Apolipoprotein E E3/E4 genotype is associated with an increased risk of coronary atherosclerosis in patients with hypertension

Guoliang Wei[1*], Bin Li[1], Hao Wang[1], Li Chen[2], Wenhao Chen[1], Kehui Chen[1], Weihong Wang[1], Shen Wang[1], Hui Zeng[1], Yuanliang Liu[1], Yue Zeng[1] and Hui Rao[3*]

Abstract

Objective *Apolipoprotein E* (*APOE*) gene polymorphisms were associated with coronary atherosclerosis and hypertension. However, the relationship between *APOE* polymorphisms and coronary atherosclerosis susceptibility in hypertensive patients is unclear. The aim of this study was to assess the relationship.

Methods A total of 1713 patients with hypertension who were admitted to Meizhou People's Hospital from November 2019 to August 2023 were retrospectively analyzed, including 848 patients with coronary atherosclerosis and 865 patients without coronary atherosclerosis. The rs429358 and rs7412 polymorphisms of *APOE* were genotyped, and relationship between *APOE* polymorphisms and the risk of coronary atherosclerosis in hypertensive patients were analyzed.

Results There were 10 (0.6%), 193 (11.3%), 30 (1.8%), 1234 (72.0%), 233 (13.6%), and 13 (0.8%) individuals with *APOE* ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, and ε4/ε4 genotype, respectively. The frequency of *APOE* ε3/ε4 was higher (16.4% vs. 10.9%, $p = 0.001$) in the patients with coronary atherosclerosis than controls. Logistic analysis showed that body mass index (BMI) ≥ 24.0 kg/m^2 (24.0 kg/m^2 vs. 18.5–23.9 kg/m^2, odds ratio (OR): 1.361, 95% confidence interval (CI): 1.112–1.666, $p = 0.003$), advanced age (≥ 65/<65, OR:1.303, 95% CI: 1.060–1.602, $p = 0.012$), history of smoking (OR: 1.830, 95% CI: 1.379–2.428, $p < 0.001$), diabetes mellitus (OR: 1.380, 95% CI: 1.119–1.702, $p = 0.003$), hyperlipidemia (OR: 1.773, 95% CI: 1.392–2.258, $p < 0.001$), and *APOE* ε3/ε4 genotype (ε3/ε4 vs. ε3/ε3, OR: 1.514, 95% CI: 1.133–2.024, $p = 0.005$) were associated with coronary atherosclerosis in hypertensive patients.

Conclusions Overweight (BMI ≥ 24.0 kg/m^2), advanced age, history of smoking, diabetes mellitus, and *APOE* ε3/ε4 genotype were independent risk factors for coronary atherosclerosis in hypertensive patients.

Keywords Coronary atherosclerosis, Hypertension, *APOE*, Susceptibility

*Correspondence:
Guoliang Wei
weiguoliangmz@126.com
Hui Rao
raohui@mzrmyy.com

[1]Center for Cardiovascular Diseases, Meizhou People's Hospital, Meizhou Academy of Medical Sciences, Meizhou, China
[2]Data Center, Meizhou People's Hospital, Meizhou Academy of Medical Sciences, Meizhou, China
[3]Department of Laboratory Medicine, Meizhou People's Hospital, Meizhou Academy of Medical Sciences, Meizhou, China

Introduction

Hypertension is a cardiovascular disease characterized by continuous elevation of systolic and/or diastolic blood pressure (SBP/DBP) in systemic arteries, and it is also an influential factor for a variety of serious cardiovascular and cerebrovascular diseases [1]. Hypertension is a worldwide chronic non-communicable disease, a major disease that endangers human health, and the leading cause of global disease burden [2]. In China, the standardized prevalence of hypertension in adults aged 18–69 is about 24.7% [3]. With the progress of population aging, the prevention and treatment of hypertension in China is facing great challenges [4–6]. Cardiovascular disease (CVD) is the leading cause of death worldwide, accounting for more than 7 million deaths each year [7]. Coronary atherosclerosis is a heart disease caused by myocardial ischemia or necrosis due to stenosis, blockage and spasm of coronary artery atherosclerosis [8, 9]. Coronary atherosclerosis is a multi-cause disease, a range of risk factors for coronary atherosclerosis, including age, gender, high blood pressure, smoking, and diabetes mellitus have been identified in Framingham Heart Study [10]. The disease has become a common disease in Europe countries and the United States [11]. And the incidence of the disease has also shown a significant increase in China in the past 10 years [12]. Major risk factors for coronary atherosclerosis include diabetes mellitus, hypertension, smoking, and obesity [13, 14].

It is not uncommon for hypertension and coronary atherosclerosis to occur in the same person at the same time, and studies have shown that people with hypertension have a higher tendency to develop coronary atherosclerosis than those with normal blood pressure [15, 16]. In a cohort study based on the electronic health records of 1.25 million adults, the risk of death from coronary atherosclerosis increased by 26% for every 20mmHg increase in unadjusted SBP [17]. The prevalence rate of hypertension combined with coronary atherosclerosis is increasing year by year [18, 19]. These two diseases share some common etiological factors, such as obesity, inflammation, oxidative stress, and microvascular and macrovascular damage [13, 20]. The treatment of patients with hypertension combined with coronary atherosclerosis is a challenge. Therefore, predicting the risk of coronary atherosclerosis in hypertensive patients may be more beneficial to the treatment and control of these diseases [21].

Lipid metabolism disorders are closely related to CVDs including hypertension and coronary atherosclerosis, and apolipoproteins play an important role in lipid metabolism. As an apolipoprotein, apolipoprotein E (ApoE) plays an important role in lipid metabolism, lipid transport and distribution, and immune regulation [22–25]. ApoE binds to cholesterol receptors to mediate cholesterol metabolism in the liver, and also acts as a cofactor to mediate the degradation of lipoproteins by lipid metabolizing enzymes [26, 27]. The function of APOE is affected by the rs429358 and rs7412 polymorphisms of the *APOE* gene [27]. Based on the variants of these two polymorphisms, APOE can form three alleles (ε2, ε3 and ε4) and 6 genotypes (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, and ε4/ε4) [28–31]. The differences in the receptor binding capacity and the rate of mediating lipoprotein metabolism of APOE encoded by different *APOE* genotypes are the mechanisms of the different lipid metabolism regulatory capacity between different *APOE* variants [32]. The relationship between *APOE* gene polymorphisms and coronary atherosclerosis susceptibility in hypertensive population is unclear. The purpose of this study was to investigate this relationship.

Materials and methods

Study participants and data collection

This study retrospectively analyzed 1713 patients with hypertension who were admitted to Meizhou People's Hospital from November 2019 to August 2023. Inclusive criteria of hypertensive patients were the following: (1) a mean SBP > 140 mmHg and/or a mean DBP > 90 mmHg [33], (2) Age ≥ 18 years old. Among these hypertensive patients, 848 patients with coronary atherosclerosis served as the study group and 865 patients without coronary atherosclerosis as the control group. The diagnostic criteria for coronary atherosclerosis: Coronary angiography (CAG) showed that at least one of the main epicardial vessels (including left main branch, anterior descending branch, circumflex branch, and right coronary artery) had a diameter stenosis, and clinically diagnosed myocardial infarction [34, 35]. Information such as age, sex, body mass index (BMI), history of smoking, history of alcohol consumption, history of diabetes mellitus, and history of hypertension were collected from the patient's medical record information system. According to the height and weight standards of the Chinese population, BMI was divided into three grades: <18.5 kg/m^2, 18.5–23.9 kg/m^2, and ≥24.0 kg/m^2 [36, 37]. A diagnosis of hyperlipidemia can be made if one of the following conditions is met: (1) total cholesterol (TC) ≥ 6.22 mmo1/L), (2) triglyceride (TG) ≥ 2.26 mmo1/L, or (3) low-density lipoprotein-cholesterol (LDL-C) ≥ 4.14 mmo1/L, according to the Guidelines for the Prevention and Control of Dyslipidemia in Chinese Adults [38, 39].

Determination of serum lipids and *APOE* genotyping

Fasting blood was collected and serum was isolated. Total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), Apolipoprotein A1 (Apo-A1), and Apolipoprotein B (ApoB) levels in serum samples were

assessed using automatic biochemical analysis system (Olympus AU5400 system, Tokyo, Japan) and corresponding kits.

Genomic DNA was extracted from venous blood collected from EDTA anticoagulant collection vessels using a blood DNA isolation kit (Qiagen GmbH, Germany). The quality and concentration of the DNA were assessed using a Nano-Drop 2000™ spectrophotometer (Thermo-Fisher Scientific, USA). *APOE* genotype was amplified by PCR - microarray method (Sinochips Bioscience Co., Ltd., China).

Statistical analysis

Continuous variables were expressed as means±standard deviations and were compared using either Student's t-test or the Mann-Whitney U test. The Hardy-Weinberg equilibrium analysis of the subjects, and the comparison of genotype composition ratio and allele frequency between the two groups were analyzed using χ^2 test. Univariate analysis and multivariate regression logistic analysis were applied to examine the relationship between *APOE* rs429358 and rs7412 genotypes and alleles and coronary atherosclerosis in patients with hypertension. $p < 0.05$ was considered to represent statistical significance. All statistical analysis were performed using SPSS statistical software version 26.0 (IBM Inc., USA).

Results

Characteristics of subjects

Among the subjects included in this study, 1071 (62.5%) men and 642 (37.5%) women had hypertension. There were 624 (36.4%) hypertensive patients with <65 years old and 1089 (63.6%) patients with ≥65 years old. About half of the subjects (50.4%) had BMI within the normal range (18.5–23.9 kg/m^2), and 767 (44.8%) were overweight (≥24 kg/m^2). There were 334 (44.8%) patients had history of smoking, 79 (4.6%) patients had history of alcohol consumption, and 561 (32.7%) patients with diabetes mellitus, respectively. There was no significant difference in gender distribution, age distribution, and history of alcohol consumption between patients with coronary atherosclerosis and controls (all $p > 0.05$). In the controls, there were 45 (5.2%), 468 (54.1%), and 352 (40.7%) patients with BMI<18.5 kg/m^2, 18.5–23.9 kg/m^2, and ≥24.0 kg/m^2, respectively. There were 38 (4.5%) patients with coronary atherosclerosis had BMI<18.5 kg/m^2 and 415 (48.9%) had BMI≥24.0 kg/m^2. The proportion of BMI≥24.0 kg/m^2 in patients with coronary atherosclerosis was higher than that in controls (48.9% vs. 40.7%, $p = 0.003$). The proportion of history of smoking (23.7% vs. 15.4%, $p < 0.001$), diabetes mellitus (37.0% vs. 28.6%, $p < 0.001$), and hyperlipidemia (27.2% vs. 16.5%, $p < 0.001$) in patients with coronary atherosclerosis was higher than that in controls, respectively. The patients

with coronary atherosclerosis had higher TC (4.57±1.20 vs. 4.46±1.03 mmol/L, $p = 0.043$) and TG (1.86±1.55 vs. 1.51±0.87 mmol/L, $p < 0.001$), and lower HDL-C (1.18±0.34 vs. 1.23±0.38 mmol/L, $p = 0.002$) levels than controls (Table 1).

Distribution frequencies of *APOE* genotypes and alleles in patients with coronary atherosclerosis and controls

The results of χ^2 test showed that the *APOE* rs429358 and rs7412 in the patients with coronary atherosclerosis ($\chi^2 = 0.797$, $p = 0.372$; and $\chi^2 = 0.0003$, $p = 0.986$), and controls ($\chi^2 = 2.094$, $p = 0.148$; and $\chi^2 = 0.448$, $p = 0.503$) conformed to the Hardy-Weinberg equilibrium, respectively. There were 10 (0.6%), 193 (11.3%), 30 (1.8%), 1234 (72.0%), 233 (13.6%), and 13 (0.8%) individuals with *APOE* ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, and ε4/ε4 genotype, respectively. The frequency of the *APOE* ε3/ε3 genotype was lower (69.7% vs. 74.3%, $p = 0.036$), and ε3/ε4 genotype was higher (16.4% vs. 10.9%, $p = 0.001$) in the patients with coronary atherosclerosis than those in controls. The frequency of the ε3 allele was lower (83.3% vs. 85.7%, $p = 0.048$), while ε4 higher (9.9% vs. 7.0%, $p = 0.003$) in the patients with coronary atherosclerosis than those in controls (Table 2).

Clinical characteristics of subjects stratified by *APOE* ε2, ε3, ε4 alleles

Because the ε2 and ε4 alleles have opposite functions in lipid metabolism, individuals carrying ε2/ε4 genotypes ($n = 30$) were not included in the analysis of the relationship between *APOE* alleles and clinical characteristics of patients in this study. Clinical characteristics and serum lipid-lipoprotein levels were compared among all subjects carried different *APOE* alleles. There was no significant difference in gender distribution, age distribution, proportion of history of smoking, history of alcohol consumption, and diabetes mellitus between patients with coronary atherosclerosis and controls (all $p > 0.05$). The level of LDL-C (2.27±0.88 vs. 2.46±0.84 and 2.63±0.83 mmol/L, $p = 0.006$) was lower in the patients with *APOE* ε2 allele than those with ε3 and ε4 allele, respectively (Table 3).

Logistic regression analysis of risk factors of coronary atherosclerosis in patients with hypertension

In univariate analysis, BMI≥24.0 kg/m^2 (BMI≥24.0 kg/m^2 vs. BMI 18.5–23.9 kg/m^2, odds ratio (OR): 1.397, 95% confidence interval (CI): 1.149–1.698, $p = 0.001$), history of smoking (Yes vs. No, OR: 1.710, 95% CI: 1.341–2.181, $p < 0.001$), diabetes mellitus (Yes vs. No, OR: 1.471, 95% CI: 1.201–1.802, $p < 0.001$), hyperlipidemia (Yes vs. No, OR: 1.890, 95% CI: 1.495–2.390, $p < 0.001$), *APOE* ε3/ε4 genotype (ε3/ε4 vs. ε3/ε3, OR: 1.609, 95% CI: 1.210–2.138, $p = 0.001$), and *APOE* ε4 allele (ε4 vs. ε3, OR: 1.562,

Wei *et al. BMC Cardiovascular Disorders*   (2024) 24:486

Page 4 of 9

Table 1 Clinical characteristics of patients with hypertension in this study

Variables	Total (n = 1713)	Controls (n = 865)	Patients with coronary atherosclerosis (n = 848)	p values
Gender				
Male, n(%)	1071(62.5%)	535(61.8%)	536(63.2%)	0.562
Female, n(%)	642(37.5%)	330(38.2%)	312(36.8%)	
Age, years				
< 65, n(%)	624(36.4%)	336(38.8%)	288(34.0%)	0.036
≥ 65, n(%)	1089(63.6%)	529(61.2%)	560(66.0%)	
BMI (kg/m^2)				
< 18.5, n(%)	83(4.8%)	45(5.2%)	38(4.5%)	0.003
18.5–23.9, n(%)	863(50.4%)	468(54.1%)	395(46.6%)	
≥ 24.0, n(%)	767(44.8%)	352(40.7%)	415(48.9%)	
History of smoking				
No, n(%)	1379(80.5%)	732(84.6%)	647(76.3%)	< 0.001
Yes, n(%)	334(19.5%)	133(15.4%)	201(23.7%)	
History of alcohol consumption				
No, n(%)	1634(95.4%)	830(96.0%)	804(94.8%)	0.260
Yes, n(%)	79(4.6%)	35(4.0%)	44(5.2%)	
Diabetes mellitus				
No, n(%)	1152(67.3%)	618(71.4%)	534(63.0%)	< 0.001
Yes, n(%)	561(32.7%)	247(28.6%)	314(37.0%)	
Hyperlipidemia				
No, n(%)	1339(78.2%)	722(83.5%)	617(72.8%)	< 0.001
Yes, n(%)	374(21.8%)	143(16.5%)	231(27.2%)	
Serum lipid-lipoprotein levels				
TC, mmol/L	4.51 ± 1.12	4.46 ± 1.03	4.57 ± 1.20	0.043
TG, mmol/L	1.69 ± 1.26	1.51 ± 0.87	1.86 ± 1.55	< 0.001
HDL-C, mmol/L	1.21 ± 0.36	1.23 ± 0.38	1.18 ± 0.34	0.002
LDL-C, mmol/L	2.44 ± 0.81	2.43 ± 0.77	2.46 ± 0.85	0.387
Apo-A1, g/L	1.09 ± 0.27	1.10 ± 0.28	1.09 ± 0.26	0.395
Apo-B, g/L	0.79 ± 0.23	0.78 ± 0.22	0.80 ± 0.25	0.020

BMI, body mass index; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; Apo-A1, apolipoprotein A1; Apo-B, apolipoprotein B

95% CI: 1.183–2.061, p = 0.002) were significantly associated with coronary atherosclerosis in patients with hypertension. In multivariate regression logistic analysis, advanced age (≥ 65/< 65, OR: 1.303, 95% CI: 1.060–1.602, p = 0.012), BMI ≥ 24.0 kg/m^2 (≥ 24.0 kg/m^2 vs. 18.5–23.9 kg/m^2, OR: 1.361, 95% CI: 1.112–1.666, p = 0.003), history of smoking (Yes vs. No, OR: 1.830, 95% CI: 1.379–2.428, p < 0.001), diabetes mellitus (Yes vs. No, OR: 1.380, 95% CI: 1.119–1.702, p = 0.003), hyperlipidemia (Yes vs. No, OR: 1.773, 95% CI: 1.392–2.258, p < 0.001), and *APOE* ε3/ε4 genotype (ε3/ε4 vs. ε3/ε3, OR: 1.514, 95% CI: 1.133–2.024, p = 0.005) were independent risk factors for coronary atherosclerosis in patients with hypertension (Table 4).

Discussion

Hypertension is a chronic disease based on vascular disease, and the long-term increase of blood pressure is easy to cause damage to some organs and cause corresponding diseases [40, 41]. Hypertension is closely related to coronary atherosclerosis and is a risk factor for coronary atherosclerosis [42, 43]. The increase of pulse pressure can increase the tension of artery vessels, increase the tension of artery wall, fatigue and even fracture of elastic fibers, damage vascular endothelial cells, and accelerate or promote the development of atherosclerosis [44]. Prospective cohort studies have shown a significantly increased risk of CVD in people with higher baseline blood pressure [45]. Foreign cohort studies have shown that changes in individual blood pressure level or progression of blood pressure classification are also associated with the long-term or lifelong risk of CVDs [46, 47]. Studies have shown that hypertension is prone to co-exist with metabolic diseases such as obesity, abnormal blood sugar and dyslipidemia, and these metabolic diseases often become an important cause of the occurrence and death of CVDs [48]. The course of disease is a multifactorial process of change. It is of great significance to understand the risk of cardiovascular and cerebrovascular events in hypertensive patients based on genetics and personal habits. In patients with hypertension, the risk factors for CAD remain unclear. Therefore, it is of

Table 2 Distribution frequencies of *APOE* genotypes and alleles in patients with coronary atherosclerosis and control

Variable	Genotype/allele	Total (*n* = 1713)	Controls (*n* = 865)	Patients with coronary atherosclerosis (*n* = 848)	χ^2	*p* values
APOE rs429358						
	T/T	1437(83.9%)	751(86.8%)	686(80.9%)	11.120	0.001
	T/C	263(15.4%)	107(12.4%)	156(18.4%)	11.966	0.001
	C/C	13(0.8%)	7(0.8%)	6(0.7%)	0.059	0.808
HWE (χ^2, *p*)		$\chi^2 = 0.064, p = 0.800$	$\chi^2 = 2.094, p = 0.148$	$\chi^2 = 0.797, p = 0.372$		
APOE rs7412						
	C/C	1480(86.4%)	744(86.0%)	736(86.8%)	0.222	0.637
	C/T	223(13.0%)	115(13.3%)	108(12.7%)	0.118	0.731
	T/T	10(0.6%)	6(0.7%)	4(0.5%)	0.363	0.547
HWE (χ^2, *p*)		$\chi^2 = 0.257, p = 0.612$	$\chi^2 = 0.448, p = 0.503$	$\chi^2 = 0.0003, p = 0.986$		
APOE genotype						
	ε2/ε2	10(0.6%)	6(0.7%)	4(0.5%)	0.363	0.753
	ε2/ε3	193(11.3%)	102(11.8%)	91(10.7%)	0.482	0.493
	ε2/ε4	30(1.8%)	13(1.5%)	17(2.0%)	0.627	0.465
	ε3/ε3	1234(72.0%)	643(74.3%)	591(69.7%)	4.580	0.036
	ε3/ε4	233(13.6%)	94(10.9%)	139(16.4%)	11.121	0.001
	ε4/ε4	13(0.8%)	7(0.8%)	6(0.7%)	0.059	1.000
APOE allele						
	ε2	243(7.1%)	127(7.3%)	116(6.8%)	0.327	0.595
	ε3	2894(84.5%)	1482(85.7%)	1412(83.3%)	4.761	0.048
	ε4	289(8.4%)	121(7.0%)	168(9.9%)	9.399	0.003

HWE, Hardy Weinberg Equilibrium

great significance to identify the risk of CAD in hypertensive patients. In this study, overweight (BMI ≥ 24.0 kg/m²), history of smoking, diabetes mellitus, *APOE* ε3/ε4 genotype, and *APOE* ε4 allele were independent risk factors for coronary atherosclerosis in patients with hypertension.

APOE polymorphism is associated with an increased risk of coronary artery disease in Finnish adults [49]. Some studies found that *APOE* ε4 allele may be associated with an increased risk of CAD in Egyptians [50], ethnic Kashmiri population [51], and Chinese populations [52, 53], respectively. Balcerzyk et al. found that the synergistic effect of the ε4 allele with some traditional risk factors (such as smoking, high cholesterol levels) is associated with an increased risk of CAD [54]. Other studies have found that *APOE* ε4 allele was associated with an increased risk of diabetes mellitus complicated with CAD [31, 55]. In addition, some studies have found that *APOE* polymorphisms are also associated with the severity of coronary atherosclerosis [56, 57]. However, some studies have found that *APOE* polymorphisms were not associated with the susceptibility of coronary atherosclerosis [58, 59].

As an indicator of the degree of obesity, studies have found that when BMI is maintained in the normal range, the occurrence of coronary atherosclerosis can be reduced [60]. Previous studies have shown that high BMI is associated with an increased risk of CVDs [61–63]. Some studies found that the risk of major adverse cardiovascular events was not affected by BMI [64, 65]. Chen et al. found that BMI ≥ 24.0 kg/m² was an independent risk factor for type 2 diabetes mellitus (T2DM) complicated with CAD [31]. In addition, BMI is associated with long-term prognosis and risk of death from CAD [66, 67]. BMI is different in population due to gender, age and race, and has certain limitations in risk prediction [68]. Therefore, comprehensive attention should be paid to the role of some risk factors in coronary atherosclerosis susceptibility in people with hypertension.

Hypertensive people with a history of smoking have a higher risk of major cardiovascular events. CVD accounts for about one third of smoking-related deaths worldwide [69]. Study has found that there is a dose-effect relationship between smoking and CVDs, and long-term small smoking will also increase the risk of CVDs [70]. The mechanism of the potential association between tobacco and CVD may be due to harmful chemicals in tobacco that promote the development of CVD by increasing heart rate, heart muscle contraction, inflammation, endothelial damage, thrombosis, and affecting lipid levels [71]. In this study, univariate regression analysis showed that smoking was a risk factor for coronary atherosclerosis in hypertensive individuals, but multivariate regression logistic analysis did not obtain this result. However, in any case, health education should be strengthened for hypertensive patients and smoking cessation intervention should be carried out to reduce the risk of coronary atherosclerosis.

Wei *et al. BMC Cardiovascular Disorders* (2024) 24:486

Page 6 of 9

Table 3 Clinical characteristics of patients with coronary atherosclerosis stratified by *APOE* ε2, ε3, ε4 alleles

Variables	ε2 (ε2/ε2 + ε2/ε3) (*n* = 95)	ε3 (ε3/ε3) (*n* = 591)	ε4 (ε3/ε4 + ε4/ε4) (*n* = 145)	*p* values
Gender				
Male, n(%)	55(57.9%)	373(63.1%)	97(66.9%)	0.371
Female, n(%)	40(42.1%)	218(36.9%)	48(33.1%)	(x^2=2.003)
Age, years				
< 65, n(%)	28(29.5%)	207(35.0%)	50(34.5%)	0.575 (x^2=1.122)
≥ 65, n(%)	67(70.5%)	384(65.0%)	95(65.5%)	
BMI (kg/m^2)				
< 18.5, n(%)	5(5.3%)	27(4.6%)	5(3.4%)	0.966
18.5–23.9, n(%)	42(44.2%)	272(46.0%)	67(46.2%)	(x^2=0.585)
≥ 24.0, n(%)	48(50.5%)	292(49.4%)	73(50.3%)	
History of smoking				
No, n(%)	74(77.9%)	451(76.3%)	108(74.5%)	0.824 (x^2=0.390)
Yes, n(%)	21(22.1%)	140(23.7%)	37(25.5%)	
History of alcohol consumption				
No, n(%)	93(97.9%)	555(93.9%)	139(95.9%)	0.219 (x^2=3.062)
Yes, n(%)	2(2.1%)	36(6.1%)	6(4.1%)	
Diabetes mellitus				
No, n(%)	60(63.2%)	383(64.8%)	82(56.6%)	0.182 (x^2=3.410)
Yes, n(%)	35(36.8%)	208(35.2%)	63(43.4%)	
Hyperlipidemia				
No, n(%)	57(60.0%)	446(75.5%)	102(70.3%)	0.005 (x^2=10.423)
Yes, n(%)	38(40.0%)	145(24.5%)	43(29.7%)	
Serum lipid-lipoprotein levels				
TC, mmol/L	4.63 ± 1.22	4.52 ± 1.20	4.72 ± 1.19	0.197
TG, mmol/L	2.20 ± 1.71*	1.80 ± 1.57[#]	1.87 ± 1.26	0.062
HDL-C, mmol/L	1.22 ± 0.35	1.18 ± 0.35	1.17 ± 0.32	0.502
LDL-C, mmol/L	2.27 ± 0.88*,$	2.46 ± 0.84[#],$	2.63 ± 0.83[#],*	0.006
Apo-A1, g/L	1.14 ± 0.24*	1.08 ± 0.27[#]	1.08 ± 0.26	0.076
Apo-B, g/L	0.75 ± 0.28$	0.81 ± 0.25	0.85 ± 0.23[#]	0.018

BMI, body mass index; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; Apo-A1, apolipoprotein A1; Apo-B, apolipoprotein B

[#]compared with ε2, *p* < 0.05

*compared with ε3, *p* < 0.05

$compared with ε4, *p* < 0.05

Table 4 Logistic regression analysis of risk factors of coronary atherosclerosis in patients with hypertension

Variables	Univariate OR (95% CI)	*p* values	Multivariate OR (95% CI)	*p* values
Gender (Female/Male)	0.944 (0.776–1.148)	0.562	1.080 (0.869–1.344)	0.487
Age (≥ 65/< 65, years)	1.235 (1.014–1.504)	0.036	1.303 (1.060–1.602)	0.012
BMI (kg/m^2)				
18.5–23.9	1.000 (reference)	-	1.000 (reference)	-
< 18.5	1.001 (0.637–1.572)	0.998	1.069 (0.674–1.696)	0.776
≥ 24.0	1.397 (1.149–1.698)	0.001	1.361 (1.112–1.666)	0.003
History of smoking (Yes/No)	1.710 (1.341–2.181)	< 0.001	1.830 (1.379–2.428)	< 0.001
History of alcoholism (Yes/No)	1.298 (0.824–2.044)	0.261	0.905 (0.549–1.492)	0.696
Diabetes mellitus (Yes/No)	1.471 (1.201–1.802)	< 0.001	1.380 (1.119–1.702)	0.003
Hyperlipidemia (Yes/No)	1.890 (1.495–2.390)	< 0.001	1.773 (1.392–2.258)	< 0.001
APOE genotypes				
ε3/ε3	1.000 (reference)	-	1.000 (reference)	-
ε2/ε2	0.725 (0.204–2.583)	0.620	0.732 (0.200-2.676)	0.637
ε2/ε3	0.971 (0.716–1.315)	0.848	0.893 (0.653–1.221)	0.478
ε2/ε4	1.423 (0.685–2.954)	0.344	1.383 (0.653–2.931)	0.397
ε3/ε4	1.609 (1.210–2.138)	0.001	1.514 (1.133–2.024)	0.005
ε4/ε4	0.933 (0.312–2.791)	0.901	0.879 (0.284–2.720)	0.822

BMI, body mass index

This study is the first to report on *APOE* gene polymorphisms and coronary atherosclerosis susceptibility in hypertensive patients. There are some inadequacies in this study. First, this study retrospectively collected data from the medical record system of the included subjects, and did not include other possible influencing factors of coronary atherosclerosis for analysis. Second, the subjects included in this study are all patients seeking treatment in Meizhou People's Hospital, so the selection of subjects may be biased. Third, the relationship between *APOE* gene polymorphisms and the risk of coronary atherosclerosis in patients with different grades of hypertension has been not analyzed in this study.

Conclusion

In summary, overweight (BMI ≥ 24.0 kg/m^2), advanced age, history of smoking, diabetes mellitus, and *APOE* ε3/ε4 genotype were independent risk factors for coronary atherosclerosis in patients with hypertension. It means that hypertensive patients who are obesity, have history of smoking and diabetes mellitus, and carried the *APOE* ε3/ε4 genotype need to be aware of the risk of developing coronary atherosclerosis.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
All participants were informed on the study procedures and goals and the study obtained written informed consent from all the participants. We confirm that all methods were performed in accordance with relevant guidelines and regulations. This study was approved by the Human Ethics Committees of Meizhou People's Hospital.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

References
1. Aune D, Mahamat-Saleh Y, Kobeissi E, Feng T, Heath AK, Janszky I. Blood pressure, hypertension and the risk of atrial fibrillation: a systematic review and meta-analysis of cohort studies. Eur J Epidemiol. 2023;38(2):145–78.
2. Worldwide trends in. Hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet. 2021;398(10304):957–80.
3. Zhang M, Shi Y, Zhou B, Huang Z, Zhao Z, Li C, Zhang X, Han G, Peng K, Li X, et al. Prevalence, awareness, treatment, and control of hypertension in China, 2004-18: findings from six rounds of a national survey. BMJ. 2023;380:e071952.
4. Bromfield S, Muntner P. High blood pressure: the leading global burden of disease risk factor and the need for worldwide prevention programs. Curr Hypertens Rep. 2013;15(3):134–6.
5. Pickering GW. The natural history of hypertension. Br Med Bull. 1952;8(4):305–9.
6. Yin R, Yin L, Li L, Silva-Nash J, Tan J, Pan Z, Zeng J, Yan LL. Hypertension in China: burdens, guidelines and policy responses: a state-of-the-art review. J Hum Hypertens. 2022;36(2):126–34.
7. Gaidai O, Cao Y, Loginov S. Global Cardiovascular diseases Death Rate Prediction. Curr Probl Cardiol. 2023;48(5):101622.
8. Shaya GE, Leucker TM, Jones SR, Martin SS, Toth PP. Coronary heart disease risk: low-density lipoprotein and beyond. Trends Cardiovasc Med. 2022;32(4):181–94.
9. Stone PH, Libby P, Boden WE. Fundamental pathobiology of coronary atherosclerosis and clinical implications for chronic ischemic heart Disease Management-the Plaque hypothesis: a narrative review. JAMA Cardiol. 2023;8(2):192–201.
10. Andersson C, Johnson AD, Benjamin EJ. 70-year legacy of the Framingham Heart Study. Nat Rev Cardiol. 2019;16(11):687–98.
11. Park H, Kim D, European, Guideline-Based US. Statin eligibility, genetically predicted coronary artery Disease, and the risk of major coronary events. J Am Heart Assoc. 2024;13(9):e032831.
12. Wang L, Li X, Li T, Liu L, Wang H, Wang C. Novel application of drug-coated balloons in coronary heart disease: a narrative review. Front Cardiovasc Med. 2023;10:1055274.
13. Flora GD, Nayak MK. A brief review of Cardiovascular diseases, Associated Risk factors and current treatment regimes. Curr Pharm Des. 2019;25(38):4063–84.
14. Sarebanhassanabadi M, Mirjalili SR. Coronary artery disease incidence, risk factors, awareness, and medication utilization in a 10-year cohort study. BMC Cardiovasc Disord. 2024;24(1):101.
15. Aronow WS. Current treatment of hypertension in patients with coronary artery disease recommended by different guidelines. Expert Opin Pharmacother. 2016;17(2):205–15.
16. Dong L, Liu J, Qin Y, Yang WJ, Nie L, Liu HN, Hu QH, Sun Y, Cao WY. Relationship between ambulatory arterial stiffness index and the severity of angiographic atherosclerosis in patients with H-type hypertension and coronary artery disease. Clin Exp Hypertens. 2023;45(1):2228517.
17. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, White IR, Caulfield MJ, Deanfield JE, Smeeth L, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. Lancet. 2014;383(9932):1899–911.
18. Yim J, Rabkin SW. A patient-specific approach to assessing blood pressure management in patients with hypertension and coronary artery disease. J Clin Hypertens (Greenwich). 2018;20(2):233–9.
19. Huang XD, Lin JY, Huang XW, Zhou TT, Xie LD. A nomogram based on endothelial function and conventional risk factors predicts coronary artery disease in hypertensives. BMC Cardiovasc Disord. 2023;23(1):217.
20. Alenazi AM, Alqahtani BA. National and regional prevalence rates of hypertension in Saudi Arabia: a descriptive analysis using the national survey data. Front Public Health. 2023;11:1092905.
21. Wang J, Ma JJ, Liu J, Zeng DD, Song C, Cao Z. Prevalence and risk factors of comorbidities among hypertensive patients in China. Int J Med Sci. 2017;14(3):201–12.
22. Singh PP, Singh M, Mastana SS. APOE distribution in world populations with new data from India and the UK. Ann Hum Biol. 2006;33(3):279–308.
23. Tersigni C, Furqan Bari M, Cai S, Zhang W, Kandzija N, Buchan A, Miranda F, Di Simone N, Redman CW, Bastie C, et al. Syncytiotrophoblast-derived extracellular vesicles carry apolipoprotein-E and affect lipid synthesis of liver cells in vitro. J Cell Mol Med. 2022;26(1):123–32.

24. Hong S, Washington PM, Kim A, Yang CP, Yu TS, Kernie SG. Apolipoprotein E regulates Injury-Induced activation of hippocampal neural stem and progenitor cells. J Neurotrauma. 2016;33(4):362–74.

25. Zhu K, Zhang H. KDM4C promotes mouse hippocampal neural stem cell proliferation through modulating ApoE expression. FASEB J. 2024;38(5):e23511.

26. Rahmany S, Jialal I. Biochemistry, Chylomicron. StatPearls. Edn. Treasure Island (FL) ineligible companies. Disclosure: Ishwarlal Jialal declares no relevant financial relationships with ineligible companies.: StatPearls Publishing Copyright © 2024. StatPearls Publishing LLC.; 2024.

27. Marais AD. Apolipoprotein E in lipoprotein metabolism, health and cardiovascular disease. Pathology. 2019;51(2):165–76.

28. Khalil YA, Rabès JP, Boileau C, Varret M. APOE gene variants in primary dyslipidemia. Atherosclerosis. 2021;328:11–22.

29. Lan X, Wang Z, Zeng Z, Yao H, Xu W, Zhang Y. Association of different combinations of ALDH2 rs671, APOE rs429358, rs7412 polymorphisms with hypertension in Middle-aged and Elderly people: a case-control study. Int J Gen Med. 2023;16:915–27.

30. Seripa D, D'Onofrio G, Panza F, Cascavilla L, Masullo C, Pilotto A. The genetics of the human APOE polymorphism. Rejuvenation Res. 2011;14(5):491–500.

31. Chen W, Li B, Wang H, Wei G, Chen K, Wang W, Wang S, Liu Y. Apolipoprotein E E3/E4 genotype is associated with an increased risk of type 2 diabetes mellitus complicated with coronary artery disease. BMC Cardiovasc Disord. 2024;24(1):160.

32. Phillips MC. Apolipoprotein E isoforms and lipoprotein metabolism. IUBMB Life. 2014;66(9):616–23.

33. Wang Z, Chen Z, Zhang L, Wang X, Hao G, Zhang Z, Shao L, Tian Y, Dong Y, Zheng C, et al. Status of hypertension in China: results from the China Hypertension Survey, 2012–2015. Circulation. 2018;137(22):2344–56.

34. Lee SE, Sung JM, Rizvi A, Lin FY, Kumar A, Hadamitzky M, Kim YJ, Conte E, Andreini D, Pontone G, et al. Quantification of coronary atherosclerosis in the Assessment of Coronary Artery Disease. Circ Cardiovasc Imaging. 2018;11(7):e007562.

35. Liu J, Huang S, Wang X, Li B, Ma J, Sun H, Xi X, Sun Y, Zhang L, Liu J, et al. Effect of the coronary arterial diameter derived from coronary computed tomography angiography on fractional Flow Reserve. J Comput Assist Tomogr. 2022;46(3):397–405.

36. He W, Li Q, Yang M, Jiao J, Ma X, Zhou Y, Song A, Heymsfield SB, Zhang S, Zhu S. Lower BMI cutoffs to define overweight and obesity in China. Obesity. 2015;23(3):684–91.

37. Tang J, Zhu X, Chen Y, Huang D, Tiemeier H, Chen R, Bao W, Zhao Q. Association of maternal pre-pregnancy low or increased body mass index with adverse pregnancy outcomes. Sci Rep. 2021;11(1):3831.

38. Joint Committee for Developing Chinese guidelines on Prevention and Treatment of Dyslipidemia in Adults. Chinese guidelines on prevention and treatment of dyslipidemia in adults. Chin J Cardiovasc Dis. 2007;35(5):390–419.

39. Pan L, Yang Z, Wu Y, Yin RX, Liao Y, Wang J, Gao B, Zhang L. The prevalence, awareness, treatment and control of dyslipidemia among adults in China. Atherosclerosis. 2016;248:2–9.

40. Brathwaite L, Reif M. Hypertensive emergencies: a review of Common presentations and Treatment options. Cardiol Clin. 2019;37(3):275–86.

41. Piskorz D. Hypertensive mediated organ damage and Hypertension Management. How to assess Beneficial effects of Antihypertensive treatments? High Blood Press Cardiovasc Prev. 2020;27(1):9–17.

42. Yoon YH, Park GM. Association of Stage 1 hypertension defined by the ACC/AHA 2017 Guideline with Asymptomatic Coronary atherosclerosis. Am J Hypertens. 2021;34(8):858–66.

43. Park HW, Jo S, Park KS, Lee H, Jeon YJ, Park S, Ann SH, Kim YG, Choi SH, Kwon WJ, et al. Differential Impact of Degree of Hypertension on subclinical coronary atherosclerosis in asymptomatic subjects with and without diabetes Mellitus. Am J Cardiol. 2023;203:343–51.

44. Gallo G, Volpe M, Savoia C. Endothelial dysfunction in hypertension: current concepts and clinical implications. Front Med. 2021;8:798958.

45. Liu J, Hong Y, D'Agostino RB, Sr., Wu Z, Wang W, Sun J, Wilson PW, Kannel WB, Zhao D. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-provincial Cohort Study. JAMA. 2004;291(21):2591–9.

46. Allen N, Berry JD, Ning H, Van Horn L, Dyer A, Lloyd-Jones DM. Impact of blood pressure and blood pressure change during middle age on the remaining lifetime risk for cardiovascular disease: the cardiovascular lifetime risk pooling project. Circulation. 2012;125(1):37–44.

47. Conen D, Ridker PM, Buring JE, Glynn RJ. Risk of cardiovascular events among women with high normal blood pressure or blood pressure progression: prospective cohort study. BMJ. 2007;335(7617):432.

48. Cavallari I, Cannon CP, Braunwald E, Goodrich EL, Im K, Lukas MA, O'Donoghue ML. Metabolic syndrome and the risk of adverse cardiovascular events after an acute coronary syndrome. Eur J Prev Cardiol. 2018;25(8):830–8.

49. Karjalainen JP, Mononen N, Hutri-Kähönen N, Lehtimäki M, Hilvo M, Kauhanen D, Juonala M, Viikari J, Kähönen M, Raitakari O, et al. New evidence from plasma ceramides links apoE polymorphism to greater risk of coronary artery disease in Finnish adults. J Lipid Res. 2019;60(9):1622–9.

50. Abd El-Aziz TA, Mohamed RH. LDLR, ApoB and ApoE genes polymorphisms and classical risk factors in premature coronary artery disease. Gene. 2016;590(2):263–9.

51. Afroze D, Yousuf A, Tramboo NA, Shah ZA, Ahmad A. ApoE gene polymorphism and its relationship with coronary artery disease in ethnic Kashmiri population. Clin Exp Med. 2016;16(4):551–6.

52. Ma W, Ren X, Zhang L, Dong H, Lu X, Feng W. Apolipoprotein E gene polymorphism and coronary artery Disease Risk among patients in Northwest China. Pharmgenomics Pers Med. 2021;14:1591–9.

53. Liu Q, Wu H. APOE gene ε4 allele (388 C-526 C) effects on serum lipids and risk of coronary artery disease in southern Chinese Hakka population. J Clin Lab Anal. 2021;35(9):e23925.

54. Balcerzyk A, Zak I, Krauze J. Synergistic effects of apolipoprotein E gene epsilon polymorphism and some conventional risk factors on premature ischaemic heart disease development. Kardiol Pol. 2007;65(9):1058–65. discussion 1066 – 1057.

55. Luo JQ, Ren H, Banh HL, Liu MZ, Xu P, Fang PF, Xiang DX. The associations between Apolipoprotein E Gene Epsilon2/Epsilon3/Epsilon4 polymorphisms and the risk of coronary artery disease in patients with type 2 diabetes Mellitus. Front Physiol. 2017;8:1031.

56. Karahan Z, Uğurlu M, Uçaman B, Uluğ AV, Kaya İ, Çevik K, Öztürk Ö, Iyem H. Relation between Apolipoprotein E Gene Polymorphism and Severity of Coronary Artery Disease in Acute Myocardial Infarction. Cardiol Res Pract. 2015; 2015:363458.

57. Long Y, Zhao XT, Liu C, Sun YY, Ma YT, Liu XY, Liu JX. A Case-Control Study of the Association of the Polymorphisms of MTHFR and APOE with risk factors and the severity of coronary artery disease. Cardiology. 2019;142(3):149–57.

58. Petrovic D, Zorc M, Peterlin B. Effect of apolipoprotein E polymorphism and apolipoprotein A-1 gene promoter polymorphism on lipid parameters and premature coronary artery disease. Folia Biol. 2000;46(5):181–5.

59. Pitsavos C, Choumerianou DM, Skoumas J, Maumus S, Stefanadis C, Dedoussis GV, Visvikis-Siest S. Apolipoprotein E polymorphism is not associated with lipid levels and coronary artery disease in Greek patients with familial hypercholesterolaemia. Clin Exp Med. 2005;5(4):196–201.

60. Formentini FS, Zaina Nagano FE, Lopes Neto FDN, Adam EL, Fortes FS, Silva LFD. Coronary artery disease and body mass index: what is the relationship? Clin Nutr ESPEN. 2019;34:87–93.

61. Wang K, Shi X, Zhu Z, Hao X, Chen L, Cheng S, Foo RSY, Wang C. Mendelian randomization analysis of 37 clinical factors and coronary artery disease in east Asian and European populations. Genome Med. 2022;14(1):63.

62. Powell-Wiley TM, Poirier P, Burke LE, Després JP, Gordon-Larsen P, Lavie CJ, Lear SA, Ndumele CE, Neeland IJ, Sanders P, et al. Obesity and Cardiovascular Disease: A Scientific Statement from the American Heart Association. Circulation. 2021;143(21):e984–1010.

63. Choi J, Wen W, Jia G, Tao R, Long J, Shu XO, Zheng W. Lifestyle factors, genetic susceptibility to obesity and their interactions on coronary artery disease risk: a cohort study in the UK Biobank. Prev Med. 2024;180:107886.

64. Lowenstern A, Ng N, Takagi H. Influence of obesity on coronary artery disease and clinical outcomes in the ADVANCE Registry. Circ Cardiovasc Imaging. 2023;16(5):e014850.

65. Šteiner I, Krbal L. Is obesity a risk factor for coronary atherosclerosis? Cesk Patol. 2022;58(2):112–4.

66. Qu Y, Yang J, Zhang F, Li C, Dai Y, Yang H, Gao Y, Pan Y, Yao K, Huang D, et al. Relationship between body mass index and outcomes of coronary artery disease in Asian population: insight from the FOCUS registry. Int J Cardiol. 2020;300:262–7.

67. Feng X, Zhang C, Jiang L, Xu L, Tian J, Zhao X, Wang D, Zhang Y, Sun K, Xu B, et al. Body mass index and mortality in patients with severe coronary

artery diseases: a cohort study from China. Nutr Metab Cardiovasc Dis. 2021;31(2):448–54.

68. Ashwell M, Gibson S. Waist-to-height ratio as an indicator of 'early health risk': simpler and more predictive than using a 'matrix' based on BMI and waist circumference. BMJ Open. 2016;6(3):e010159.

69. Kondo T, Nakano Y, Adachi S, Murohara T. Effects of Tobacco Smoking on Cardiovascular Disease. Circ J. 2019;83(10):1980–5.

70. Teo KK, Ounpuu S, Hawken S, Pandey MR, Valentin V, Hunt D, Diaz R, Rashed W, Freeman R, Jiang L, et al. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. Lancet. 2006;368(9536):647–58.

71. Barua RS, Ambrose JA. Mechanisms of coronary thrombosis in cigarette smoke exposure. Arterioscler Thromb Vasc Biol. 2013;33(7):1460–7.

Publisher's note