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ORIGINAL RESEARCH

Association of Different Combinations of *ALDH2* rs671, *APOE* rs429358, rs7412 Polymorphisms with Hypertension in Middle-Aged and Elderly People: A Case–Control Study

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Background: Hypertensive patients have a younger trend, and studies on the role of genetic factors in hypertension susceptibility have been inconsistent. Aldehyde dehydrogenases 2 (ALDH2) and apolipoprotein E (APOE) are involved in the pathophysiological processes of hypertension. To investigate the relationship of *ALDH2* and *APOE* polymorphisms with hypertension in middle-aged (30–59 years old) and elderly (≥60 years old) persons.

Methods: Two thousand six hundred and ten hypertensive patients and 1921 controls were included (between 30 and 100 years old). The genotypes of common polymorphisms in *APOE* and *ALDH2* genes (*APOE* rs429358, rs7412, and *ALDH2* rs671) of the subjects were analyzed by polymerase-chain reaction (PCR)-microarray. Statistical analyses (Student's *t*-test, Mann–Whitney *U*-test, χ^2 test, and logistic regression analysis) were performed with SPSS v21.0.

Results: There were 4531 participants (66.60 ± 12.10 years old) in this study, including 3057 (67.5%) males and 1474 (32.5%) females. There were no significant differences in distributions of *ALDH*2 rs671, *APOE* rs429358/rs7412 genotypes and alleles between hypertensive patients and controls. Persons with *ALDH2* rs671 G/A or A/A genotype were less likely to have hypertension (G/A+A/A vs G/G: gender-, age-, smoking-, and drinking-adjusted OR 0.885, 95% CI 0.785–0.997, *P*=0.045), while *ALDH2* rs671 A/A+*APOE* rs429358 or rs7412 wild-type genotype may decrease the risk of hypertension. In middle-aged group, *ALDH2* rs671 G/A+*APOE* rs429358 T/C carriers (adjusted OR 0.547, 95% CI 0.350–0.856, *P*=0.008), and *ALDH2* rs671 A/A+*APOE* rs7412 C/C genotypes (adjusted OR 0.567, 95% CI 0.361–0.891, *P*=0.014) were less likely to have hypertension. In elderly group, *APOE* rs7412 T/T carriers were more likely to have hypertension (rs671 T/T vs C/C: adjusted OR 4.755, 95% CI 1.075–21.027, *P*=0.040; rs671 T/T vs C/C or C/T: adjusted OR 4.734, 95% CI 1.071–20.928, *P*=0.040).

Conclusion: Polymorphism–polymorphism interactions of *ALDH2* rs671 and *APOE* rs429358/rs7412 may effect on hypertension susceptibility. Different genotypes comparison shows different roles in middle-aged and elderly people, respectively.

Keywords: apolipoprotein E, aldehyde dehydrogenases, polymorphism, hypertension

Introduction

The incidence of cardiovascular and cerebrovascular diseases, mainly stroke and ischemic heart disease, has been increasing year by year.[1,2] Prevention of cardiovascular and cerebrovascular diseases is a crucial task to further improve healthy life expectancy.[3] Hypertension is the primary risk factor of cardiovascular and cerebrovascular diseases.[4,5] Hypertension and its complications not only seriously affect the life expectancy and quality of life of patients but also cause huge social harm and economic burden. Age, history of diabetes, overweight, family history of hypertension, high-

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salt diet, history of alcohol consumption, history of smoking and other adverse lifestyles are recognized risk factors for hypertension.[6–9] In addition, genetic factors are also important factors influencing the risk of hypertension susceptibility.[10] There is obvious genetic susceptibility to hypertension, and genetic factors have a certain proportion in the risk factors of hypertension.[11]

Apolipoprotein E (ApoE) is an amphiphilic plasma protein belonging to the exchangeable apolipoprotein family, whose main role is to mediate the transmission of lipids between the circulation and tissues by binding to membrane receptors.[12] In addition, ApoE specifically binds lipophilic inflammatory components (amyloid beta, lipopolysaccharide, lipoic acid, and β-glucan) with high affinity, leading to pathogen clearance and promoting autoimmune development in the body.[13] ApoE plays a role in lipid metabolism regulation,[14] cardiovascular diseases,[15] neuropsychiatric diseases,[16,17] diabetes,[18] nephropathy[19] and other diseases[20,21] through the interaction with the antioxidative and immune system. ApoE is encoded by the *APOE* gene. Previous studies have shown that *APOE* polymorphisms can alter the progression of arterial vascular disease by affecting the transcription of the *APOE* gene as well as cholesterol and triglyceride (TG) levels.[15] There are two common polymorphisms in *APOE* gene: rs429358 (388T>C, Cys112Arg) and rs7412 (526C>T, Arg158Cys), and these two polymorphisms constitute three major alleles: ε2(388T-526T), ε3(388T-526C), ε4(388C-526C).[22,23]

Aldehyde dehydrogenases (ALDH) are a class of nicotinamide adenine dinucleotide (NAD) (P)+ dependent enzymes, which can utilize NAD (P) + as a cofactor to participate in the oxidation and metabolism of active aldehydes.[24] Among ALDH family members, ALDH2 has been studied most extensively. In alcohol metabolism, ALDH2 can catalyze acetaldehyde to non-toxic acetic acid.[25] In addition, ALDH2 can catalyze the metabolism of 4-hydroxynonenal (4-HNE), acrolein and other toxic unsaturated aldehydes.[26] When the oxidative stress of cardiomyocytes increases during ischemia and hypoxia, reactive oxygen species produced in mitochondria will accelerate the production of 4-HNE, and 4-HNE can damage cardiomyocytes.[27,28] ALDH2 plays a protective role against oxidative stress by metabolizing related toxic aldehydes.[29] ALDH2 can also be used as nitrate reductase to catalyze the formation of 1,2-dinitrate and nitrite from nitroglycerin, thereby ultimately producing cyclic guanosine phosphate (cGMP) and nitric oxide (NO) to dilate blood vessels.[30] ALDH2 plays an anti-oxidative stress role in vivo by metabolizing 4-HNE and inhibit the occurrence of hypertension, indicating that it has a certain association with hypertension.[31] ALDH2 is encoded by the *ALDH2* gene. The *ALDH2* gene rs671 polymorphism (G1510A, Glu504Lys) changed the structure of ALDH2 enzyme, and the binding of coenzyme NAD (P) + to the ALDH2 enzyme was impaired, and the dehydrogenation effect was weakened, leading to the decrease of the activity of ALDH2.

The different regions, populations, lifestyles and interactions between gene polymorphisms will affect the occurrence of hypertension. Studies have confirmed the association of polymorphisms in *APOE* and *ALDH2* with hypertension,[32,33] but the relationship between different combinations of these polymorphisms and hypertension remains unclear. Therefore, this study aims to clarify the relationship between them. In addition, hypertensive patients have a younger trend. There are significant differences in clinical characteristics between young and middle-aged patients with hypertension and elderly patients.[34] Another aim of this study was to investigate the relationship between *APOE* and *ALDH2* polymorphisms and hypertension susceptibility in middle-aged and elderly adults, respectively. It is of great significance for the early screening of high-risk individuals with hypertension and prevention of hypertension.

Materials and Methods

Subjects and Data Collection

Hypertension was defined as systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg.[35,36] Inclusion criteria for hypertensive patients were the following: (1) Diagnosed as hypertension clinically; (2) Medical records were complete; (3) Adults. The exclusion criteria were: (1) Incomplete data of medical records; (2) Minors. The control group consisted of healthy people who did not have hypertension. Subjects' information was collected, such as gender, age, and lifestyle habits. This study was approved by the Human Ethics Committees of Meizhou People's Hospital.

The study included 4531 participants, including 2610 hypertensive patients and 1921 controls. The data of this retrospective study including age, gender, history of smoking, history of alcohol consumption, medical history, and serum lipid level from April 2016 to December 2020, were collected from the Hospital Information System (HIS) and Laboratory Information System (LIS) of Meizhou People's Hospital in Guangdong Province.

Genotyping of *APOE* rs429358, rs7412 and *ALDH2* rs671

The most common polymorphisms in the two genes (rs429358, rs7412 in *APOE* gene and rs671 in *ALDH2* gene) were included in the analysis of this study. Genomic DNA was extracted from whole blood using a QIAamp DNA Blood Mini Kit (Qiagen GmbH, North Rhine-Westphalia, Germany) according to the protocol. *APOE*- and *ALDH2*-related polymorphisms were amplified by polymerase-chain reaction (PCR). The *APOE* gene was amplified using PCR at 50°C for 2 minutes, 95°C for 15 minutes, followed by 45 thermal cycles (94°C for 30s and 65°C for 45s) (Sinochips Bioscience Co., Ltd., Zhuhai, Guangdong, China). The *ALDH2* gene was amplified using PCR at 94°C for 5 minutes, followed by 35 thermal cycles (94°C for 25s, 56°C for 25s, and 72°C for 25s) (BaiO Technology Co, Ltd, Shanghai, China). The PCR products were hybridized with wild-type or mutant probes fixed on the chip, and the genotypes of the samples were determined by the hybridization reaction. Positive control, negative control, and blank control were used for quality control. When the positive control, negative control, and blank control were controlled, the test results of this batch of samples are reliable.

Serum Lipid and Homocysteine Measurements

Serum lipid levels of the samples were evaluated by an Olympus AU5400 system (Olympus Corporation, Tokyo, Japan). Total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoprotein A1 (Apo-A1), and apolipoprotein B (Apo-B) analyses were performed. Serum homocysteine (Hcy) levels of all subjects were measured by enzymatic cycling assay on an Olympus AU5800 system (Olympus Corporation, Tokyo, Japan) according to the protocol.

Statistical Analysis

Data analysis was performed using SPSS statistical software version 21.0 (IBM Inc., USA). Student's *t*-test or the Mann–Whitney *U*-test was used for continuous data analysis. Genotype composition ratios and allele frequencies of groups were analyzed by the χ^2 test. Logistic regression analysis was applied to examine the relationship between *APOE* and *ALDH2* polymorphisms and various factors in hypertension. $P< 0.05$ was considered statistically significant.

Results

Characteristics of Subjects

There were 4531 participants in this study, including 3057(67.5%) males and 1474(32.5%) females; 1328(29.3%) have a history of smoking and 299(6.6%) have a history of alcohol consumption. There were 1741(66.7%) men and 869 (33.3%) women in hypertensive patients and 1316(68.5%) men and 605(31.5%) women in controls. The average age was 67.35±11.70 years and 65.59±12.56 years in patients and controls, respectively. There were statistically significant differences in the percentage of subjects with a history of smoking ($P<0.001$) and in the percentage of history of alcohol consumption ($P<0.001$) between patients and non-hypertensive controls. The serum Hcy ($P<0.001$), triglyceride (TG) ($P=0.007$), total cholesterol (TC) ($P<0.001$), low-density lipoprotein cholesterol (LDL-C) ($P=0.001$), apolipoprotein A1 (Apo-A1) ($P<0.001$), and apolipoprotein B (Apo-B) ($P<0.001$) levels in the hypertensive subjects were higher than that in controls (Table 1).

Frequencies of *APOE* rs429358, rs7412, and *ALDH2* rs671 Genotypes in Patients and Controls

The PCR-microarray test results of all genotypes are illustrated in Figure 1. The frequencies of *ALDH2* rs671 and *APOE* rs429358, rs7412 genotypes and alleles were compared between patients and non-hypertensive controls. The distributions

Table 1 Clinical Characteristics of Hypertensive Patients and Control Participants

	Total (n=4531)	Controls (n=1921)	Hypertensive Patients (n=2610)	*P* values
Age, years	66.60±12.10	65.59±12.56	67.35±11.70	<0.001
Gender				
Male, n(%)	3057(67.5%)	1316(68.5%)	1741(66.7%)	0.211
Female, n(%)	1474 (32.5%)	605(31.5%)	869(33.3%)	
History of smoking, n(%)	1328(29.3%)	631(32.8%)	697(26.7%)	<0.001
History of alcohol consumption, n(%)	299(6.6%)	162(8.4%)	137(5.2%)	<0.001
Hcy, μmol/L	16.70±8.09	16.04±8.07	17.18±8.08	<0.001
TG, mmol/L	1.77±1.69	1.69±1.79	1.83±1.61	0.007
TC, mmol/L	4.89±1.40	4.79±1.49	4.95±1.32	<0.001
HDL-C, mmol/L	1.26±0.39	1.25±0.40	1.27±0.38	0.070
LDL-C, mmol/L	2.73±0.98	2.68±1.03	2.77±0.94	0.001
Apo-A1, g/L	1.10±0.33	1.07±0.34	1.12±0.31	<0.001
Apo-B, g/L	0.85±0.29	0.83±0.30	0.86±0.28	<0.001

Note: Values for age expressed as mean±SD.
Abbreviations: Hcy, homocysteine; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; Apo-A1, apolipoprotein A1; Apo-B, apolipoprotein B.

of *ALDH2* rs671 and *APOE* rs429358, rs7412 genotypes in controls (χ^2=1.842, *P*=0.175; χ^2=0.160, *P*=0.689; and χ^2=0.982, *P*=0.322) and hypertensive patients (χ^2=2.633, *P*=0.105; χ^2=0.401, *P*=0.527; and χ^2=2.182, *P*=0.140) were consistent with Hardy-Weinberg equilibrium, respectively. There were no significant differences in the distributions of genotypes and alleles of *ALDH2* rs671 and *APOE* rs429358, rs7412 between patients and controls (all *P*>0.05) (Table 2).

Comparison of Clinical Characteristics and Frequencies of Gene Polymorphisms Between Hypertensive Patients and Controls in the Middle-Aged Group and Elderly Group

In this study, there were 1285 (28.36%) middle-aged (30–59 years old) subjects (666 hypertensive patients and 619 controls) and 3246 (71.64%) elderly (≥60 years old) subjects (1944 hypertensive patients and 1302 controls). In middle-aged group, patients had higher Hcy levels (15.32±6.71 μmol/L vs 14.48±8.39 μmol/L, *P*=0.047), TC levels (5.17±1.36 mmol/L vs 4.99±1.60 mmol/L, *P*=0.025), Apo-A1 levels (1.14±0.32 g/L vs 1.09±0.34 g/L, *P*=0.007), and Apo-B levels (0.90±0.29 g/L vs 0.85±0.31 g/L, *P*=0.005) than controls, while hypertensive patients had lower percentage of history of alcohol consumption (5.7% vs 9.5%, *P*=0.011) than controls. There were no significant differences in the distributions of genotypes *ALDH2* rs671 and *APOE* rs429358, rs7412 between patients and controls (all *P*>0.05) (Table 3).

In elderly group, hypertensive patients had higher Hcy (17.81±8.41 μmol/L vs 16.78±7.80 μmol/L, *P*<0.001), TG (1.70±1.38 mmol/L vs 1.53±1.32 mmol/L, *P*<0.001), TC (4.88±1.30 mmol/L vs 4.70±1.42 mmol/L, *P*<0.001), LDL-C (2.73±0.93 mmol/L vs 2.63±1.01 mmol/L, *P*=0.003), Apo-A1 (1.11±0.31 g/L vs 1.07±0.34 g/L, *P*<0.001), and Apo-B levels (0.85±0.27 g/L vs 0.82±0.29 g/L, *P*=0.001) than controls, while hypertensive patients had lower percentages of history of smoking (25.1% vs 32.0%, *P*<0.001) and history of alcohol consumption (5.1% vs 7.9%, *P*=0.001) than controls. No significant differences were detected in the distributions of *ALDH2* rs671 and *APOE* rs429358, rs7412 genotypes between patients and controls (all *P*>0.05) (Table 3).

Association of *ALDH2* rs671 and *APOE* rs429358, rs7412 with Hypertension

Multivariate logistic regression analysis was performed to analyze the relationship of *ALDH2* and *APOE* polymorphisms with hypertension (gender-, age-, smoking-, and drinking-adjusted). Compared with G/G carriers, persons with *ALDH2* rs671 G/A or A/A genotype were less likely to have hypertension (G/A plus A/A vs G/G: adjusted OR 0.885, 95% CI 0.785–0.997, *P*=0.045). Compared with *ALDH2* rs671 G/G combined with *APOE* rs429358 T/T carriers, persons with

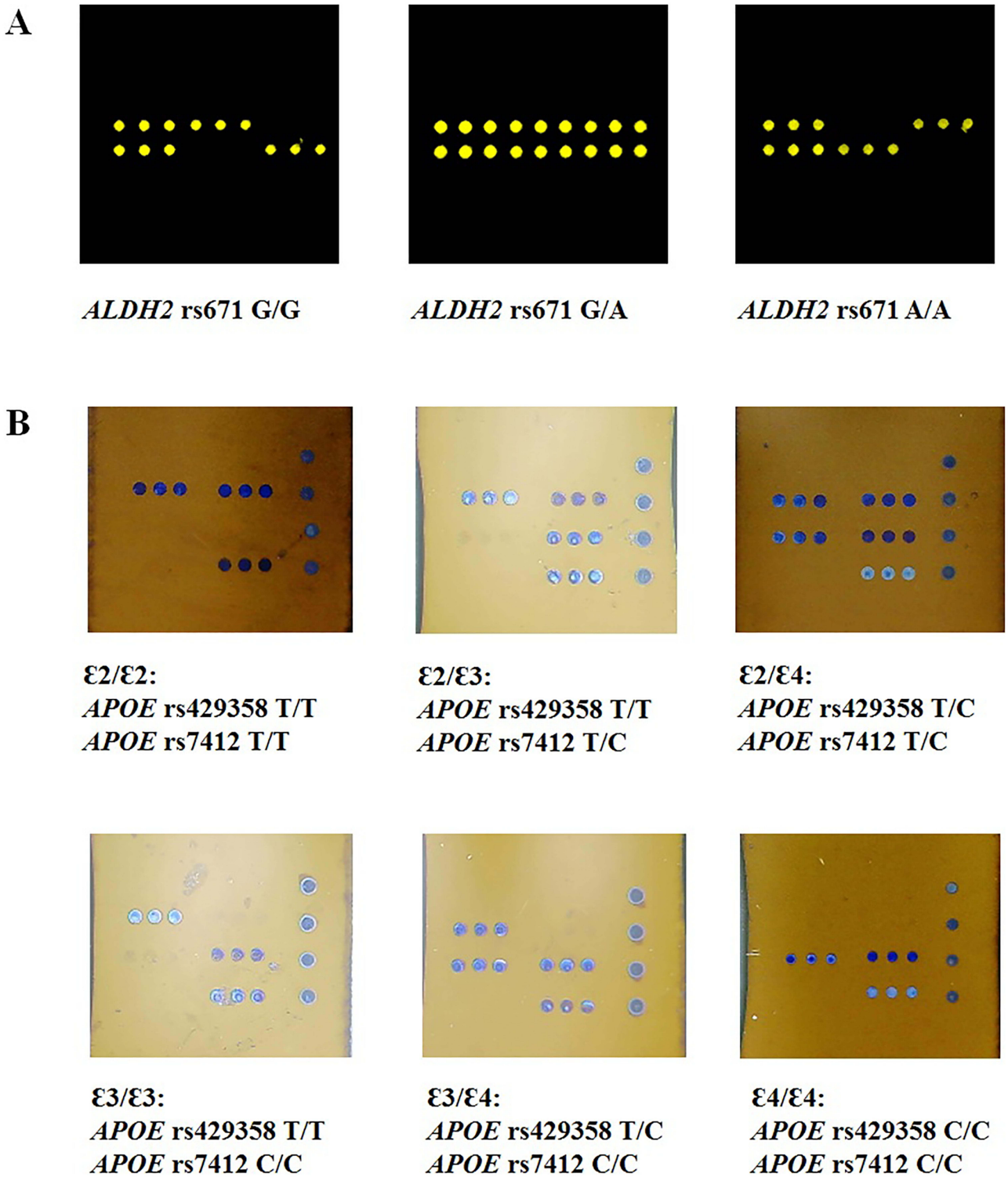

Figure 1 The PCR-microarray test results of all genotypes in different polymorphisms. *ALDH2* rs671 (**A**); *APOE* rs429358 and rs7412 (**B**).

ALDH2 rs671 A/A combined with *APOE* rs429358 T/T genotypes were less likely to have hypertension (rs671 A/A + rs429358 T/T vs rs671 G/G + rs429358 T/T: adjusted OR 0.748, 95% CI 0.586–0.953, *P*=0.019). Compared with *ALDH2* rs671 G/G combined with *APOE* rs7412 C/C carriers, persons with *ALDH2* rs671 A/A combined with *APOE* rs7412 C/C

Table 2 Frequencies of *APOE* rs429358, rs7412, *ALDH2* rs671 Genotypes in Hypertensive Patients and Controls

	Genotype/Allele	Controls (n=1921)	Hypertensive Patients (n=2610)	χ^2	*P* value
ALDH2 rs671	G/G	877(45.65%)	1246(47.74%)	2.452	0.293
	G/A	861(44.82%)	1140(43.68%)		
	A/A	183(9.53%)	224(8.58%)		
	G	2615(68.06%)	3632(69.58%)	2.372	0.124
	A	1227(31.94%)	1588(30.42%)		
	HWE (χ^2, *P*), p	χ^2=1.842, *P*=0.175	χ^2=2.633, *P*=0.105		
APOE rs429358	T/T	1551(80.74%)	2113(80.96%)	0.061	0.965
	T/C	352(18.32%)	474(18.16%)		
	C/C	18(0.94%)	23(0.88%)		
	T	3454(89.90%)	4700(90.04%)	0.046	0.832
	C	388(10.10%)	520(9.96%)		
	HWE (χ^2, *P*), p	χ^2=0.160, *P*=0.689	χ^2=0.401, *P*=0.527		
APOE rs7412	C/C	1668(86.83%)	2259(86.55%)	2.993	0.227
	C/T	247(12.86%)	333(12.76%)		
	T/T	6(0.31%)	18(0.69%)		
	C	3583(93.26%)	4851(92.93%)	0.368	0.558
	T	259(6.74%)	369(7.07%)		
	HWE (χ^2, *P*)	χ^2=0.982, *P*=0.322	χ^2=2.182, *P*=0.140		

Abbreviation: HWE, Hardy Weinberg Equilibrium.

Table 3 Comparison of Clinical Characteristics and Frequency of Gene Polymorphisms Between Hypertensive Patients and Controls in the Middle-Aged Group (30–59 Years Old) and Elderly Group (≥60 Years Old)

Clinical Characteristics	Middle-Aged Group (30–59 Years Old) (n=1285)				Elderly Group (≥60 Years Old) (n=3246)			
	Total (n=1285)	Controls (n=619)	Hypertensive Patients (n=666)	*P* values	Total (n=3246)	Controls (n=1302)	Hypertensive Patients (n=1944)	*P* values
Age, years	51.60±6.02	51.16±6.41	52.02±5.60	0.011	72.54±8.11	72.45±8.20	72.60±8.06	0.608
Gender								
Male, n(%)	907(70.6%)	439(70.9%)	468(70.3%)	0.807	2150(66.2%)	877(67.4%)	1273(65.5%)	0.272
Female, n(%)	378(29.4%)	180(29.1%)	198(29.7%)		1096(33.8%)	425(32.6%)	671(34.5%)	
History of smoking, n(%)	423(32.9%)	214(34.6%)	209(31.4%)	0.235	905(27.9%)	417(32.0%)	488(25.1%)	<0.001
History of alcohol consumption, n(%)	97(7.5%)	59(9.5%)	38(5.7%)	0.011	202(6.2%)	103(7.9%)	99(5.1%)	0.001
Hcy, μmol/L	14.92±7.58	14.48±8.39	15.32±6.71	0.047	17.40±8.19	16.78±7.80	17.81±8.41	<0.001
TG, mmol/L	2.12±2.29	2.03±2.47	2.20±2.11	0.198	1.63±1.36	1.53±1.32	1.70±1.38	<0.001
TC, mmol/L	5.08±1.48	4.99±1.60	5.17±1.36	0.025	4.81±1.35	4.70±1.42	4.88±1.30	<0.001
HDL-C, mmol/L	1.23±0.38	1.22±0.38	1.25±0.39	0.132	1.27±0.39	1.26±0.41	1.28±0.38	0.340
LDL-C, mmol/L	2.83±1.01	2.78±1.06	2.89±0.96	0.065	2.70±0.96	2.63±1.01	2.73±0.93	0.003
Apo-A1, g/L	1.12±0.33	1.09±0.34	1.14±0.32	0.007	1.09±0.32	1.07±0.34	1.11±0.31	<0.001
Apo-B, g/L	0.87±0.30	0.85±0.31	0.90±0.29	0.005	0.84±0.28	0.82±0.29	0.85±0.27	0.001
ALDH2 rs671								
G/G	617(48.0%)	286(46.2%)	331(49.7%)	0.255	1506(46.4%)	591(45.4%)	915(47.1%)	0.628
G/A	558(43.4%)	273(44.1%)	285(42.8%)		1443(44.5%)	588(45.2%)	855(44.0%)	
A/A	110(8.6%)	60(9.7%)	50(7.5%)		297(9.1%)	123(9.4%)	174(9.0%)	
APOE rs429358								
T/T	1033(80.4%)	488(78.8%)	545(81.8%)	0.375	2631(81.1%)	1063(81.6%)	1568(80.7%)	0.723
T/C	237(18.4%)	124(20.0%)	113(17.0%)		589(18.1%)	228(17.5%)	361(18.6%)	
C/C	15(1.2%)	7(1.1%)	8(1.2%)		26(0.8%)	11(0.8%)	15(0.8%)	
APOE rs7412								
C/C	1112(86.5%)	531(85.8%)	581(87.2%)	0.761	2815(86.7%)	1137(87.3%)	1678(86.3%)	0.075
C/T	165(12.8%)	84(13.6%)	81(12.2%)		415(12.8%)	163(12.5%)	252(13.0%)	
T/T	8(0.6%)	4(0.6%)	4(0.6%)		16(0.5%)	2(0.2%)	14(0.7%)	

Table 4 Association of *ALDH2* rs671 and *APOE* rs429358, rs7412 Polymorphisms with Hypertension

SNP	Genotype	Univariate OR (95% CI)	*P* values	Multivariate OR (95% CI)	*P* values*
ALDH2 rs671	G/G	1.000(reference)		1.000(reference)	
	G/A	0.932(0.824–1.055)	0.264	0.899(0.794–1.019)	0.097
	A/A	0.862(0.696–1.067)	0.171	0.815(0.657–1.012)	0.064
	G/A+ A/A	0.920(0.817–1.035)	0.164	0.885(0.785–0.997)	0.045
	G/G+ G/A	1.000(reference)		1.000(reference)	
	A/A	0.892(0.726–1.094)	0.272	0.860(0.699–1.057)	0.151
APOE rs429358	T/T	1.000(reference)		1.000(reference)	
	T/C	0.988(0.848–1.151)	0.881	0.992(0.850–1.156)	0.914
	C/C	0.938(0.504–1.744)	0.840	0.950(0.509–1.774)	0.873
	T/C+C/C	0.986(0.849–1.145)	0.853	0.990(0.851–1.150)	0.891
	T/T+T/C	1.000(reference)		1.000(reference)	
	C/C	0.940(0.506–1.747)	0.845	0.952(0.510–1.775)	0.877
APOE rs7412	C/C	1.000(reference)		1.000(reference)	
	C/T	0.995(0.835–1.187)	0.960	0.984(0.824–1.175)	0.861
	T/T	2.215(0.877–5.592)	0.092	2.300(0.906–5.840)	0.080
	C/T+T/T	1.024(0.861–1.219)	0.786	1.015(0.852–1.208)	0.870
	C/C+C/T	1.000(reference)		1.000(reference)	
	T/T	2.216(0.878–5.594)	0.092	2.304(0.908–5.850)	0.079
Comparison of polymorphisms	rs671 G/G + rs429358 T/T	1.000(reference)		1.000(reference)	
	rs671 G/G + rs429358 T/C	1.000(0.799–1.252)	1.000	1.010(0.805–1.266)	0.934
	rs671 G/G + rs429358 C/C	1.696(0.595–4.835)	0.323	1.684(0.588–4.821)	0.332
	rs671 G/A + rs429358 T/T	0.960(0.837–1.101)	0.560	0.930(0.809–1.069)	0.307
	rs671 G/A + rs429358 T/C	0.856(0.680–1.077)	0.184	0.818(0.649–1.031)	0.089
	rs671 G/A + rs429358 C/C	0.578(0.238–1.402)	0.226	0.585(0.239–1.428)	0.239
	rs671 A/A + rs429358 T/T	0.797(0.626–1.013)	0.064	0.748(0.586–0.953)	0.019
	rs671 A/A + rs429358 T/C	1.192(0.762–1.866)	0.441	1.178(0.751–1.848)	0.477
	rs671 A/A + rs429358 C/C	0.707(0.099–5.028)	0.729	0.638(0.089–4.560)	0.654
	rs671 G/G + rs7412 C/C	1.000(reference)		1.000(reference)	
	rs671 G/G + rs7412 C/T	1.003(0.774–1.299)	0.985	0.983(0.758–1.276)	0.900
	rs671 G/G + rs7412 T/T	1.883(0.498–7.122)	0.351	1.708(0.448–6.512)	0.433
	rs671 G/A + rs7412 C/C	0.938(0.821–1.072)	0.347	0.904(0.790–1.034)	0.140
	rs671 G/A + rs7412 C/T	0.892(0.688–1.155)	0.385	0.846(0.651–1.097)	0.207
	rs671 G/A + rs7412 T/T	1.883(0.498–7.122)	0.351	2.125(0.556–8.116)	0.270
	rs671 A/A + rs7412 C/C	0.838(0.668–1.051)	0.126	0.785(0.625–0.987)	0.038
	rs671 A/A + rs7412 C/T	1.039(0.557–1.937)	0.905	1.034(0.552–1.935)	0.918
	rs671 A/A + rs7412 T/T	–	0.999	–	0.999

Note: **P* values are estimated by logistic regression adjusted for gender, age, smoking, and drinking.

genotypes were less likely to have hypertension (rs671 A/A + rs7412 C/C vs rs671 G/G + rs7412 C/C: adjusted OR 0.785, 95% CI 0.625–0.987, *P*=0.038) (Table 4).

In middle-aged group, compared with *ALDH2* rs671 G/G combined with *APOE* rs429358 T/T carriers, persons with *ALDH2* rs671 G/A combined with *APOE* rs429358 T/C genotypes were less likely to have hypertension (rs671 G/A + rs429358 T/C vs rs671 G/G + rs429358 T/T: adjusted OR 0.547, 95% CI 0.350–0.856, *P*=0.008). Compared with *ALDH2* rs671 G/G combined with *APOE* rs7412 C/C carriers, persons with *ALDH2* rs671 A/A combined with *APOE* rs7412 C/C genotypes were less likely to have hypertension (rs671 A/A + rs7412 C/C vs rs671 G/G + rs7412 C/C: adjusted OR 0.567, 95% CI 0.361–0.891, *P*=0.014). In elderly group, persons with *APOE* rs7412 T/T were more likely to have hypertension (rs671 T/T vs rs671 C/C: adjusted OR 4.755, 95% CI 1.075–21.027, *P*=0.040; rs671 T/T vs rs671 C/C or C/T: adjusted OR 4.734, 95% CI 1.071–20.928, *P*=0.040) (Table 5).

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Table 5 Association of *ALDH2* rs671 and *APOE* rs429358, rs7412 Polymorphisms with Hypertension in Middle-Aged Group and Elderly Group

		Middle-Aged Group				Elderly Group			
SNP	**Genotype**	**Univariate OR (95% CI)**	***P* values**	**Multivariate OR (95% CI)**	***P* values***	**Univariate OR (95% CI)**	***P* values**	**Multivariate OR (95% CI)**	***P* values***
ALDH2 rs671	G/G	1.000(reference)		1.000(reference)		1.000(reference)		1.000(reference)	
	G/A	0.902(0.717–1.135)	0.378	0.868(0.689–1.095)	0.233	0.939(0.810–1.088)	0.404	0.913(0.787–1.060)	0.233
	A/A	0.720(0.479–1.082)	0.114	0.679(0.451–1.025)	0.065	0.914(0.709–1.177)	0.485	0.878(0.681–1.134)	0.319
	G/A+ A/A	0.869(0.698–1.082)	0.210	0.834(0.668–1.042)	0.110	0.935(0.812–1.076)	0.348	0.907(0.787–1.046)	0.181
	G/G+ G/A	1.000(reference)		1.000(reference)		1.000(reference)		1.000(reference)	
	A/A	0.756(0.511–1.120)	0.163	0.728(0.490–1.080)	0.115	0.942(0.739–1.201)	0.631	0.919(0.721–1.173)	0.499
APOE rs429358	T/T	1.000(reference)		1.000(reference)		1.000(reference)		1.000(reference)	
	T/C	0.816(0.615–1.083)	0.158	0.820(0.617–1.090)	0.171	1.073(0.894–1.289)	0.449	1.067(0.887–1.282)	0.492
	C/C	1.023(0.368–2.843)	0.965	1.037(0.370–2.901)	0.946	0.924(0.423–2.021)	0.844	0.913(0.416–2.001)	0.820
	T/C+C/C	0.827(0.628–1.090)	0.177	0.831(0.630–1.097)	0.192	1.067(0.891–1.277)	0.483	1.059(0.884–1.269)	0.531
	T/T+T/C	1.000(reference)		1.000(reference)		1.000(reference)		1.000(reference)	
	C/C	1.063(0.383–2.949)	0.907	1.075(0.385–3.004)	0.891	0.913(0.418–1.993)	0.819	0.902(0.412–1.976)	0.797
APOE rs7412	C/C	1.000(reference)		1.000(reference)		1.000(reference)		1.000(reference)	
	C/T	0.881(0.635–1.222)	0.449	0.874(0.629–1.215)	0.423	1.048(0.848–1.294)	0.666	1.036(0.838–1.280)	0.744
	T/T	0.914(0.227–3.673)	0.899	0.928(0.229–3.757)	0.916	4.743(1.076–20.910)	0.040	4.755(1.075–21.027)	0.040
	C/T+T/T	0.883(0.641–1.216)	0.446	0.877(0.635–1.210)	0.423	1.092(0.887–1.345)	0.406	1.081(0.877–1.332)	0.467
	C/C+C/T	1.000(reference)		1.000(reference)		1.000(reference)		1.000(reference)	
	T/T	0.929(0.231–3.731)	0.917	0.943(0.233–3.817)	0.935	4.715(1.070–20.781)	0.040	4.734(1.071–20.928)	0.040
Comparison of polymorphisms	rs671 G/G + rs429358 T/T	1.000(reference)		1.000(reference)		1.000(reference)		1.000(reference)	
	rs671 G/G + rs429358 T/C	1.056(0.698–1.598)	0.796	1.067(0.702–1.619)	0.762	0.975(0.746–1.275)	0.854	0.969(0.740–1.269)	0.819
	rs671 G/G + rs429358 C/C	3.521(0.391–31.720)	0.262	3.504(0.386–31.833)	0.265	1.288(0.386–4.302)	0.680	1.319(0.393–4.423)	0.654
	rs671 G/A + rs429358 T/T	1.028(0.797–1.327)	0.830	0.991(0.766–1.282)	0.945	0.928(0.788–1.093)	0.371	0.904(0.766–1.066)	0.231
	rs671 G/A + rs429358 T/C	0.567(0.364–0.884)	0.012	0.547(0.350–0.856)	0.008	0.992(0.754–1.305)	0.952	0.954(0.724–1.258)	0.740
	rs671 G/A + rs429358 C/C	0.587(0.164–2.105)	0.413	0.578(0.159–2.094)	0.404	0.644(0.186–2.237)	0.489	0.597(0.171–2.080)	0.418
	rs671 A/A + rs429358 T/T	0.685(0.426–1.101)	0.118	0.644(0.399–1.041)	0.072	0.824(0.622–1.091)	0.177	0.789(0.595–1.048)	0.102
	rs671 A/A + rs429358 T/C	0.880(0.421–1.839)	0.734	0.846(0.403–1.775)	0.658	1.478(0.827–2.642)	0.188	1.437(0.802–2.574)	0.223
	rs671 A/A + rs429358 C/C	-	-	-	-	0.644(0.090–4.589)	0.661	0.601(0.084–4.306)	0.612
	rs671 G/G + rs7412 C/C	1.000(reference)		1.000(reference)		1.000(reference)		1.000(reference)	
	rs671 G/G + rs7412 C/T	0.686(0.427–1.103)	0.120	0.680(0.422–1.098)	0.115	1.183(0.863–1.621)	0.295	1.171(0.853–1.607)	0.328
	rs671 G/G + rs7412 T/T	0.410(0.037–4.547)	0.468	0.435(0.039–4.869)	0.500	4.646(0.570–37.871)	0.151	4.066(0.498–33.182)	0.190
	rs671 G/A + rs7412 C/C	0.858(0.670–1.097)	0.222	0.827(0.644–1.060)	0.134	0.970(0.828–1.136)	0.705	0.943(0.803–1.106)	0.470
	rs671 G/A + rs7412 C/T	0.868(0.527–1.429)	0.578	0.823(0.498–1.360)	0.447	0.893(0.659–1.209)	0.464	0.853(0.629–1.157)	0.306
	rs671 G/A + rs7412 T/T	0.410(0.037–4.547)	0.468	0.419(0.037–4.737)	0.482	4.646(0.570–37.871)	0.151	5.118(0.624–41.986)	0.128
	rs671 A/A + rs7412 C/C	0.603(0.386–0.943)	0.027	0.567(0.361–0.891)	0.014	0.928(0.711–1.210)	0.581	0.889(0.680–1.162)	0.388
	rs671 A/A + rs7412 C/T	1.054(0.387–2.872)	0.918	1.018(0.372–2.784)	0.972	1.062(0.478–2.358)	0.883	1.041(0.466–2.322)	0.922
	rs671 A/A + rs7412 T/T	-	0.999	-	0.999	-	-	-	-

Note: **P* values are estimated by logistic regression adjusted for gender, age, smoking, and drinking.

Discussion

China is currently facing the dual pressure of aging population and the increasing incidence of chronic metabolic diseases. The morbidity and mortality of cardiovascular disease (CVD) continue to increase, becoming the first cause of death in China.[37] Hypertension is one of the major risk factors for CVD, and its prevalence in China is on the rise, especially in rural areas.[38] The age-standardized rate of hypertension prevalence was 34.7% in 2012 and 36.9% in 2019 with a slight increase in the population of Guangdong Province, located in southern China.[39] Studies have shown that hypertension has obvious family aggregation.[40,41] A series of genes have been found to be associated with essential hypertension.[42] There are significant differences in clinical characteristics between young and middle-aged patients with hypertension and elderly patients.[34] In this study, the association of *ALDH2* rs671 and *APOE* rs429358, rs7412 polymorphisms with hypertension in the middle-aged and elderly persons was analyzed, respectively.

There is evidence of a relationship between hypertension and lipid metabolism.[43] *APOE* gene is closely related to blood pressure, and its potential mechanism may be that *APOE* gene affects blood pressure by regulating lipid metabolism.[44] Some studies of this relationship have been reported before. Studies have found that *APOE* ε4 allele was a risk factor for hypertension.[45–47] Misra et al[48] found that *APOE* ε4 allele was an independent risk factor for recurrent intracerebral hemorrhage in hypertensive patients in an Indians population. However, some scholars have argued that *APOE* polymorphisms were not related to hypertension.[49,50] *APOE* genotype was not associated with hypertension in elderly persons.[51] Leite et al[52] found that differences in systolic blood pressure between *APOE* genotypes are age-related in the elderly, suggesting that different *APOE* genotypes are involved in different mechanisms leading to hypertension in elderly subjects. Rao et al[32] showed that *APOE* rs7412 T/T was likely a risk factor for hypertension. In present study, elderly persons carrying *APOE* rs7412 T/T genotype were more likely to have hypertension, but not middle-aged persons.

4-HNE produced during ischemia and hypoxia will damage vascular endothelial cells, leading to the increase of oxidative stress level and thus induce hypertension.[31] ALDH2 can play an anti-oxidative stress role in vivo by catalyzing the metabolism of 4-HNE, and inhibit the occurrence of hypertension.[31] Wu et al found that *ALDH2* rs671 G>A may increase the risk of hypertension.[33,53] However, some studies showed that *ALDH2* rs671 G>A may decrease the risk of hypertension.[54–56] In a study in a Korean population, the *ALDH2* rs671 A allele was associated with a lower risk of hypertension, but increased risk among people who consumed more fried food.[57] In addition, a study showed that *ALDH2* rs671 polymorphism was not associated with the risk of hypertension.[58] Another study has shown that *ALDH2* rs671 polymorphism was associated with the carotid intima-media thickness of hypertensive patients in a Chinese Han population.[59] In this study, persons with *ALDH2* rs671 G/A or A/A genotype were less likely to develop hypertension compared with those who carried G/G. That is to say, *ALDH2* rs671 G>A polymorphism may decrease the risk of hypertension.

Hypertension mostly occurs in the elderly people, but in recent years, the hypertensive patients have a younger trend. The relationship of *ALDH2* and *APOE* polymorphisms with hypertension in the middle-aged and elderly persons was analyzed in this study, respectively. The results showed that elderly persons with *APOE* rs7412 T/T were more likely to have hypertension, but not middle-aged persons. Other *APOE* rs7412 genotypes, *ALDH2* rs671 and *APOE* rs429358 polymorphisms were not associated with hypertension in middle-aged and elderly people, respectively. In mechanism, white matter hyperintensities (WMH) is a risk factor for Alzheimer's disease, and the risk of developing Alzheimer's disease increases with age in APOE-ε4 carriers, which may be associated with older age predicted faster WMH increase in APOE-ε4 carriers.[60] *APOE* gene polymorphism is associated with small vessel disease, which may cause hypertensive vascular disease.[61] Lipid metabolism of the elderly people was more affected by *APOE* polymorphism than that of the middle-aged people,[62] age-dependent lipid changes were also observed in ApoE/LDLR$^{-/-}$ mice.[63]

In addition, there is a significant relationship of the gene–gene and polymorphism–polymorphism interactions with hypertension.[64,65] The relationship of different combinations of *ALDH2* and *APOE* polymorphisms with hypertension was analyzed. Compared with *ALDH2* rs671 G/G combined with *APOE* rs429358 T/T carriers, persons with *ALDH2* rs671 A/A combined with *APOE* rs429358 T/T genotypes were less likely to have hypertension; compared with *ALDH2* rs671 G/G combined with *APOE* rs7412 C/C carriers, persons with *ALDH2* rs671 A/A combined with *APOE* rs7412 C/C genotypes were less likely to have hypertension. That is to say, *ALDH2* rs671 A/A genotype combined with *APOE*

rs429358 or rs7412 wild-type genotype may decrease the risk of hypertension. In middle-aged persons, compared with *ALDH2* rs671 G/G combined with *APOE* rs429358 T/T carriers, persons with *ALDH2* rs671 G/A combined with *APOE* rs429358 T/C genotypes were less likely to have hypertension; compared with *ALDH2* rs671 G/G combined with *APOE* rs7412 C/C carriers, persons with *ALDH2* rs671 A/A combined with *APOE* rs7412 C/C genotypes were less likely to have hypertension. That is to say, *ALDH2* rs671 G/A combined with *APOE* rs429358 T/C, *ALDH2* rs671 A/A combined with *APOE* rs7412 C/C may decrease the risk of hypertension in middle-aged persons, but not elderly people. In mechanism, ALDH2 plays a protective role against oxidative stress by metabolizing related toxic aldehydes.[29] ALDH2 can also be used as nitrate reductase to catalyze the formation of 1,2-dinitrate and nitrite from nitroglycerin, thereby ultimately producing cyclic guanosine phosphate (cGMP) and NO to dilate blood vessels.[30] ApoE is a major apolipoprotein involved in lipoprotein metabolism.[14] The mechanism might be, when the protective effect of ALDH2 against oxidative stress, vasodilation and the regulation of lipid metabolism by APOE were simultaneously changed, they have a greater effect on blood pressure.

Our study is the first to study on the relationship of comparison of *APOE* and *ALDH2* polymorphisms with middle-aged and elderly persons, respectively. And the results showed that the different combinations of *ALDH2* rs671, *APOE* rs429358 and rs7412 polymorphisms play different roles in the risk of hypertension in middle-aged and elderly people. It also demonstrates the relationship between the interaction of genetic polymorphisms and the risk of hypertension. The study on the relationship between *APOE* and *ALDH2* gene polymorphisms and hypertension susceptibility, especially the risk of hypertension in middle-aged adults, is of great significance for the early screening of high-risk individuals with hypertension and prevention of hypertension.

The present study has some limitations. First, the association between these polymorphisms and the grade of hypertension was not investigated in this study because some medical records about hypertension of some patients were incomplete. Second, it is a study conducted in a single medical institution, there was inevitably selection bias as the population is not completely representative. Third, the association between common polymorphisms of *APOE* and *ALDH2* genes and hypertension was analyzed, but this study did not investigate the relationship between the full-length variation of these two genes, gene expression and the risk of hypertension. So studies with larger sample sizes and more gene–gene and polymorphism–polymorphism interactions are needed to study this relationship in middle-aged persons and elderly respectively in the future.

Conclusion

In this study, after adjusting gender, age, smoking, and alcohol consumption, we found: (1) *ALDH2* rs671 G>A polymorphism may decrease the risk of hypertension, while *ALDH2* rs671 A/A genotype combined with *APOE* rs429358 or rs7412 wild-type genotype may decrease the risk of hypertension; (2) elderly persons with *APOE* rs7412 T/T were more likely to have hypertension, but not middle-aged persons; (3) *ALDH2* rs671 G/A combined with *APOE* rs429358 T/C, *ALDH2* rs671 A/A combined with *APOE* rs7412 C/C may decrease the risk of hypertension in middle-aged adults, but not elderly adults.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The study was performed under the guidance of the Declaration of Helsinki and approved by the Ethics Committee of Meizhou People's Hospital, Meizhou Academy of Medical Sciences (Clearance No.: 2021-A-60).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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