

Correlation between Apolipoprotein E genetic polymorphism and atrial fibrillation

Huankun Lou

The Second People's Hospital of Lianyungang <https://orcid.org/0000-0003-2942-4918>

Lou Huankun

The Second People's Hospital of Lianyungang

Minglang Wang

The Second People's Hospital of Lianyungang

Liming Sun

The Second People's Hospital of Lianyungang

Yilian Wang (✉ 497857934@qq.com)

<https://orcid.org/0000-0002-7167-1958>

Research article

Keywords: Atrial Fibrillation; Apolipoprotein E; Gene; Polymorphism; Inflammatory mediators; Blood lipid; Correlation; Arteriosclerosis

Posted Date: October 14th, 2019

DOI: <https://doi.org/10.21203/rs.2.16004/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background We speculated that there was a correlation between apolipoprotein E (ApoE) genetic polymorphisms and the occurrence of atrial fibrillation (AF) based on the AF inflammatory mechanism. The high-risk alleles of ApoE were examined in patients with AF and controls to determine the distribution of genotype and allele frequencies. **Methods** From January 2017 to January 2019, 64 patients with AF in the department of cardiovascular medicine of the Lianyungang Second People's Hospital, and 49 healthy outpatient volunteers, were enrolled. ApoE gene polymorphisms were examined using allele-specific polymerase chain reaction. Statistical analyses were performed to identify high-risk ApoE alleles. **Results** A total of 113 patients were enrolled in this study. Among them, 64 patients were in the AF group (38 male and 26 female), with an average age of 74.38 ± 8.37 years. The control group consisted of 49 cases (29 male and 20 female), with an average age of 65.24 ± 12.14 years. The six ApoE phenotypes $\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$, $\epsilon 2/\epsilon 4$, $\epsilon 3/\epsilon 3$, $\epsilon 3/\epsilon 4$, and $4/\epsilon 4$ were observed in 0.9%, 13.2%, 2.7%, 58.4%, 19.5%, and 5.3%. The proportions of our study population with ApoE protective, general, and risk genotypes accounted for 14.1%–61.1%, and 24.8%, respectively. There was no statistically significant difference in ApoE gene polymorphism frequencies related to gender, height, weight, smoking status, hypertension, type 2 diabetes mellitus, and coronary heart disease ($P \geq 0.05$). There were significant differences in age, body mass index (BMI), larger left atrial diameter (LAD), and left ventricle ejection fraction (LVEF) ($P < 0.05$). The observed genotype frequencies were in Hardy–Weinberg equilibrium and were representative of the population. **Conclusion** There is a correlation between the ApoE genetic polymorphism and the occurrence of AF, and ApoE $\epsilon 4$ is a high-risk genotype for AF.

Background

Apolipoprotein E (ApoE) is plasma protein that plays an important role in regulating lipoprotein metabolism. *ApoE* is involved in lipid metabolism, oxidative stress, neuroimmunoregulation, and the inflammatory response^[1-2]. There are three polymorphic *ApoE* alleles ($\epsilon 2$, $\epsilon 3$, and $\epsilon 4$) and six genotypes can be formed^[3]. Some of these genotypes may be susceptible to hyperlipoproteinemia and arteriosclerosis (AS)^[4-5]. AS, cardiovascular, and cerebrovascular accident risk can be divided into three types with respect to *ApoE*. These are the *ApoE* protective ($\epsilon 2/\epsilon 2$ and $\epsilon 2/\epsilon 3$), popular ($\epsilon 2/\epsilon 4$ and $\epsilon 3/\epsilon 3$), and risk ($\epsilon 3/\epsilon 4$, $\epsilon 4/\epsilon 4$) genotypes^[6-8].

Atrial Fibrillation (AF) is one of the most common cardiac arrhythmias seen clinically. The mechanism of AF is very complicated. AF is closely related to old age, smoking^[9-10], hypertension, diabetes, metabolic syndrome, dyslipidemia, being overweight or obese, and various cardiovascular diseases^[11]. A large TARCS study in the United States found that elevated levels of lipids, especially LDL and cholesterol, increased the incidence of AF^[12]. *ApoE* is involved in all aspects of blood lipid metabolism, including the synthesis, secretion, transport, and metabolism of lipoprotein, and has significant effects on blood lipid metabolism^[13]. Therefore, it is likely that the *ApoE* gene is related to the occurrence of AF.

Inflammatory mediators including HS-CRP, IL-6, IL-8, TNF- α , TGF- β , and WBC are closely related to the occurrence and development of all types of AF^[14-16]. An earlier study of myocardial biopsies in healthy individuals and patients with AF demonstrated that the irreversibility of AF is associated with myocardial remodeling due to persistent inflammatory infiltration of cardiomyocytes^[17]. While *ApoE* has anti-inflammatory and anti-oxidative effects, *ApoE* $\epsilon 4$ has a strong proinflammatory effect^[18] and activates NF- κ B. Some studies show that NF- κ B is involved in the process of atrial remodeling^[19]. This further supports the hypothesis that *ApoE* is associated with AF. In this study, the association between *ApoE* genetic polymorphisms and AF was inferred based on the mechanisms of inflammation and lipid metabolism, and the *ApoE* allele representing a high AF risk was identified based on genotype and allele frequency distributions.

Methods

Patient population

Sixty-four patients (AF group) with AF (paroxysmal, persistent, long-term persistent, and permanent) and 49 healthy outpatients (control group) were randomly selected between January 2017 and January 2019 in the Department of Cardiovascular Medicine of the Lianyungang Second People's Hospital. There were 38 males and 26 females (mean age: 74.38 ± 8.37) in the AF group and 29 males and 20 females (mean age: 65.24 ± 12.14) in the control group.

Inclusion Criteria

The inclusion criteria were: clear ECG or Holter monitor data (absence of sinus P wave, presence of fast and irregular f wave, frequency 350-600 beats per minute, normal QRS complex shape and duration, and irregular R interval); clear clinical symptoms; a history of AF; and complete medical records and blood samples. This study was approved by the Medical Ethics Committee of the Second People's Hospital of Lianyungang (Grant no. L1618). All subjects signed an informed consent form.

Exclusion Criteria

The exclusion criteria were: serious infections; liver and kidney dysfunction; tumors; tuberculosis; metabolic syndrome; various major diseases affecting inflammatory factors and lipid metabolism; no complete medical history and blood samples; and failure to provide informed consent.

ApoE Polymorphism Test

Peripheral blood (4 ml) was extracted from fasting patients. The blood was extracted in the early morning into an EDTA anticoagulant blood vessel, and stored in the refrigerator at 4°C. All patient samples were sent to the unified medical examination center for ApoE gene polymorphism detection, and the test results were reported within 1 week.

Statistical analysis

All data were statistically analyzed using SPSS21.0 software. Measurement data was denoted by $\bar{x} \pm s$, and comparisons were made between two independent samples using an adapted t test. BMI measurements did not conform to normal distribution, and one-way ANOVA was used for comparison. The χ^2 test was used to compare the counting data. Multivariate conditional logistic regression analysis was used to comprehensively evaluate the relationship between various factors and AF. $P < 0.05$ was considered statistically significant.

Results

Table 1. General comparison data between AF and control groups

Number of cases	Gender (male: female)	Age (years)	height[cm]	body mass [kg]	BMI	Smoking [case (%)]	T2DM [case %]	Hypertension[case %]	Coronary Heart disease [case %]	LAD(mm)	LVEF(mm)
9	29:20	65.24	164.04±9.05	70.61	26.13±3.57	20	7	29[59.18%]	17	35.67	58.29
		±12.14		±11.19		[40.82%]	[14.19%]		[34.69%]	±4.54	±9.33
4	38:26	74.38	165.22	67.09	24.33±3.52	28	8	34[53.12%]	12	42.91	53.59
		±8.37	±8.28	±12.51		[43.75%]	[12.50%]		[18.75%]	±10.90	±9.59
	0.0004	4.733	0.721	1.551	507.6	0.098	0.116	0.413	3.698	4.365	2.612
					(F)						
	0.983	<0.000	0.472	0.123	0.000	0.754	0.733	0.520	0.545	0.001	0.010

Table 2 Hardy-Weinberg equilibrium test

The ApoE genotype and allele frequency distributions were in Hardy-Weinberg equilibrium ($P \geq 0.05$).

Table 2. Hardy-Weinberg equilibrium test

Group	Genotype						P
	$\epsilon 2/\epsilon 2$	$\epsilon 2/\epsilon 3$	$\epsilon 2/\epsilon 4$	$\epsilon 3/\epsilon 3$	$\epsilon 3/\epsilon 4$	$\epsilon 4/\epsilon 4$	
Group [n=49]							0.832 [Fisher]
Frequency	0	7	1	35	6	0	
theoretical	0.161	7.042	0.740	28.615	8.634	0.79	
Group [n=64]							0.626
Frequency	1	8	2	31	16	6	
theoretical	0.218	9.198	1.692	37.319	11.260	3.397	

Table 3 ApoE polymorphism distribution

The proportions of the six ApoE phenotypes ($\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$, $\epsilon 2/\epsilon 4$, $\epsilon 3/\epsilon 3$, $\epsilon 3/\epsilon 4$, and $\epsilon 4/\epsilon 4$) in the two groups were 0.9%, 13.2%, 2.7%, 58.4%, 19.5%, and 5.3%, respectively. The proportion of ApoE protected, popular, and risk genotypes were 14.1%, 61.1%, and 24.8%, respectively.

Table 3. ApoE polymorphism distribution

Group	Protected genotype		Popular genotype		Risk genotype		Summation[n(%)]
	$\epsilon 2/\epsilon 2$	$\epsilon 2/\epsilon 3$	$\epsilon 2/\epsilon 4$	$\epsilon 3/\epsilon 3$	$\epsilon 3/\epsilon 4$	$\epsilon 4/\epsilon 4$	
AF Group	0	7	1	35	6	0	49(60.5%)
Control Group	1	8	2	31	16	6	64(39.5%)
P							0.037 [Fisher]
Summation[n(%)]	1(0.9%)	15(13.2%)	3(2.7%)	66(58.4%)	22(19.5%)	6(5.3%)	113(100%)

Table 4 ApoE genotype distribution in the AF and control groups

ApoE gene phenotype in both groups was dominated by ApoE3, but ApoE4 gene phenotype in the atrial fibrillation group was significantly increased compared with the control group, and the distribution of ApoE gene phenotype in the two groups was statistically significant. Furthermore, there was a significant difference in ApoE phenotype distribution between the two groups (P = 0.05).

Table 4. ApoE genotype distribution

Phenotype	ApoE2	ApoE3	ApoE4
Control Group	7	36	6
AF Group	9	33	22
Frequency[%]	14.1	61.1	24.8
P [C ²]	0.022 [7.667]		

Table 5 Regression analysis of AF correlative factors

Age, BMI, LVEF, ApoE ϵ 2, and ApoE ϵ 4 were identified as AF risk factors .

Table 5. Regression analysis of correlative factors of AF

Risk Factor	<i>B</i>	<i>S.E.</i>	<i>P</i>
Age	-.051	.003	.001
BMI	.192	.009	.002
LAD	-.172	.006	.006
LVEF	.039	.003	.001
ApoEε2	-	-	.000
ApoEε3	-21.322	968.654	.982
ApoEε4	-.625	.072	.000

Discussion

ApoE is mainly expressed in the liver and brain and is an indispensable lipoprotein in physiological functions. The most important function of *ApoE* is to act as a ligand for the LDL receptor. After binding to the LDL receptor, *ApoE* enters liver cells for lipid metabolism and regulates lipid levels in the blood and brain. Anne et al.^[20-21] reported that the occurrence and duration of AF may be related to electrical and structural remodeling induced by electro-mechanical feedback. Their results showed that *ApoE* activates NF-κB and induces the expression of monocyte chemoattractant protein-1 (MCP-1), TNF-α, IL-1β, and IL-10^[16]. In turn, MCP-1 induces IL-1, IL-6, and TNF-α expression in cardiomyocytes. This causes negative inotropic action in the heart, reduces heart function, and causes heart muscle structure reconstruction^[24-25]. Furthermore, TNF-α may increase Ca²⁺ concentration in cardiac myocytes^[22] and the downregulation of L-type calcium (I_{Ca-L}) channels leads to the shortening of action potential duration and the effective refractory period, and the formation of multiple reentry loops. At the same time, Ca²⁺ overload activates Ca²⁺-activated proteins, which can degrade cardiac contractile proteins such as troponin and lead to decreased atrial contractile function^[23]. This can then cause atrial fibrosis, and further lead to abnormal intra-atrial impulse conduction and induced electrical remodeling of the atrium. This suggests an association between AF and the *ApoE* gene.

Our results showed no significant differences in sex, height, body mass, smoking status, hypertension, type 2 diabetes mellitus, and CHD between the AF and control groups ($P \geq 0.05$). We also observed no sex difference in the *ApoE* gene frequency^[26]. Significant differences in age, BMI, LAD, and LVEF ($P \leq 0.05$) were observed between the two groups. These results suggest that the risk of AF increases with increasing age. Moreover, these results indicate that higher BMIs lead to a larger LAD and lower ejection fraction (EF) and higher incidence of AF. Old age is an independent risk factor for AF^[27-28]. People with a high BMI may have a greater amount of body fat, which increases the prevalence of AF. The changes in LAD and EF caused by organic heart disease enlarges the atrium and changes its special structure. However, whether AF first affects the LAD or whether heart disease first increases the LAD, leading to AF, requires further research.

The distribution of the six *ApoE* phenotypes was uneven in the general population. The frequency of the *ApoEε3* genotype was the highest, reaching more than 60%. Six phenotypes including ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, and ε4/ε4 were detected in 113 *ApoE* genotyping subjects. The frequency of ε3/ε3 was the highest, ε3/ε4 was the second most common, and ε2/ε2 was the least common. The distribution of the *ApoEε3* genotype frequency in this study was 61.1%, accounting for more than half of the total. This was similar to that reported previously^[29]. The risk of coronary heart disease, Alzheimer's disease, and stroke was normal for patients with the *ApoEε3* phenotype, low for those with the *ApoEε2* phenotype, and highest for those with the *ApoEε4* phenotype. In this study, subjects with *ApoE* protective, general and risk genotypes were measured in the two groups, accounting for 14.1%, 61.1% and 24.8%, respectively. Among them, subjects with ε4 phenotype were 24.8%, which were high risk groups. Compared with those in the control group, there were slightly fewer patients with the *ApoEε3* genotype and significantly more with the *ApoEε4* genotype in the AF group. These results suggest that expression of the *ApoEε4* genotype is related to AF.

Previous studies have shown that obesity is a risk factor for AF. This may be related to oxidative stress, inflammation, and other factors caused by abnormal lipid metabolism in obese individuals, which may lead to myocardial fibrosis atrial remodeling followed by AF^[30]. Some studies suggest that *ApoEε4* is one cause of hyperlipidemia^[31]. The association between obesity and hyperlipidemia may indirectly indicate that *ApoEε4* is a high risk factor for AF.

Here, we have shown that the risk factors of AF include age, BMI, LAD and LVEF. It is not clear whether *ApoE* genotype and allele frequency distribution are related to AF. We hypothesize that *ApoEε4* may play a role in the development of AF, and many of the results

presented here suggest that *ApoEε4* gene plays an important role in the development of AF. A large number of studies have shown that atrial fibrillation can be caused in part by dyslipidemia, overweight or obesity, and inflammatory infiltration [11,17]. If we can establish the relationship between the *ApoE* gene and AF and intervene at the gene level, it will be of great practical significance for the prevention and treatment of AF.

The disadvantages of this study are the limited sample size and the lack of large-scale and multi-region sampling. Moreover, all blood samples were tested externally, and the entire process of sample preservation, transportation, and detection was not able to be monitored.

Abbreviations

ApoE: apolipoprotein E; AF: atrial fibrillation; BMI: body mass index; LAD: left atrial diameter; LVEF: left ventricle ejection fraction; AS: arteriosclerosis; MCP-1: monocyte chemoattractant protein-1.

Declarations

Acknowledgements

We thank Rebecca Porter, PhD, from Liwen Bianji, Edanz Editing China (www.liwenbianji.cn/ac), for editing the English text of a draft of this manuscript.

Funding

High-level Health Personnel "Six one Project" top Talent Scientific Research Project of Jiangsu Province [LGY2017065]; "Six Talent Peak" High-Level Talent Selection and Training Project of Jiangsu Province (WSN-247); Science and Technology Project of Jiangsu Province (SH1618).

Availability of data and materials

The data that support the findings of this study are available from The Second People's Hospital of Lianyungang.

Authors' contributions

WYL and SLM were involved in the study concept and design. LHK, WLQ, DZ, CRY, and TSJ were involved in the field study and data acquisition. WYL, WML, and LHK were involved in the analysis and interpretation of the data. WYL, WML, and LHK were involved in the drafting of manuscript. WYL and SLM were involved in the critical revision of manuscript. All authors have read and approved the manuscript.

Ethics approval and consent to participate

This study was approved by the institutional review board ethical committee (The Second People's Hospital of Lianyungang Ethics Committee No L1618).

Consent for publication

Not applicable.

Competing interests

The authors declare they have no competing interests.

References

- [1] Zerche M, Weissenborn K, Ott C, et al. Preexisting serum autoantibodies against the NMDAR subunit NR1 modulate evolution of lesion size in acute ischemic stroke [J]. *Stroke*, 2015, 46(5):1180-1186. DOI:10.1161/strokeaha.114.008323.
- [2] Herz J, Sabellek P, Lane TE, et al. Role of neutrophils in exacerbation of brain injury after focal cerebral ischemia in hyperlipidemic mice [J]. *Stroke*, 2015, 46(10):2916-2925. DOI:10.1161/strokeaha.115.010620.
- [3] Lagos J, Zambrano T, Rosales A, et al. ApoE Poly-morphisms contribute to reduced atorvastatin response in Chilean Amerindian subjects [J]. *Int J Mol Sci*, 2015, 16(4):7890-7899. DOI:10.3390/ijms16047890.
- [4] Toops K A, Tan L X, Lakkaraju A. Apolipoprotein E isoforms and AMD [J]. *Adv Exp Med Biol*, 2016, 24(1):1-10. DOI:10.1007/978-3-319-17121-0_1.
- [5] Ellulu M S, Patimah I, Khazaal H, et al. Atherosclerotic cardiovascular disease: a review of initiator and protective factors [J]. *Inflammopharmacology*, 2016, 24(1):1-10. DOI:10.1007/s10787-015-0255-y.
- [6] Liu C-C, Kanekiyo T, Xu H, et al. Apolipoprotein E and Alzheimer disease: risk, mechanisms, and therapy [J]. *Nature reviews Neurology*, 2013, 9(2):106-118. DOI:10.1038/nrneurol.2013.32.
- [7] Baptista R, Rebelo M, Decqmot J, et al. Apolipoprotein E epsilon-4 polymorphism is associated with younger age at referral to a lipidology clinic and poorer response to lipid-lowering therapy [J]. *Lipids Health Dis*, 2011, 10(1):48. DOI:10.1186/1476-511x-10-48.
- [8] Chasman D I, Giulianini F, Macfadyen J, et al. Genetic determinants of statin-induced low-density lipoprotein cholesterol reduction: the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial [J]. *Circulation Cardiovascular genetics*, 2012, 5(2):257-264. DOI:10.1161/circgenetics.111.961144.
- [9] Chamberlain AM, Agarwal SK, Folsom AR, et al. Smoking and incidence of atrial fibrillation—results from the Atherosclerosis Risk in Communities (ARIC) study [J]. *Heart Rhythm* 2011; 8(8):1160-1166. DOI:10.1016/j.hrthm.2011.07.011.
- [10] Suzuki S, Sagara K, Otsuka T, et al. Effects of smoking habit on the prevalence of atrial fibrillation in Japanese patients with special reference to sex differences [J]. *Circ J* 2013; 77(12):2948-2953. DOI:10.1253/circj.CJ-13-0446.
- [11] Shinya Suzuki. "Cholesterol Paradox" in Atrial Fibrillation. *Circulation Journal*, 2011, 75:2749-2750. DOI:10.1253/circj.CJ-11-1134.
- [12] Faye L, Lopez, Sunil K, Agarwal, Richard F, MacLehose, et al. Blood Lipid Levels, Lipid-Lowering Medications, and the Incidence of Atrial Fibrillation The Atherosclerosis Risk in Communities Study. *Circ Arrhythm Electrophysiol*. 2012, 5:155-162. DOI:10.1161/circep.111.966804.
- [13] Vaarhorst AA, Beekman M, Suchiman EH, et al. Lipid metabolism in long-lived families: the Leiden Longevity Study [J]. *Age (Dordr)*, 2011, 33(2):219-227. DOI:10.1007/s11357-010-9172-6.
- [14] Sokal A, Wojcik S, Pruszkowska P, et al. Ferritin as a potential biomarker of efficacy of treatment of atrial fibrillation—preliminary report [J]. *Postepy Hig Med Dosw (Online)*, 2017, 71(0):876-880. DOI:10.5604/01.3001.0010.5267.
- [15] Hermida J, Lopez FL, Montes R, et al. Usefulness of high-sensitivity C-reactive protein to predict mortality in patients with atrial fibrillation (from the Atherosclerosis Risk In Communities [ARIC] Study) [J]. *Am J Cardiol*, 2012, 109(1):95-99. DOI:10.1016/j.amjcard.2011.08.010.
- [16] Huebbe P, Lodge JK, Rimbach G. Implications of apolipoprotein E genotype on inflammation and vitamin E status [J]. *Mol Nutr Food Res*. 2010, 54(5):623-630. DOI:10.1002/mnfr.200900398.

- [17] Frustaci A,Chimentc C,Bellocci F,et al.Histological substrate of atrial biopsies in patients with lone atrial fibrillation[J].Circulation,1997,96:1180-1184.DOI:10.1161/01.cir.96.4.1180.
- [18] Hall G,Hasday J D,Rogers T B.Regulating the regulator:NF-κB signaling in heart[J].J Mol Cell Cardiol,2006,41(4):580-591.DOI:10.1016/j.yjmcc.2006.07.006.
- [19] Jofre-Monseny L,Minihane AM,Rimbch G.Impact of ApoE genotype on oxidative stress,inflammation and disease risk[J].Mol Nutr Food Res,2008,52(1):131-145.DOI:10.1002/mnfr.200700322
- [20] Stanley A,Masahide H.Atrial remodeling and atrial fibrillation [J].J Am Coll Cardiol,2014,63(22):2336-2344.DOI:10.1016/j.jacc.2014.02.555.
- [21] Rodriguez-Rodriguez Luis, Gonzalez-Juanatey Carlos, Garcia-Bermudez Mercedes, et al. CCR5Δ32 variant and cardiovascular disease in patients with rheumatoid arthritis: a cohort study. [J]Arthritis Res Ther. 2011;13(4):R133.DOI:10.1186/ar3444.
- [22] Brundel BJ, Ausma J, Van Gelder IC, et al. Activation of proteolysis by calpains and structural changes in human paroxysmal and persistent atrial fibrillation [J]. Cardiovasc Res 2002;54(2):380-389. DOI:10.1016/s0008-6363(02)00289-4.
- [23] Peng B. Progress of Relationship Between Monocyte Chemoattractant Protein-1 and Heart Failure [J]. ADVANCES IN CARDIOVASCULAR DISEASES, 2007, 28(4):570-572.
- [24] Damas JK, Aukrust P, Ueland T, et al. Monocyte chemoattractant protein-1 enhances and interleukin-10 suppresses the production of inflammatory cytokines in adult rat cardiomyocytes [J]. Basic Res Cardiol, 2001, 96(5):345-352. DOI:10.1007/s003950170042
- [25] Peng C, Ma YP, Wang J, et al. Analyze the relationship between atrial fibrillation and plasma Mononuclear cells or cardiac function [J]. Chongqing Medicine, 2014, 43(20):2589-2591.
- [26] Liu JF, Ma HS, Li F. Correlation between ApoE gene polymorphism and lipid metabolism [J]. Chinese Journal of Gerontology, 2012, 32(9):1802-1804.
- [27] Canestaro WJ, Brooks DG, Chaplin D, et al. Statin pharmacogenomics: opportunities to improve patient outcomes and healthcare costs with genetic testing. [J] J Pers Med 2015;2(4):158-174. DOI:10.3390/jpm2040158.
- [28] Chai YL, Yeo HK, Wang J, et al. Apolipoprotein varepsilon4 is Associated with Dementia and Cognitive Impairment Predominantly Due to Alzheimer's Disease and Not with Vascular Cognitive Impairment: A Singapore-Based Cohort [J]. J Alzheimers Dis, 2016, 51(4):1111-1118.
- [29] Hanh NTH, Nhung BT, Dao DTA, et al. Association of apolipoprotein E polymorphism with plasma lipid disorders, independent of obesity-related traits in Vietnamese children [J]. Lipids Health Dis, 2016, 15(1):176. DOI:10.1186/s12944-016-0349-6.
- [30] Farnaz A, Marcia LS, Elena SB, et al. Obesity, physical activity, and their interaction in incident atrial fibrillation in postmenopausal women [J]. J Am Heart Assoc, 2014, 3:e001127. DOI:10.1161/jaha.114.001127.
- [31] Torres-Perez E, Ledesma M, Garcia-sobrevielam P, et al. Apolipoprotein E4 association with metabolic syndrome depends on body fatness [J]. Atherosclerosis, 2016, 245(1):35-42. DOI:10.1016/j.atherosclerosis.2015.11.029.