be a "risk factor" for hyperuricemia, which was consistent with the aforementioned research results, but there was no significant association between SBP and hyperuricemia. This may be because the study population included mainly elderly individuals; DBP tends to increase during middle age and then stabilize or slightly decrease, whereas the risk of SBP increases with age until 80–90 years[21,22], potentially obscuring the relationship between SBP and hyperuricemia. Smoking (OR=1.931, P=0.003<0.05) may also be a "risk factor" for hyperuricemia according to the results of this study, which is consistent with the findings of Yun-Yun Wang and others[23]. This may be related to the fact that smoking can cause oxidative stress in the body, leading to inflammation and cell damage, thereby affecting uric acid levels and increasing the risk of hyperuricemia. However, the complex mechanism of action between oxidative stress and hyperuricemia requires further research[24,25]. Therefore, smoking may indirectly increase the risk of hyperuricemia by causing oxidative stress in the body. A BMI of 23–27.5 (kg/m^2) and TG may be "protective factors" for hyperuricemia. However, in studies by other scholars[23,26], overweight (24.0–27.9 kg/m^2), obesity (≥28 kg/m^2), triglycerides, and the triglyceride and glycemic index (TyG index) are associated with an increased risk of hyperuricemia. In contrast to our findings, these findings may be related to changes in people's lifestyles after they become overweight or may be related to different obesity standards. The specific reasons still require further exploration to uncover their potential connections. Additionally, as LDL-C increases, the risk of hyperuricemia also increases[27].

The results of the gene polymorphism analysis showed that the distributions of alleles at the selected SNP loci rs429358, rs7259620, and rs405509 of the APOE gene were significantly different between the hyperuricemic population and the healthy control group (P<0.05). In terms of genotype distribution, only the rs7259620 locus was significantly different between the two groups (P<0.05). However, logistic regression analysis using codominant, recessive, dominant, and overdominant models did not reveal a significant association between APOE gene polymorphism and hyperuricemia. Experiments with APOE knockout mice[28] revealed that uric acid levels in these mice were significantly higher than those in wild-type mice. These findings suggest that the APOE gene can influence changes in uric acid levels in the body. A population study in the Ningxia Hui Autonomous Region revealed that the APOE genotype might be independently associated with hyperuricemia[18]; furthermore, the distribution of the APOE allele and genotype frequencies in Xinjiang Uygur males is uniquely associated with the risk of hyperuricemia, with APOE E4 being slightly associated with an increased risk of primary hyperuricemia[19]. However, in the population of this study, no association was observed between APOE gene polymorphism and hyperuricemia, which may be related to the following factors: the population included people from different regions, people who were members of difference races, and people with different dietary habits. Previous studies have shown that the prevalence of hyperuricemia varies by region, with Guangxi being one of the areas in China with a relatively high prevalence of hyperuricemia[29]. Different dietary practices, such as the characteristic dietary feature of Gongcheng, Guangxi (oil tea), can affect blood uric acid levels[30]. Research has shown that oil tea has a weight-reducing effect, and the interaction of various active substances such as gingerol and tea polyphenols may be the reason for its lipid-lowering effect. Moreover, high doses of oil tea intake can significantly reduce the risk of HDL-C abnormalities[31]. Therefore, dietary factors

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may mask genetic effects. Another possible reason is that the subjects of this study included mainly Yao residents from a certain county in Guangxi. However, previous studies have shown that the prevalence of hyperuricemia varies by ethnicity, and that genetic background may have a potential impact on the prevalence of hyperuricemia among these different ethnic groups. Additionally, the impact of the APOE gene may differ among different ethnicities[32,33]. These factors may contribute to the inconsistency between this study and other studies.

In studies on the associations between genetic polymorphisms and diseases, research on gene–environment interactions often plays an important role. Potential gene–environment interactions are key features in the development of complex diseases[34]. Further analysis of the relationships among APOE gene polymorphisms, environmental interactions, and hyperuricemia (HUA) was conducted using multiplicative and additive interaction models to analyze possible gene–environment interactions. The results revealed no significant multiplicative or additive interactions between rs429358, rs7259620, rs405509, and environmental factors related to the occurrence of hyperuricemia. Research has shown that certain specific environmental or dietary conditions may lead to potential disadvantages in the APOE genotype[35]. Consequently, the risk of developing hyperuricemia is influenced by gene–environment interactions. However, APOE gene polymorphisms and their interactions with environmental factors may not have been observed due to the unique environment or diet of the study population. Therefore, further research is needed to verify the impact of the complex interaction between APOE gene polymorphisms and environmental factors on the risk of hyperuricemia.

The strengths of this study are as follows: (1) The study subjects were from the same region and had a relatively consistent genetic background and living environment, which helps control for confounding factors; (2) Case–control matching was conducted by sex and age, reducing the influence of sex and age on the results to some extent. The limitations are as follows: (1) The study population is only from the Gongcheng area of Guangxi, which presents limitations; (2) Relatively few SNP loci were selected in this study, and they may not include the APOE gene loci that are truly associated with HUA.

5. Conclusion

In this study, the susceptibility to hyperuricemia in the study population may be related to factors such as smoking, diastolic blood pressure (DBP), low-density lipoprotein cholesterol (LDL-C), BMI of 23–27.5 kg/m2, and triglyceride (TG) levels. On the other hand, the polymorphisms rs429358, rs7259620, and rs405509 in the APOE gene are not directly associated with susceptibility to hyperuricemia, and no significant impact on the risk of developing hyperuricemia was found through gene–environment interaction analysis.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Our research protocol was approved by the Ethics Committee of Guilin Medical University (No.20180702-3). All participants or a next of kin of the participants were provided written informed consent before data collection. The present study was performed in accordance with the Declaration of Helsinki.

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Competing interests

The authors declare that they have no competing interests.

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