A nonlinear relationship between low-density-lipoprotein cholesterol levels and atrial fibrillation among patients with hypertension in China

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Background: The association between low-density-lipoprotein cholesterol (LDL-C) and atrial fibrillation (AF) in hypertensive population remains controversial. Therefore, we explored the relationship between LDL-C and AF among patients with hypertension in a Chinese community.

Methods: This is a retrospective cross-sectional study that enrolled 7,808 hypertensive patients between January 2013 and December 2013 in Guangdong, China. AF was diagnosed by 12-lead electrocardiogram (ECG) or self-reported status. LDL-C value were categorized by quartiles. Univariate and multivariate logistic regression were performed to examine the relation between LDL-C and AF. LDL-C values were expressed in continuous (every 1 mg/dL increment) or categorical variables in each regression model.

Results: Among 7,808 (47.1% man, with mean age 62.3 years) participants, 78 AF cases were identified. In multivariate logistic regression, when LDL-C was presented as continuous variable, it was inversely associated with the occurrence of new onset AF (OR =0.99, 95% CI: 0.98, 1.00; P=0.018). Meanwhile, when LDL-C was presented as categorical variable, the negative association between LDL-C and AF was attenuated after adjusting for confounders. Adjusted restricted cubic spline demonstrated a non-linear correlation between LDL-C and AF.

Conclusions: Lower levels of LDL-C was associated with increased incidence of AF in a Chinese community hypertensive population.

Keywords: Atrial fibrillation (AF); hypertension; low-density-lipoprotein cholesterol

Introduction

Hypertension is one of the most common chronic diseases in worldwide (1). In China, 23.2% (approximately 244.5 million) of the adult population has hypertension (2).

Elevated blood pressure can lead to numerous target organs damage and related complications such as heart failure, stroke, chronic kidney disease, and death (3). Meanwhile, atrial fibrillation (AF) as a common complication of

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hypertension (4), which can cause cardiovascular events such as stroke (5,6). The estimated number of individuals with AF in the world was 33.5 million in 2010 (7). In a large cohort prospective study that included 34,221 initially healthy women. After 12.4 years of follow up, 644 incident of AF events occurred and demonstrated blood pressure (BP) was strongly associated with a higher risk of AF (8). Similar result was found in another study with 35 years of follow-up that included 2014 initially healthy men, systolic BP ≥140 mmHg had 1.6-fold (95% CI: 1.15–2.21) risk of AF compared with those with systolic BP <128 mmHg (9).

However, the mechanism of AF remains unclear now. A large number of previous studies have shown that AF was a multifactorial disease, and demonstrated that gender, race, obesity, and high density lipoprotein cholesterol (HDL-C) were all closely related to AF (4,10-12). Previous studies also manifested AF was closely associated with inflammatory response and oxidative stress (13-15). Low-density-lipoprotein cholesterol (LDL-C) was also reported to be related to inflammatory and oxidative stress (16,17). Meanwhile, several studies have identified that LDL-C had negative association with AF (18,19), and some identified null association. (20).

In brief, the epidemiological evidence on the association between LDL-C and the risk of AF is still inconsistent (18-21), especially among people with hypertension. Therefore, we investigated the relationship between LDL-C and AF in a group of hypertensive patients in China. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/apm-20-451).

Methods

Study population and design

This was a cross-sectional study in one Chinese community. The population cohort comprised of 8,169 hypertensive patients aged ≥18 years old, who were attending annual physical examinations in the community health care center in Liaobu, Guangdong, China. Participants were consecutively enrolled during January 2013 and December 2013. All enrolled participants were diagnosed with essential hypertension and had complete sets of data. The participants who were did not provide data of BP (n=38), blood lipid (n=245), serum creatinine (n=255), demographic features (n=45), or data of electrocardiograph (ECG) (n=71) were excluded (*Figure 1*). Finally, 7,808 subjects were included
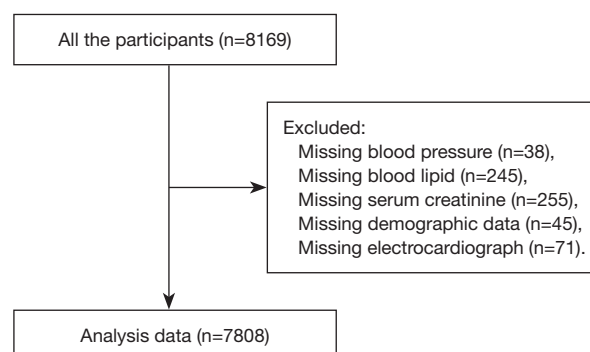

Figure 1 The flowchart of selecting participants for analysis.

in the data analysis. The study was in compliance with the principles outlined in the Declaration of Helsinki (as revised in 2013) and was approved by the institutional medical ethical committee (NO. GDREC2012143H). Written informed consent was obtained from all participants.

Measurement of covariates

At baseline, a structured questionnaire was administered by trained study personnel to acquire demographic characteristics, including demographic data, medical history [beta-blockers, calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACEI)/ angiotensin-receptor blockers (ARB), statins), and medical history (coronary heart disease (CAD), diabetes mellitus (DM), stroke]. Parameters for physical measurements included systolic BP (SBP), diastolic BP (DBP), and body mass index (BMI). Blood samples were collected after at least 8 hours of fasting. Fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), LDL-C, HDL-C was measured using standardized laboratory methods. Hypertension was defined as SBP ≥140 mmHg, and/ or DBP ≥90 mmHg, and/or the use of antihypertensive medicine within 2 weeks, with reference to 2010 Chinese guidelines for the management of hypertension (2). ECG was standard resting 12-lead recordings at a paper speed of 50 mm/s and a calibration of 1 mV per 10 mm and were collected from all subjects at the baseline. Participants were considered to have AF if AF rhythm have been captured in ECG. AF rhythm was defined as (I) irregular R-R intervals, (II) absence of distinct repeating P waves, (III) irregular atrial activity show on ECG, according to 2014 ACC/AHA/ HRS Guideline for the Management of Patients With Atrial Fibrillation (4). Left ventricular hypertrophy (LVH)

was defined as Cornell criteria (S-wave in V3 and R-wave in aVL >24 mm in men, and S in V3 and R in aVL >20 mm in women) and the Sokolow-Lyon criteria (tallest R wave in V5 or V6 and S-wave in V1 >35 mm) with or without concomitant strain pattern (T-wave inversion in lateral leads) (22). All ECG results were identified and diagnosed by qualified practitioners. Estimated glomerular filtration rate (eGFR) was calculated from the simplified MDRD equation (23).

Statistical analysis

Continuous variables were expressed as means ± standard deviations, while categorical variables were presented as absolute values and percentages. One-way ANOVA, Kruskal-Wallis H test and chi-square test were performed to determine any significant subgroup differences According to LDL-C levels in quartile (Q1, Q2, Q3, Q4). Univariate and multivariate logistic regression were performed to evaluate the association between LDL-C and AF, and the results were reported as odds ratio (OR) with 95% confidence intervals (CI). LDL-C values were treated as both continuous (every 1 mg/dL increment) or categorical variables in different regression models. Model 1 only included LDL-C values. Model 2 was adjusted for age, sex and SBP. Meanwhile, Model 3 was adjusted for age, eGFR, sex, diabetes, CAD, SBP, smoking, drinking, FBG, TC, TG, LDL-C, HDL-C, antihypertensive drugs and statin. To visualize the relationship between LDL-C and AF, we fitted restricted cubic spine by adjusting for potential confounders. A two-tailed P value less than 0.05 was considered as significant. Data management and analyses were performed using the statistical software package R version 3.32 (http://www.R-project.org, The R Foundation, Vienna, Austria).

Results

Baseline characteristics

Baseline characteristics for participants were summarized in *Table 1*. The present analysis included 7,808 participants, including 3,678 men (47.1%). The average age was 62.3±13.7 years. A total of 78 AF cases were identified, including 42 men (53.8%) and average age were 72.3±11.3 years. Participants with AF were older, had higher prevalence of CAD and had lower levels of LDL-C, TG and TC compared to those without AF (all P<0.05).

The statin usage was significantly higher in AF group than in non-AF group.

Table 2 showed baseline characteristics according to LDL-C quartiles (Q1: LDL-C <78.9 mg/dL, Q2: 78.9–96.6 mg/dL, Q3: 96.6–115.6 mg/dL, Q4: ≥115.6 mg/dL). Each group had 1,952 subjects. We found that age, sex, SBP, DBP, BMI, eGFR, TC, TG, HDL-C, diabetes, CAD, stroke and statin consumption were significantly different among four LDL-C groups (all P<0.05). However, there was no statistically significant difference in smoking, drinking, FBG, LVH among four groups (all P>0.05).

The association between LDL-C and AF

As shown in *Table 3*, LDL-C (OR =0.99, 95% CI: 0.98, 0.99, P=0.001), SBP (OR =0.96, 95% CI: 0.94, 0.98, P=0.001), TC (OR =0.99, 95% CI: 0.98, 1.0, P=0.001), TG (OR =1.0, 95% CI: 0.99,1.00, P=0.009) were negatively associated with AF. Meanwhile, without taking statin (OR =2.06, 95% CI: 1.24, 3.40, P<0.01) was positively associated with the incident of AF. In addition, the multivariate logistic regression demonstrated LDL-C was still significantly inversely with AF (OR =0.98, 95% CI: 0.97, 1.00; P=0.045).

The non-linear relationship between LDL-C and AF

As shown in *Table 4*, when LDL-C was presented as a continuous variable, it was inversely associated with AF in all regression models (Model 1: OR: 0.99, 95% CI: 0.98–0.99; Model 2: OR: 0.99, 95% CI: 0.98–0.99; Model 3: OR: 0.99, 95% CI: 0.98–1.00; all P<0.05). When LDL-C was presented as categorical variable, when using Q1 as reference, the OR was 0.51 (95% CI: 0.28–0.92) for Q2, 0.33 (95% CI: 0.17–0.65) for Q3, and 0.51 for Q3 (95% CI: 0.28–0.92) (P<0.05) in model 1. However, after fully adjusted for potential confounding factors, Q2 and Q4 had no significant statistical association with AF (P>0.05), but Q3 was negatively related with AF (OR: 0.40, 95% CI: 0.20–0.81, P=0.011) in model 3. To better demonstrate the relation between LDL-C and AF, we fitted the restricted cubic spline for LDL-C, and a non-linear relationship was found after adjusting for multiple confounders (*Figure 2*).

Discussion

In the present study, we found that LDL-C was inversely associated with AF. Interestingly, when LDL-C was

Table 1 Baseline characteristics of participant patients

	Total	Non-AF	AF	P value
Number	7,808	7,730	78	
Age (y)	62.28±13.69	62.18±13.67	72.28±11.51	<0.001
Male (n, %)	3,678 (47.11%)	3,636 (47.04%)	42 (53.85%)	0.231
SBP (mmHg)	130.65±15.85	130.70±15.86	125.90±14.38	0.008
DBP (mmHg)	80.58±10.02	80.61±10.04	76.92±8.18	0.001
BMI (kg/m^2)	24.90±3.95	24.90±3.96	24.61±3.88	0.515
FBG (mmol/L)	5.14±1.61	5.14±1.61	5.08±1.63	0.770
eGFR (mL/min/1.73 m^2)	105.75±49.29	105.89±49.42	91.73±30.94	0.012
TC (mg/dL)	201.15±44.82	201.34±44.79	182.33±45.01	<0.001
TG (mg/dL)	162.46±140.21	162.83±140.63	125.47±82.31	0.019
LDL-C (mg/dL)	98.37±28.33	98.48±28.32	87.61±27.08	<0.001
HDL-C (mg/dL)	48.67±14.30	48.68±14.34	48.39±9.89	0.861
Smoking (n, %)	2,076 (26.59%)	2,055 (26.58%)	21 (26.92%)	0.946
Drinking (n, %)	1,053 (13.49%)	1,048 (13.56%)	5 (6.41%)	0.066
Diabetes (n, %)	1,506 (19.29%)	1,493 (19.31%)	13 (16.67%)	0.555
CAD (n, %)	244 (3.12%)	232 (3.00%)	12 (15.38%)	<0.001
LVH (n, %)	239 (3.06%)	236 (3.05%)	3 (3.85%)	0.686
Stroke (n, %)	282 (3.61%)	278 (3.60%)	4 (5.13%)	0.471
Anti-hypertension drugs (n, %)	4,312 (55.23%)	4,264 (55.16%)	48 (61.54%)	0.260
Beta-blocker (n, %)	637 (8.16%)	619 (8.01%)	18 (23.08%)	<0.001
CCB (n, %)	2,463 (31.54%)	2,438 (31.54%)	25 (32.05%)	0.923
ACEI/ARB (n, %)	3,367 (43.12%)	3,334 (43.13%)	33 (42.31%)	0.884
Statin (n, %)	1,196 (15.32%)	1,175 (15.20%)	21 (26.92%)	0.004

Data are expressed as mean ± standard deviation or percentage. AF, atrial fibrillation; CAD, coronary heart disease; LVH, left ventricular hypertrophy; CCB, calcium channel blockers; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; eGFR, estimated glomerular filtration.

presented as categorical variables, the negative association between LDL-C and AF was attenuated.

It has been demonstrated in a secondary analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) which included 14,837 participants. They found that LDL-C was lower in the participants with AF/atrial flutter (AFL) group than the group without AF/AFL (P<0.001) (24). Our results also indicted that AF patients have lower LDL-C compared to patients without AF. Although AFL was not measured in the present study, the results are still consistent because the

prevalence of AFL is much lower than that of AF (25).

In our analysis, the inverse association between LDL-C and AF was independent of multiple risk factors. Similar result was found in the Atherosclerosis Risk in Communities Study (ARIC) (26). When compared to LDL-C level <2.59 mmol/L (100.15 mg/dL), people with LDL-C level ranged 2.59–4.13 mmol/L (100.15–159.71 mg/dL) had lower risk of AF (HR =0.84, 95% CI: 0.72–0.97). Also, a prospective cohort study in Kailuan, China, suggested that LDL-C >110 mg/dL was inversely associated with AF (HR =0.60, 95% CI: 0.43–0.83). However, participants

Table 2 Baseline characteristics of participant patients by LDL-C quartiles

	Q1: <78.9 mg/dL	Q2: 78.9–96.6 mg/dL	Q3: 96.6–115.6 mg/dL	Q4: ≥115.6 mg/dL	P value
Number	1,952	1,952	1,952	1952	
Age (y)	61.85±14.51	60.97±14.08	62.70±13.50	63.58±12.43	<0.01
Male (n, %)	975 (49.95%)	947 (48.51%)	927 (47.49%)	829 (42.47%)	<0.01
SBP (mmHg)	129.37±15.43	130.30±15.94	131.07±15.95	131.86±15.96	<0.01
DBP (mmHg)	79.67±9.82	80.81±10.10	80.84±10.25	80.97±9.87	<0.01
BMI (kg/m^2)	24.92±4.02	24.72±3.85	24.84±3.99	25.12±3.94	0.01
FBG (mmol/L)	5.18±1.61	5.15±1.79	5.08±1.46	5.13±1.57	0.28
eGFR (mL/min/1.73 m^2)	109.36±56.72	108.35±45.52	104.77±46.28	100.49±47.35	<0.01
TC (mg/dL)	157.15±32.31	187.81±24.17	210.58±27.42	249.06±34.05	<0.01
TG (mg/dL)	178.43±174.82	162.17±140.88	156.69±122.95	152.55±112.94	<0.01
LDL-C (mg/dL)	64.90±11.62	88.00±4.99	105.34±5.49	135.23± 19.61	<0.01
HDL-C (mg/dL)	47.09±14.72	48.05±12.01	48.90±13.91	50.65±16.04	<0.01
Smoking (n, %)	517 (26.49%)	531 (27.21%)	539 (27.61%)	489 (25.05%)	0.28
Drinking (n, %)	269 (13.78%)	278 (14.24%)	264 (13.53%)	242 (12.40%)	0.38
Diabetes (n, %)	466 (23.87%)	382 (19.57%)	330 (16.91%)	328 (16.81%)	<0.01
CAD (n, %)	110 (5.64%)	53 (2.72%)	45 (2.30%)	36 (1.84%)	<0.01
AF (n, %)	33 (1.69%)	17 (0.87%)	11 (0.56%)	17 (0.87%)	<0.01
LVH (n, %)	70 (3.59%)	51 (2.61%)	68 (3.48%)	50 (2.56%)	0.11
Stroke (n, %)	109 (5.59%)	58 (2.97%)	63 (3.23%)	52 (2.66%)	<0.01
Anti-hypertension drugs (n, %)	1,231 (63.06%)	1,104 (56.56%)	1,029 (52.72%)	948 (48.57%)	<0.001
Statin (n, %)	515 (26.38%)	298 (15.27%)	231 (11.83%)	152 (7.79%)	<0.01

Data are expressed as mean ± standard deviation or percentage. SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; FBG, fasting blood glucose; eGFR, estimated glomerular filtration; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; CAD, coronary heart disease; AF, atrial fibrillation; LVH, left ventricular hypertrophy; CCB, calcium channel blockers; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers.

LDL-C ≤110 mg/dL did not have significantly higher risk for AF (19).

Moreover, an analysis on the Multi-Ethnic Study of Atherosclerosis (MESA) and the Framingham Heart Study (FHS) showed that LDL-C was not associated with the risk of AF (MESA: HR =1.15, 95% CI: 0.99–1.35; FHS: HR =0.95, 95% CI: 0.82–1.09; combined: HR =1.04, 95% CI: 0.94–1.15) in the fully adjusted model (20). The regional and ethnical difference may account for the inconsistent findings. In addition, confounders being adjusted may not be the same across studies.

Although the exact mechanisms between LDL-C and AF remains unresolved, several mechanisms may help to explain the inverse association. First, some researchers

considered that high levels of LDL-C might have an anti-inflammatory effect (27,28), and AF was closely associated with inflammatory reaction (15). Low level of LDL-C probably contributes to the pathogenesis of AF via enhancing inflammatory response. Second, membrane lipid composition is the main determinant of cell excitability, previous vitro studies have identified that cholesterol regulates the function of ion channels, such as Kv1.5 K+ channel, Na+ channel in myocardial cell. Lowered cholesterol levels reduce cell excitability which might be potentially contributing to the development of AF (29,30). Third, subclinical hyperthyroidism decreases LDL-C (31) and is also associated with increased risk of AF (32). In addition, a latest article purposed the concept

Table 3 Univariate and multivariate logistic regression for the relationship between clinical variables and AF

	Univariate, OR (95% CI), P value	Multivariate, OR (95% CI), P value
Age	1.07 (1.05, 1.09), <0.0001	1.07 (1.05, 1.09), <0.0001
Gender		
Male	1.0	1.0
Female	0.76 (0.49, 1.19), 0.232	0.52 (0.30, 0.91), 0.022
Smoking		
No	1.0	1.0
Yes	1.02 (0.62, 1.68), 0.946	0.74 (0.40, 1.40), 0.359
Drinking		
No	1.0	1.0
Yes	0.44 (0.18, 1.08), 0.074	0.52 (0.20, 1.35), 0.177
Diabetes		
No	1.0	1.0
Yes	0.84 (0.46, 1.52), 0.556	0.85 (0.45, 1.60), 0.616
LVH		
No	1.0	1.0
Yes	1.27 (0.40, 4.06), 0.687	0.97 (0.30, 3.17), 0.959
Statin		
Yes	1.0	1.0
No	2.06 (1.24, 3.40), 0.005	1.58 (0.92, 2.74), 0.100
Antihypertensive drugs		
Yes	1.0	1.0
No	1.30 (0.82, 2.06), 0.261	1.44 (0.86, 2.42), 0.168
SBP (mmHg)	0.96 (0.94, 0.98), 0.001	1.01 (0.98, 1.04), 0.656
BMI (kg/m^2)	0.98 (0.93, 1.04), 0.515	1.06 (1.00, 1.12), 0.061
TC (mg/dL)	0.99 (0.98, 1.00), 0.001	1.00 (0.99, 1.01), 0.505
TG (mg/dL)	1.00 (0.99, 1.00), 0.009	1.00 (0.99, 1.00), 0.102
LDL-C (mg/dL)	0.99 (0.98, 0.99), 0.001	0.98 (0.97, 1.00), 0.045
HDL-C (mg/dL)	1.00 (0.98, 1.02), 0.860	1.00 (0.98, 1.02), 0.777

AF, atrial fibrillation; CAD, coronary heart disease; LVH, left ventricular hypertrophy; Beta, beta-blockers; CCB, calcium channel blockers; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; FBG, fasting blood glucose; eGFR, estimated glomerular filtration; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.

of cardiac lipotoxicity in which heart tissue uptake increased lipoproteins, therefore the circulatory lipids may be reduced. The imbalance of lipids distribution among tissue and circulation may be another explanation for the paradoxical relation between LDL-C and AF (33).

Some limitations should be considered when interpreting our findings. First, this was a cross-sectional study, which indicate correlation but not causation. Second, in the present study, AF was diagnosed by ECG at the baseline but not by the 24 hours ECG, which might miss out

Table 4 The results of two-piecewise linear regression model between LDL-C and AF

	Model I, OR (95% CI), P value	Model II, OR (95% CI), P value	Model III, OR (95% CI), P value
LDL-C (every 1 mg/dL increased)	0.99 (0.98, 0.99), 0.001	0.99 (0.98, 0.99), 0.001	0.99 (0.98, 1.00), 0.018
LDL-C groups			
Q1	1.0	1.0	1.0
Q2	0.51 (0.28, 0.92), 0.025	0.56 (0.31, 1.02), 0.058	0.64 (0.35, 1.17), 0.145
Q3	0.33 (0.17, 0.65), 0.002	0.33 (0.17, 0.66), 0.002	0.40 (0.20, 0.81), 0.011
Q4	0.51 (0.28, 0.92), 0.025	0.52 (0.29, 0.95), 0.033	0.66 (0.35, 1.25), 0.204
P for trend	0.007	0.007	0.046

Adjusted for age, sex, smoking, drinking, diabetes, CAD, LVH, stroke, beta-blocker, CCB, ACEI/ARB, stains, SBP, DBP, BMI, FBG, eGFR, TC, TG and HDL-C. OR, odd ratio, CI, confidence interval. AF, atrial fibrillation; CAD, coronary heart disease; LVH, left ventricular hypertrophy; Beta, beta-blockers; CCB, calcium channel blockers; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; FBG, fasting blood glucose; eGFR, estimated glomerular filtration; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.
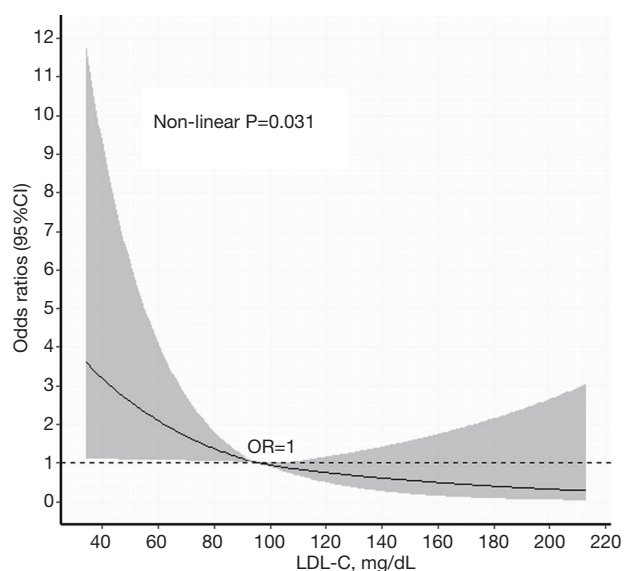

Figure 2 Restricted cubic spline of low-density lipid cholesterol levels and atrial fibrillation. Adjusted for age, sex, smoking, drinking, diabetes, CAD, LVH, stroke, Beta-blocker, CCB, ACEI/ARB, statin, SBP, DBP, BMI, FBG, eGFR, TC, TG and HDL-C. The solid curve shows the association between LDL-C levels and AF. AF, atrial fibrillation; CAD, coronary heart disease; LVH, left ventricular hypertrophy; Beta, beta-blockers; CCB, calcium channel blockers; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; FBG, fasting blood glucose; eGFR, estimated glomerular filtration; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.

paroxysmal or subclinical AF and lead to the relatively low incidence of AF. Third, we did not examine the levels of inflammatory biomarkers, and did not performed tests on thyroid function, heart function, and did not obtain the data of central obesity. Forth, despite the adjustment of multiple confounders, effects of residual confounders may exist, such as the impact of uric acid and sleep. Finally, this was a single center study, therefore the conclusions could not be directly extrapolated to other populations.

In conclusion, we found that lower levels of LDL-C were associated with increased incidence of AF in a Chinese community hypertensive population. However, when LDL-C was presented as categorical variables, after adjusted potential confounders, the negative association between LDL-C and AF was attenuated.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The research was performed according to the Declaration of Helsinki (as revised in 2013) and the guidelines of the local ethics committee (Guangdong Provincial People's Hospital, NO. GDREC2012143H). All patients have provided written consent.

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