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The association between circulating palmitic acid levels and risk of premature coronary artery disease in Chinese patients: a case-control study

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Abstract

Background Palmitic acid (PA) is a risk factor for atherosclerosis but its significance in premature coronary artery disease (PCAD) remains poorly understood. Herein, we investigated the impact of circulating PA levels on the risk of PCAD occurrence in Chinese patients.

Methods In this case control study, we included patients diagnosed with PCAD and age-matched non-CAD controls between June 2022 and December 2023. Participants' serum PA levels were quantified using ultra-performance liquid chromatography-mass spectrometry, and correlations with PCAD were determined using R (v4.2.2). The potential mediating effect of low density lipoprotein cholesterol (LDL-C) for the association between PA and PACD was also evaluated.

Results In this study of 393 adults (206 PCAD patients and 187 non-CAD controls), serum PA levels showed significant positive correlations with LDL-C and total cholesterol. Compared to controls, PCAD patients had higher proportions of males, smokers, and diabetics, along with elevated PA, LDL-C, and triglycerides, but reduced HDL-C (all $P < 0.05$). Elevated serum PA (per 10μmol/L increase, OR = 1.12, 95% CI = 1.05–1.20) was significantly associated with an increased risk of PCAD after adjustment for multivariable factors. Further adjustment for LDL-C levels attenuated, but remained statistically significant, the association between PA and PCAD (per 10μmol/L increase, OR = 1.10, 95% CI = 1.03–1.18). Mediation analysis showed that LDL-C mediated 16% of PA's total effect on PCAD.

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Conclusions Elevated PA circulating levels were found to be related with PCAD risks among Chinese, and increased LDL-C levels could partly mediate this effect.

Keywords Palmitic acids, Risk factors, Coronary artery disease, Saturated fatty acid, Young patients

Introduction

Coronary artery disease (CAD) continues to be the predominant cause of global mortality [1]. While typically associated with older populations, there has been a notable rise in the incidence of premature CAD (PCAD) among younger individuals in recent years [2, 3]. Patients with PCAD represent a distinctive subgroup necessitating increased attention due to the considerable burden they impose on families and society at large. Notably, PCAD is characterized by an increased incidence of ischemic recurrences and premature mortality compared to CAD in the elderly [4, 5]. Importantly, the risk factors in patients with PCAD differ greatly from those in the elderly [6], with nearly 40% of younger myocardial infarction patients presenting either none or only one of the typical CAD risk factors, often categorizing them as low-risk according to current scoring systems [7]. Therefore, the early identification of PCAD risk factors is essential for timely treatment and improved outcomes.

According to the classical diet-heart hypothesis, saturated fatty acids (SFA) elevate total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C) levels, thereby augmenting CAD risk [7, 8]. Palmitic acid (PA), a 16-carbon SFA prevalent in our consumed food, constitutes approximately 65% of SFAs and 32% of total serum total FAs [9]. Previous studies have demonstrated that consumption of PA may increase the risk of CAD [10]. Similarly, circulating PA levels were found to be influenced by PA consumption and associated with CAD risks [11]. However, these previous studies mainly focused on elderly patients. In modern industrialized societies, young people are increasingly exposed to diets high in saturated fats [12], which can elevate serum cholesterol levels, leading to atherosclerosis. However, PA's precise contribution to PCAD pathogenesis and its underlying mechanisms remain poorly elucidated.

Therefore, our study aimed to explore the relationship between circulating PA levels and PCAD risks in Chinese patients and further determine the mediation role of LDL-C in this population.

Materials and methods

Participants

In this case control study, we included patients diagnosed with PCAD and age-matched non-CAD controls between June 2022 and December 2023. All participants were recruited from three hospitals in Foshan city, Southern China, including The Eighth Affiliated Hospital, Southern Medical University (The First People's Hospital of Shunde), Lecong Hospital of, Shunde district, Foshan, Guangdong Province, and Affiliated Foshan Hospital, Southern Medical University, Foshan (The second people's hospital of Foshan), China. PCAD was defined as the initial presentation of CAD symptoms in men ≤ 55 years or women ≤ 65 years old. CAD was considered for those with ≥ 50% stenosis of the lumen diameter in at least a major coronary artery [13], and its severity was independently quantified by two interventional cardiologists using coronary angiography (CAG), with concurrent assessment by a radiologist from the same hospital. CAG was performed using Judkins techniques via the radial artery; but when unsuccessful, we used the femoral artery [13].

The exclusion criteria were as follows: (1) acute myocarditis or stress cardiomyopathy, (2) uncontrolled infectious disease, (3) autoimmune disease, (4) end-stage renal disease, (5) acute hepatitis, (6) psychiatric disorders, (7) malignancy, (8) use of fish oil or polyunsaturated fatty acid supplements within the past 3 months.

This study follows the STROBE guidelines and the Declaration of Helsinki.

Blood biochemical indicators assessments

Blood biochemical indicators, including hemoglobin (Hb), platelets (PLT), fasting blood glucose (FBG), glycated hemoglobin (HbA1c), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine (Scr), estimated glomerular filtration rate (eGFR) and uric acid (UA), were measured by the laboratories of the participating hospitals. Data extraction was conducted from the medical record system at each participating hospitals.

Detection of PA

Venous blood samples were collected following an overnight fast and centrifuged to obtain serum, which was subsequently stored at -80 °C until PA analysis. Based on established protocol [13] the following steps were performed: Serum samples were thawed at 4 °C and 50 mg serum was homogenized using 100 µL of distilled water. Subsequently, 0.5 mL of methanol was added to the mixture, which was then vortexed for 30 min. Following centrifugation at 14,000 rpm

(4 °C, 5 min), the supernatant was combined with 5 μL of standard solution (fa19:025 μ G/ml, diluted with methanol), briefly rotated, and stored in 2 mL injection vials until mass spectrometry analysis using a Waters ACQUITY I-class LC system (Waters, Milford, MA, USA) and Masslynx Analysis software (version 4.1, SCIEX, Boston, MA, USA). Data analysis was conducted using Skyline (MacCoss, WA, USA).

Traditional CAD risk factors

Conventional risk factors comprised: (1) A family history of premature cardiovascular disease, considered positive if a first-degree male aged < 55 years or a female aged < 65 years were diagnosed with CAD. (2) Hypertension, if systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or undergoing related therapy. (3) Diabetes mellitus, if FBG ≥ 7.0 mmol/L, HbA1c ≥ 6.5%, or receiving hypoglycemic treatment. (4) Dyslipidemia, defined as TC ≥ 5.18 mmol/L, LDL-C ≥ 3.37 mmol/L, HDL-C < 1.04 mmol/L, TG ≥ 1.7 mmol/L, or receiving lipid-lowering therapy. (5) Patients were considered current smokers if regularly smoked in the past year before enrollment or non-current smokers if never smoked or quit at least 1 year before enrollment.

Statistical analysis

Regarding the estimation of the study population needed, the sample size was calculated using PASS 2023, version 23.0.2. Based on the case control design of the study, each set of matched case-controls was expected to be consist of one case and one matched control. We assumed that a participants with a PA levels above the median will have an increased odds of PCAD. The sample estimation was made using a two-sided odds ratio score test from a conditional logistic regression analysis. The assumed R^2 when regressing the exposure variable (PA) on any other covariates is 0.2. To detect an odds ratio of 2 with 80% power and a Type I error rate (α) of 0.05, 164 matched sets of subjects will be needed, totaling 328 subjects.

Statistical analyses were conducted using the R (v4.2.2, Lucent Technologies Inc., New Providence, NJ, USA). Multiple imputation was performed to handle missing baseline data. Categorical variables are shown as numbers (percentages) and compared using chi-square or Fisher's exact test. Continuous variables were assessed for normality and expressed as medians (interquartile range) or means (standard deviations). Wilcoxon rank sum test or Student's *t*-test was employed for group comparisons. Correlations between LDL-C and PA were examined using the Pearson product-moment correlation coefficient (r). The relationship between PA and PCAD was assessed using multivariable logistic regression, presenting odds ratios (ORs) with corresponding 95% confidence intervals (CIs). We adjusted variables based on well-known risk factors for heart disease and performed in previous studies [13, 14]. Potential nonlinear effects were explored using restricted cubic spline models. Mediation analysis was conducted using the mediation package to assess mediation effects quantitatively. A two tail *P* value < 0.05 was used to represent statistical significance.

Results

Group comparisons

Among the 393 adults included in this study (206 PCAD patients and 187 non-CAD controls), significant differences were observed in 16 out of 25 measured parameters (Table 1). The PCAD group exhibited a significantly higher proportion of males (77.7% vs. 42.8%, $P < 0.001$), smokers (45.1% vs. 21.4%, $P < 0.001$) and diabetics (34.0% vs. 20.3%, $P < 0.01$). Highly significant differences ($P < 0.01 – 0.001$) were found for PA, FBG, HbA1c, TG, HDL-C, AST, ALT, eGFR and UA levels, while significant differences ($P < 0.02–0.04$) were observed for LDL-C and Scr levels. Furthermore, HDL-C levels were significantly reduced in PCAD patients (0.96 vs. 1.12 mmol/L, $P < 0.001$). The remaining 9 parameters (age, BMI, hypertension, family history of CAD, HR, SBP, DBP, TC, and Hb) showed no significant differences (all $P > 0.05$).

Higher PA quartiles were related to increased PCAD incidence and were more commonly found in males, smokers and diabetics (Table 2). Additionally, participants in higher PA quartiles showed significantly elevated levels of LDL-C, TC, TG, Scr, eGFR, UA, and PLT.

Relationships of PA concentration and serum lipid metrics

Pearson correlation analysis revealed a positive correlation between serum PA levels and LDL-C (Peason $r = 0.31$, $P < 0.001$) and TC (Peason $r = 0.29$, $P < 0.001$) but no significant difference for HDL-C and TG (Fig. 1).

Association of PA concentration and risk of PCAD

Using four logistic regression models for evaluating the relationship between PA concentration (continuous and quartile forms) and PCAD risk (Table 3), PA levels showed a positive association with PCAD risk across all models. After adjusting for LDL-C in model 4, the ORs for PA on the risk of PCAD, decreased slightly but remained significant. Additionally, logistic regression models with restricted cubic splines indicated a significant linear relationship between PA levels and PCAD risk ($P_{overall}$ <0.001, $P_{nonlinearity}$ =0.43) (Fig. 2).

Table 1 Baseline characteristics of the study population based on the presence of PCAD

	Control (*n* = 187)	PCAD (*n* = 206)	*P* value
PA (μmol/L)	78.50 [62.82, 96.82]	89.90 [72.37, 119.02]	< 0.001
Age (years)	49.00 [44.00, 53.00]	49.00 [45.00, 53.00]	0.99
Male (%)	80 (42.8)	160 (77.7)	< 0.001
BMI (kg/m^2)	24.10 [21.10, 27.80]	24.25 [21.60, 28.60]	0.38
Smoking (%)	40 (21.4)	93 (45.1)	< 0.001
Hypertension (%)	93 (49.7)	114 (55.3)	0.31
Diabetes (%)	38 (20.3)	70 (34.0)	< 0.01
Family history of CAD (%)	14 (7.5)	10 (4.9)	0.38
HR (beats/min)	76.00 [67.00, 85.00]	75.00 [66.00, 86.00]	0.96
SBP (mmHg)	130.00 [116.00, 146.00]	128.00 [116.00, 143.75]	0.76
DBP (mmHg)	82.00 [75.00, 90.50]	83.50 [74.00, 92.00]	0.50
FBG (mmol/L)	5.59 [4.89, 6.54]	6.01 [5.24, 8.39]	< 0.001
HbA1C (%)	5.60 [5.40, 6.00]	5.90 [5.53, 6.40]	< 0.001
TC (mmol/L)	4.66 [3.95, 5.32]	4.72 [4.00, 5.70]	0.11
TG (mmol/L)	1.35 [0.97, 1.88]	1.60 [1.15, 2.35]	< 0.001
LDL-C (mmol/L)	2.53 [2.07, 2.94]	2.65 [2.06, 3.35]	0.04
HDL-C (mmol/L)	1.12 [0.96, 1.30]	0.96 [0.84, 1.18]	< 0.001
ALT (IU/L)	22.40 [17.00, 30.00]	29.00 [21.00, 92.25]	< 0.001
AST (IU/L)	24.00 [18.00, 37.00]	34.00 [22.00, 56.00]	< 0.001
Scr (mmol/L)	72.57 [61.30, 88.95]	76.59 [68.18, 88.47]	0.01
eGFR (ml/min)	91.59 (21.00)	86.77 (20.24)	0.02
hsCRP (mg/L)	3.99 [1.45, 8.30]	4.78 [2.20, 8.24]	0.15
UA (μmol/)	358.34 [259.50, 462.00]	396.00 [326.30, 500.48]	0.001
Hb (g/L)	134.00 [121.50, 149.00]	139.00 [127.00, 147.00]	0.16
PLT (10^9/L)	228.00 [179.50, 276.00]	243.00 [200.25, 284.00]	0.03

Data are presented as mean (SD), median (IQR) or n (%). BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein-cholesterol; Hb, hemoglobin; LDL-C, low density lipoprotein-cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; UA, uric acid; Scr, serum creatinine; PLT, platelets

Mediating effect analysis

Mediation analysis, for determining LDL-C effects on PA and PCAD, indicated significant mediated and direct effects, with the mediated effect by LDL-C accounting for 16% (95% CI: 1-70%) of the total effect (Fig. 3, Table 4).

Discussion

The results of the current research showed that higher serum PA level led to increased risks of PCAD in Chinese patients following adjustments for multiple conventional risk factors, and that the association between circulating PA levels and PCAD was partly mediated by LDL-C.

Modern diets generally contain high levels of main saturated fatty acids-PA. (9) A high intake of PA is considered a risk factor for coronary heart disease (CHD) [15]. Circulating PAs originate from both exogenous dietary fat and endogenous de novo fat production and lipolysis pathways [16–18]. Notably, endogenous PA production through de novo lipogenesis is particularly active in insulin-resistant states, potentially explaining why some individuals exhibit high circulating PA levels despite moderate dietary intake. Previous investigations described inconsistent associations between circulating PA levels and CHD risks. For instance, the European Prospective Investigation into Cancer study showed a positive association between PA levels or content and CHD risk (OR: 1.24, 95% CI: 1.07–1.45) among 7,354 participants aged 40–79 years without CHD at baseline [19]. Similarly, a study on Japanese subjects aged 40–85 years reported an association between higher circulating PA levels and increased CHD risks (OR: 2.7, 95% CI: 1.4–5.5) [20]. However, a prospective investigation in an older population (≥ 65 years) did not find any association between PA from de novo fat lipolysis and CHD events [21]. These disparate findings could be attributed to variations in participant age groups across studies. The stronger association in younger populations may reflect their more vulnerable vascular endothelial function and higher metabolic activity, making them more susceptible to PA-induced lipotoxicity and inflammation [21]. In the present study on young and middle-aged patients, we observed an association between increased circulating PA levels with heightened PCAD risks in Chinese patients. These findings suggest that, as compared to CHD in older adults,

Table 2 Baseline characteristics according to the PA quartiles

	Q1(*n* = 99)	Q2(*n* = 98)	Q3(*n* = 98)	Q4(*n* = 98)	*P* value
PCAD (%)	39 (39.4)	46 (46.9)	59 (60.2)	62 (63.3)	< 0.01
Age (years)	48.00 [42.00, 51.00]	49.50 [45.25, 54.00]	49.00 [46.00, 53.00]	50.00 [45.25, 53.00]	0.04
male (%)	55 (55.6)	51 (52.0)	64 (65.3)	70 (71.4)	0.02
BMI (kg/m2)	24.80 [21.95, 28.30]	24.10 [21.33, 27.90]	24.80 [21.22, 29.70]	23.40 [21.20, 27.12]	0.23
Smoking (%)	29 (29.3)	32 (32.7)	35 (35.7)	37 (37.8)	0.62
Hypertension (%)	50 (50.5)	51 (52.0)	59 (60.2)	47 (48.0)	0.35
Diabetes (%)	28 (28.3)	25 (25.5)	27 (27.6)	28 (28.6)	0.96
Family history of CAD (%)	7 (7.1)	6 (6.1)	4 (4.1)	7 (7.1)	0.79
HR (beats/min)	75.00 [65.00, 82.50]	78.00 [67.25, 89.75]	76.50 [67.00, 85.75]	73.00 [65.25, 82.75]	0.10
SBP (mmHg)	128.00 [115.50, 141.00]	126.00 [112.75, 146.25]	131.50 [119.25, 144.00]	127.50 [115.25, 148.00]	0.59
DBP (mmHg)	81.00 [74.50, 88.00]	82.00 [71.00, 91.75]	84.50 [76.00, 90.75]	83.00 [74.00, 95.75]	0.38
FBG (mmol/L)	5.69 [5.03, 7.12]	5.79 [5.11, 7.42]	5.86 [5.07, 7.31]	5.86 [5.20, 7.57]	0.83
HbA1C (%)	5.80 [5.50, 6.30]	5.80 [5.40, 6.27]	5.75 [5.40, 6.18]	5.70 [5.40, 6.20]	0.72
TC (mmol/L)	4.15 [3.78, 4.90]	4.82 [3.95, 5.37]	4.75 [4.06, 5.70]	5.18 [4.22, 6.55]	< 0.001
TG (mmol/L)	1.24 [0.92, 1.74]	1.38 [1.03, 1.99]	1.65 [1.23, 2.55]	1.60 [1.12, 2.18]	< 0.001
LDL-C (mmol/L)	2.32 [1.88, 2.76]	2.62 [2.13, 2.94]	2.63 [2.17, 3.26]	2.92 [2.15, 3.76]	< 0.001
HDL-C (mmol/L)	1.08 [0.88, 1.26]	1.09 [0.88, 1.28]	1.00 [0.85, 1.21]	1.10 [0.92, 1.25]	0.13
ALT (IU/L)	23.00 [18.00, 32.50]	25.00 [19.00, 37.00]	26.00 [19.00, 77.00]	26.00 [19.00, 47.75]	0.29
AST (IU/L)	26.00 [20.00, 40.00]	28.52 [19.00, 47.80]	28.50 [20.25, 50.50]	31.50 [20.25, 44.01]	0.65
Scr (mmol/L)	72.60 [64.71, 83.78]	72.57 [62.40, 83.97]	78.95 [68.93, 90.30]	78.18 [66.62, 92.50]	< 0.01
eGFR (ml/min)	90.75 (21.62)	90.81 (19.52)	90.57 (20.13)	84.11 (21.06)	0.06
hsCRP (mg/L)	4.20 [1.20, 8.35]	6.30 [3.19, 8.30]	4.40 [1.73, 8.00]	2.74 [1.40, 7.41]	< 0.01
UA (μmol/)	359.80 [265.92, 465.05]	365.70 [282.28, 463.28]	395.35 [311.85, 502.72]	371.40 [291.72, 455.40]	0.13
Hb (g/L)	133.00 [119.50, 147.50]	136.50 [125.00, 146.75]	138.00 [129.00, 144.75]	139.00 [126.00, 149.75]	0.37
PLT (10^9/L)	228.88 (72.85)	236.23 (69.65)	233.93 (65.32)	242.19 (58.95)	0.57

Data are presented as mean (SD) or n (%). BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein-cholesterol; Hb hemoglobin; LDL-C, low density lipoprotein-cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; UA, uric acid; Scr, serum creatinine; PLT, platelets

circulating PA may exert a stronger influence on the risk of PCAD in younger populations.

Palmitic Acid inhibits LDL receptor activity, leading to increased LDL-C levels and contributing to atherosclerosis [22]. The PA has a greater propensity to elevate LDL-C compared to other fatty acids [23]. In our multiple logistic regression models, the association between circulating PA and CAD remained significant even after adjusting for LDL-C levels, suggesting that LDL-C partially mediates the link between PA and PCAD, alongside potential other mechanisms. Mediation analysis revealed that PA exerted a significant indirect effect on CAD through LDL-C mediation, accounting for 16% of the total effect. This suggests that LDL-C only partially explains the impact of PA, indicating the potential involvement of other unidentified mechanisms. In addition, both experimental research and prospective cohort studies have demonstrated that PA can elevate inflammation levels [24, 25], which may increase the development of atherosclerosis. Furthermore, PA can increase ceramide synthesis [26], which may in turn increase CAD risks. It was reported that serum ceramide levels is a strong predictor of CAD [27–29] and an indicator for poor prognosis in CAD [30]. This ceramide-CAD relationship may explain part of PA's LDL-C-independent atherogenic effects.

This research had several strengths. Firstly, it focuses on a cohort of patients with PCAD, a group particularly sensitive to lifestyle influences and provides valuable insights into early disease mechanisms and potential preventive strategies. Secondly, we utilized circulating markers to quantify PA levels, which reduces measurement bias compared to relying solely on dietary assessments or food scales. Lastly, our study yielded consistent results using dependent variables (quartiles and continuous measures of PA concentration), enhancing the robustness and reliability of our findings.

However, there were some limitations that should be clarified. Firstly, we did not establish definitive cause-and-effect relationships. While associations were identified, longitudinal studies would be required to confirm causality. Secondly, while our analysis revealed that LDL-C partially mediated the relationship between PA and CAD, we did not assess other potential mediators, such as inflammatory markers. Subsequent studies could incorporate these elements

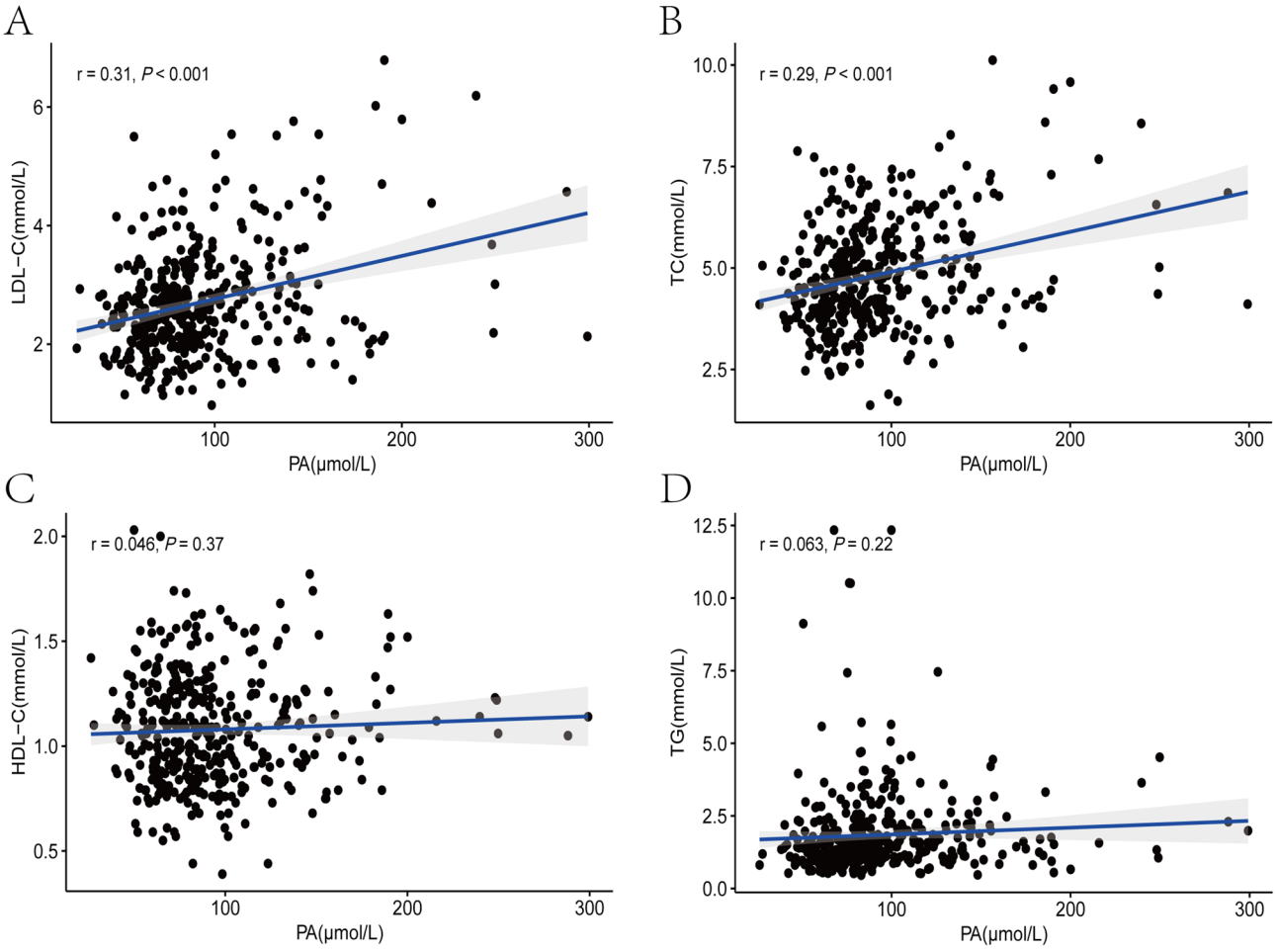

Fig. 1 Positive correlation between palmitic acid (PA) and serum lipid metrics

Table 3 Multivariate logistic regression analyses for the association between PA level and PACD

	Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Continuous (per 10 μmol/L)	1.13 (1.07, 1.20)	< 0.001	1.11 (1.05, 1.19)	< 0.001	1.12 (1.05, 1.20)	< 0.001	1.10 (1.03, 1.18)	0.007
Categorical (quartiles)								
Q1	Ref		Ref		Ref		Ref	
Q2	1.36 (0.77, 2.40)	0.29	1.47 (0.79, 2.74)	0.22	1.53 (0.81, 2.91)	0.20	1.45 (0.76, 2.78)	0.26
Q3	2.33 (1.32, 4.15)	0.004	2.15 (1.17, 4.02)	0.02	2.19 (1.17, 4.15)	0.02	2.03 (1.08, 3.86)	0.03
Q4	2.65 (1.50, 4.75)	< 0.001	2.30 (1.23, 4.32)	0.009	2.42 (1.28, 4.63)	0.007	2.00 (1.03, 3.92)	0.04
P for trend	< 0.001		< 0.01		< 0.01		0.02	

Data are presented as ORs (95% CIs) *P* value

Model 1: Non-adjusted

Model 2: Adjusted for age, sex and BMI

Model 3: Adjusted for age, sex, BMI, smoking, diabetes and hypertension

Model 4: Adjusted for age, sex, BMI, smoking, diabetes, hypertension and LDL-C

to offer a more thorough insight into how PA influences CAD risks. Thirdly, our study included cases from Guangdong Province, affecting the generalizability of our results in other geographic regions with potentially different dietary patterns and genetic backgrounds. Lastly, the use of medications affecting fatty acid metabolism among our patients might have introduced confounding variables, and addressing these factors in future research would enhance the validity and applicability of our findings. The interpretation of the results may be influenced by unmeasured

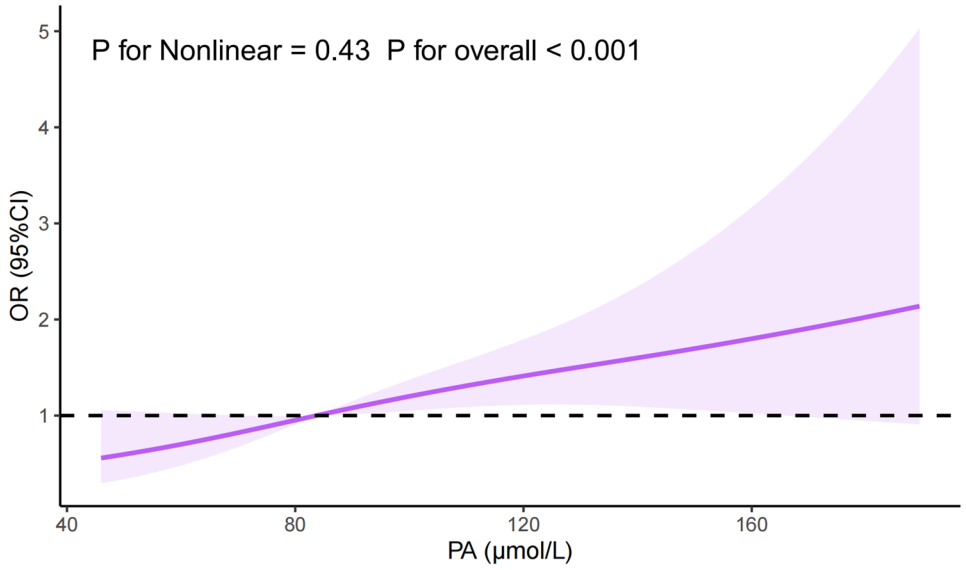

Fig. 2 Nonlinear relationship between palmitic acid (PA) and premature coronary artery disease (PCAD), adjusted for age, sex, BMI, smoking, diabetes, hypertension, and LDL-C

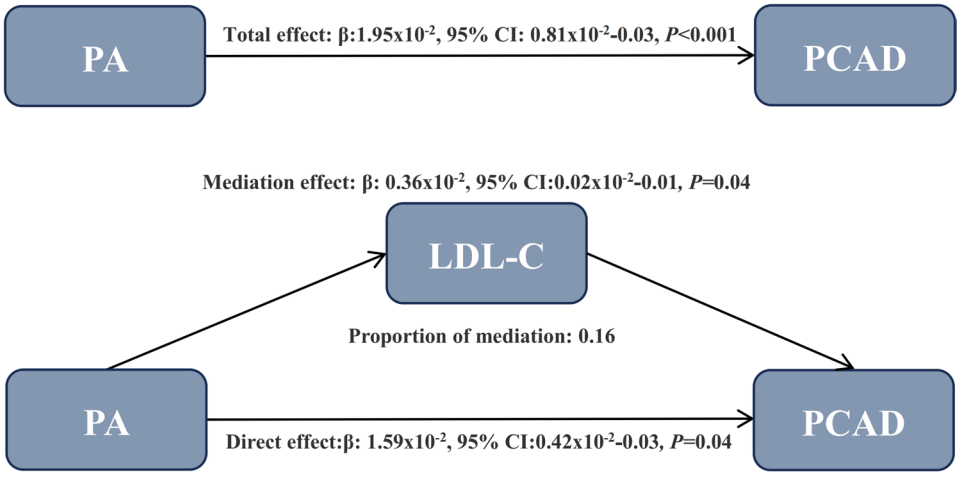

Fig. 3 The mediating effect of LDL-C between palmitic acid (PA) and premature coronary artery disease (PCAD)

Table 4 The mediating effect of LDL-C between PA and PCAD

	Estimate	95% CI Lower	95% CI Upper	*P* value
ACME	0.36×10^{-2}	0.20×10^{-3}	0.01	0.04
ADE	1.59×10^{-2}	4.18×10^{-3}	0.03	0.04
Total Effect	1.95×10^{-2}	8.12×10^{-3}	0.03	< 0.001
Prop.Mediated	0.16	0.01	0.70	0.04

ACME: stands for average causal mediation effects

ADE: stands for average direct effects

Total Effect: stands for the total (direct + indirect) effect

Prop. Mediated: stands for the proportion of the effect of the PA on the PCAD that goes through the mediator (LDL-C)

confounders, particularly medication effects, which should be further explored in future studies.

Conclusions

High levels of PA in circulation were found to be related to PCAD risks in Chinese patients, which might be partially affected by elevated LDL-C levels.

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Not applicable.

Author contributions

Yunzhao Hu, and Zaopeng He, Yuli Huang are joint corresponding authors and were equally involved in the study. Yingwen Chen, Yue Cao, Lingxiao Li, Peng Chen, and Xiaomei Zhang searched the literature and extracted data. Yingwen Chen, Yue Cao, Shali Hao, Min Qiu, Yangguang Liu, Jiandi Wu and Zaopeng He analyzed the data. Yingwen Chen, Yue Cao, Yangxin Chen, Zaopeng He, Yunzhao Hu, Yuli Huang drafted the manuscript, which was critically revised for important intellectual content by all authors. Yuli Huang supervised the

study. All authors have read and approved the final manuscript. Yuli Huang is the guarantor. The corresponding author attests that all listed authors meet author ship criteria and that no others meeting the criteria have been omitted.

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

Declarations

Ethics approval and consent to participate
This sub-study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of The Eighth Affiliated Hospital, Southern Medical University China (No.KY20191103). All participants provided individual written consent to participate in the study, and the individual privacy of the participants is well protected.

Consent for publication
All participants provided written informed consent for the publication of their data.

Competing interests
The authors declare no competing interests.

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