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Association of Lipoprotein-Associated Phospholipase A2 with the Prevalence of Nonalcoholic Fatty Liver Disease: A Result from the APAC Study

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Zhongni Liu[1], Hong Li[1], Yinghong Zheng[1], Ziyu Gao[1], Lin Cong[1], Liming Yang[1] & Yong Zhou[2]

Nonalcoholic fatty liver disease (NAFLD) is a worldwide chronic liver disease. Few studies have investigated the association between NAFLD and Lipoprotein-associated phospholipase A_2 (Lp-PLA_2), a unique enzyme correlated with oxidative stress. The aim of this study was to assess the relationship between Lp-PLA_2 and NAFLD in a Chinese community-based cohort. A total of 1587 adults aged ≥40 years were enrolled in the current study. Participants underwent a standardized evaluation. The serum Lp-PLA2 concentration was measured by ELISA and NAFLD was diagnosed by ultrasonography. Multivariable logistic regression was used to assess the association between Lp-PLA2 and NAFLD. Increased Lp-PLA2 levels were significantly associated with decreased NAFLD prevalence after adjusting for other potential confounders. The adjusted ORs of NAFLD in Q2, Q3 and Q4 compared with Q1 were 0.88 (0.64–1.21), 0.71 (0.51–0.98) and 0.67 (0.48–0.95), respectively ($P < 0.05$). Furthermore, the adjusted ORs of moderate and heavy NAFLD in Q2, Q3 and Q4 compared to Q1 were 0.64 (0.41–1.01), 0.48 (0.29–0.80) and 0.47 (0.28–0.79), respectively ($P < 0.01$). In conclusions, increased Lp-PLA2 levels were independently associated with decreased NAFLD prevalence.

Nonalcoholic fatty liver disease (NAFLD), one of the most common causes of chronic liver disease, is now regarded as a manifestation of metabolic syndrome with abnormal lipid deposition in liver[1,2]. Currently, the prevalence of NAFLD approaches 30% in the general population worldwide[3]. An increasing number of studies have indicated that NAFLD is linked to increased risk of cardiovascular disease (CVD)[4–6]. Meanwhile, some studies have demonstrated that lipoprotein-associated phospholipase A2 (Lp-PLA_2), which was named firstly as platelet-activating factor acetylhydrolase (PAF-AH), is significantly associated with CVD[7,8].

Oxidative stress is regarded as a major leading cause of NAFLD[9,10], and the anti-oxidative property of Lp-PLA_2 has been well addressed by several studies[11,12]. However, few studies were performed to explore the relationship between Lp-PLA_2 and NAFLD occurrence. Previous studies have mainly focused on small, foreign populations[13,14], but no studies have investigated this association specifically in a Chinese population.

Therefore, we hypothesized that an association between Lp-PLA_2 and NAFLD also exists in Chinese populations. In this study, we aimed to investigate the association between serum Lp-PLA_2 levels and NAFLD occurrence in a large Chinese community.

Results

Baseline characteristics. A total of 1587 participants (68.8% men) were included in the final analysis. According to the Lp-PLA_2 quartiles, the baseline characteristics of participants are shown in Table 1. The mean Lp-PLA_2 concentrations from the lowest to the highest quartile were 128.1 ± 2.8 ng/mL, 136.6 ± 2.7 ng/mL, 149 ± 5.1 ng/mL, and 227.3 ± 96.8 ng/mL, respectively. Age, BMI, smoking, education level, ALT, hypertension, hyperlipidaemia, triglyceride and HDL were significantly different among the participants. The mean age, HDL

[1]Department of Pathophysiology, Key Laboratory of Cardiovascular Pathophysiology, Harbin Medical University, Harbin, China. [2]Beijing Institute of Heart, Lung and Blood Vessel Disease, Beijing Anzhen Hospital, Capital Medical University, Beijing, China. Zhongni Liu and Hong Li contributed equally to this work. Correspondence and requests for materials should be addressed to L.Y. (email: limingyang@ems.hrbmu.edu.cn) or Y.Z. (email: yongzhou78214@163.com)

	Total	Lp-PLA$_2$ quartiles				*P-value*
		Q1	Q2	Q3	Q4	
Overall (n)	1587	396	397	397	397	
Lp-PLA$_2$ mass (ng/mL)	160.3 ± 62.5	128.1 ± 2.8	136.6 ± 2.7	149 ± 5.1	227.3 ± 96.8	
Men (n, %)	1092(68.8)	278(70.2)	274(69.0)	261(65.7)	279(70.3)	0.47
Age (years)	61.6 ± 11.8	56.5 ± 9.1	59.6 ± 10.6	62.9 ± 11.7	67.3 ± 12.8	<0.01
BMI (kg/m^2)						<0.01
<25	845(53.25)	185(46.72)	204(51.39)	222(55.92)	234(58.94)	
25–30	648(40.83)	185(46.72)	160(40.30)	158(39.80)	145(36.52)	
>30	94(5.92)	26(6.57)	33(8.31)	17(4.28)	18(4.53)	
Current smoking (n, %)	496(31.3)	154(38.9)	126(31.7)	111(28.0)	105(26.4)	<0.01
Physical activity (n, %)						0.91
Inactive	564(35.5)	142(35.9)	141(35.5)	137(34.5)	144(36.3)	
Moderate	358(22.6)	95(24.0)	90(22.7)	83(20.9)	90(22.7)	
Active	665(41.9)	159(40.2)	166(41.8)	177(44.6)	163(41.1)	
Education level (n, %)						<0.01
Illiterate or primary	310(19.5)	67(16.9)	63(15.9)	85(21.4)	95(23.9)	
Middle or high school	686(43.2)	187(47.2)	191(48.1)	155(39.0)	153(38.5)	
College or above	591(37.2)	142(35.9)	143(36.0)	157(39.5)	149(37.5)	
ALT (U/L)	17.7 ± 10.7	18.9 ± 10.3	18.6 ± 10.8	17.6 ± 11.6	15.8 ± 9.9	<0.01
Diabetes (n, %)	259(16.3)	60(15.2)	61(15.4)	75(18.9)	63(15.9)	0.45
Hypertension (n, %)	910(57.3)	198(50.0)	211(53.1)	241(60.7)	260(65.5)	<0.01
Hyperlipidaemia (n, %)	839(52.9)	231(58.3)	213(53.7)	209(52.6)	186(46.9)	0.01
Triglyceride (mmol/L)	1.6 ± 1.3	1.9 ± 1.7	1.6 ± 1.0	1.5 ± 1.0	1.4 ± 1.2	< 0.01
Total cholesterol (mmol/L)	5.2 ± 1.1	5.3 ± 1.2	5.1 ± 1.0	5.1 ± 1.0	5.1 ± 1.1	0.29
HDL (mmol/L)	1.6 ± 0.5	1.6 ± 0.7	1.5 ± 0.4	1.6 ± 0.5	1.7 ± 0.5	0.02
LDL (mmol/L)	2.7 ± 0.8	2.8 ± 0.9	2.7 ± 0.7	2.6 ± 0.7	2.6 ± 1.0	0.06
NAFLD (n, %)	650(41.0)	190(48.0%)	174(43.8)	150(37.8)	136(34.3)	<0.01

Table 1. Baseline characteristics according to Lp-PLA$_2$ quartiles. Data are expressed as the means ± SD or n (%). Abbreviation: NAFLD = nonalcoholic fatty liver disease; BMI = body mass index; ALT = alanine aminotransferase; TG = triglyceride; TC = total cholesterol; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol.

values and the percentage of participants with a low education level, low BMI, hypertension increased across the Lp-PLA$_2$ quartiles. In contrast, the mean ALT, triglyceride levels and percentage of participants who were currently smoking and had hyperlipidaemia decreased as the Lp-PLA$_2$ level increased.

NAFLD prevalence according to the Lp-PLA$_2$ quartiles. In our study, 41.0% (650/1587) participants were diagnosed with NAFLD. Among these participants, 26.4% (419/1587) presented with light NAFLD, 12.1% (192/1587) with moderate NAFLD and 2.5% (39/1587) with heavy NAFLD. The prevalence of no NAFLD was positively associated with Lp-PLA$_2$ quartiles, whereas the prevalence of moderate and heavy NAFLD was negatively associated with Lp-PLA$_2$ quartiles (Fig. 1).

Correlation between Lp-PLA$_2$ level and NAFLD. Figure 2 shows the cross-sectional relationship between Lp-PLA$_2$ concentration and the NAFLD prevalence. Comparing to the Q1, the ORs (95% CI) of NAFLD in Q2, Q3 and Q4 for model 1 were 0.85 (0.64–1.12), 0.66 (0.50–0.87) and 0.57 (0.42–0.75), respectively. The model 2 result, which adjusted for age and sex, was still consistent with model 1 ($P < 0.01$). In model 3, which adjusted for age, sex, BMI, physical activity, education level, smoking, ALT, diabetes, hypertension, hyperlipidaemia, the ORs (95% CI) of NAFLD in Q2, Q3 and Q4 compared with Q1 were 0.88 (0.64–1.21), 0.71 (0.51–0.98) and 0.67 (0.48–0.95), respectively.

The association between Lp-PLA$_2$ concentration and different NAFLD levels in was similar to the above results in Fig. 2. In model 1, the ORs (95% CI) for moderate to heavy NAFLD in Q2, Q3 and Q4 compared with Q1 were 0.71 (0.46–1.07), 0.49 (0.31–0.77) and 0.41 (0.25–0.66), respectively ($P < 0.01$). This relationship also persisted in models 2 and 3 even after adjusting for other potential confounders (Table 2). Our results indicated that increased Lp-PLA$_2$ levels are associated with a decreased prevalence of NAFLD.

Discussion

In this present, large community-based study, we first demonstrated that higher Lp-PLA$_2$ concentrations are associated with decreased NAFLD prevalence, and multivariate analysis revealed a significant trend over the Lp-PLA$_2$ quartiles and a decreasing NAFLD OR gradient. In addition, a similar association was seen between the Lp-PLA$_2$ quartiles and different NAFLD levels.

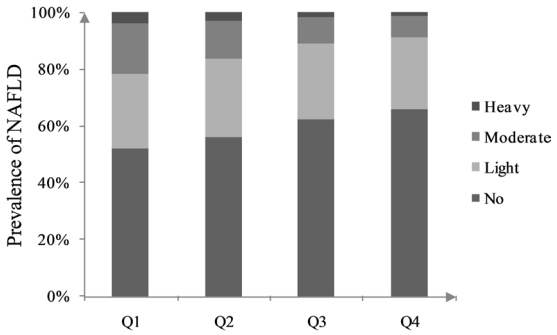

Figure 1. Prevalence of NAFLD according to Lp-PLA2 quartiles. No = No NAFLD; Light = Light NAFLD; Moderate = Moderate NAFLD; Heavy = Heavy NAFLD.

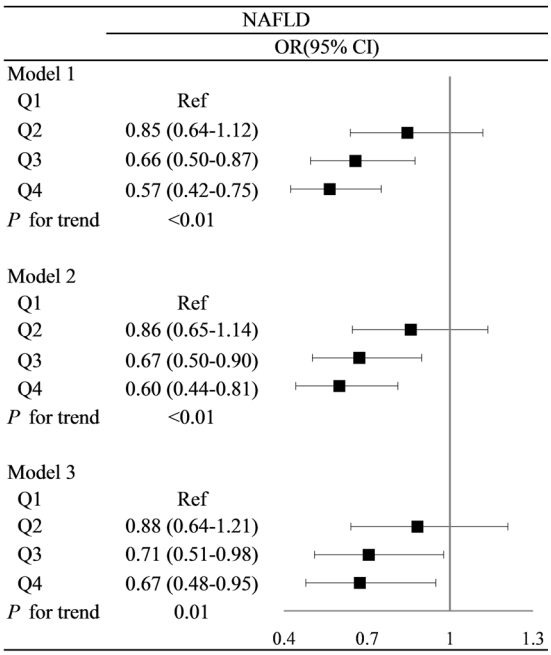

Figure 2. Multivariate-adjusted OR and 95% CI for NAFLD according to Lp-PLA2 quartiles. *P < 0.05. OR: odd ratio; CI: confidence interval. The Q1 group was regarded as a reference. Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: adjusted for age, sex, BMI, physical activity, education level, smoking, ALT, diabetes, hypertension and hyperlipidaemia.

	OR (95% CI)		
	Model 1	**Model 2**	**Model 3**
Q1	Ref	Ref	Ref
Q2	0.71 (0.46–1.07)	0.74 (0.48–1.12)	0.64 (0.41–1.01)
Q3	0.49 (0.31–0.77)	0.54 (0.34–0.86)	0.48 (0.29–0.80)
Q4	0.41 (0.25–0.66)	0.46 (0.28–0.76)	0.47 (0.28–0.79)
P for trend	<0.01	<0.01	<0.01

Table 2. Multivariate-adjusted OR and 95% CI for moderate and heavy NAFLD compared with light NAFLD at different Lp-PLA2 levels. OR: odd ratio; CI: confidence interval. The group of Q1 was regard as reference. Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: adjusted for age, sex, BMI, physical activity, education level, smoking, ALT, diabetes, hypertension and hyperlipidaemia.

Our finding is inconsistent with a small sample sized study. A case-control analysis of 95 Turkish participants age around 40 years conducted by Yasar Colak revealed that Lp-PLA_2 levels are higher in NAFLD patients than in healthy controls[13]. The study of Colak is a small sample size case-control study. Some unavoidable biases

such as recall bias may exist in this type of retrospective study. Therefore, association between Lp-PLA_2 and NAFLD was explored in our cohort study with a large sample size. Moreover, NAFLD is strongly associated with cardiovascular disease, hence we excluded participants suffering from cardiovascular diseases (stroke, coronary disease, transient ischemic attack). Therefore, the study population in the present study is a cardiovascular disease-free population, which might explain the inconsistency with Colak's study. In addition, our participants were middle-aged and elder people (mean ages 61.6 ± 11.8) but subjects in Colak study were relative young. Hence, the relationship between Lp-PLA_2 and NAFLD should be further explored.

However, several studies have also similar findings with us. Nozomu Kono, *et al*. indicated that Lp-PLA_2 was protective against ox-LDL-induced hepatic injury, which is regarded as a leading cause of NAFLD[15,16]. In addition, Stanislav, *et al*. demonstrated that the serum Lp-PLA_2 secretion was increased in response to endotoxin-induced hepatic damage. Increased Lp-PLA_2 levels promoted the elimination of excess oxidized phospholipids to prevent further hepatic damage[17]. Meanwhile, Grypioti further determined that Lp-PLA_2 inhibits oxidative stress-induced liver damage and promotes liver recovery through animal experiments[18]. These studies suggest that Lp-PLA_2 has a positive effect on liver tissue protection. In addition, our results supported the idea that increased Lp-PLA_2 levels are associated with decreased NAFLD prevalence.

We proposed several explanations to analyze the results in our study. First, serum Lp-PLA_2 can hydrolyze oxidized phospholipids (oxPL), a part of ox-LDL, to decrease oxidative stress which has been demonstrated as a major leading cause of NAFLD[9,11,12,19–21]. Second, Lp-PLA_2 may hydrolyze oxPL to increase paraoxonase (PON) expression, which is a beneficial enzyme for NAFLD[22,23]. Third, serum Lp-PLA_2 may bind HDL to form HDL-Lp-PLA_2; then, HDL-Lp-PLA_2 exerts a positive regulatory effect on inflammation and dyslipidaemia to protect against NAFLD[24–27]. In addition, several studies have revealed the serum lipid regulatory effect of Lp-PLA_2[24,25,28], so our results that hyperlipidaemia significantly decreased with the elevation of Lp-PLA_2 level in baseline further supported our finding. However, these proposed underlying mechanisms require further study.

To the best of our knowledge, previous studies have mainly focused on basic studies, not epidemiological studies, to show evidence that Lp-PLA_2 plays a protective effect in the liver. Our study is the first epidemiological study especially indicates that Lp-PLA_2 is beneficial for NAFLD in a large Chinese population. NAFLD is a worldwide health problem, particularly in subjects with middle or old age. Currently, diagnosis of NAFLD mainly depends on imaging examination and liver biopsy, therefore exploring a new effective serum biomarker is necessary for the diagnosis and prevention of NAFLD. Our finding that Lp-PLA_2 associates with the initiation and progression of NAFLD might suggests that detection of Lp-PLA_2 is helpful for the diagnosis and prevention of NAFLD.

Nevertheless, several limitations in our study must be noted. We were unable to measure the hepatic Lp-PLA_2 expression, which is a better marker to study. Liver biopsies had the more accuracy to diagnose NAFLD than abdominal ultrasonography did, but it was with invasive property. So, abdominal ultrasonography was used in the current study for diagnosis of NAFLD. Besides, we did not measure Lp-PLA_2 activity, which is more representative, but the Lp-PLA_2 concentration is closely correlated with activity; thus, we selected concentration in our study. In addition, the present study was a cross-sectional study. These results need to be further investigated in a longitudinal design for testing the causality. Since the study is ongoing, more data are needed to further confirm the correlation between Lp-PLA_2 and NAFLD in the future.

In conclusion, we have demonstrated that Lp-PLA_2 is significantly associated with decreased NAFLD risk in a large Chinese population, and increased Lp-PLA_2 levels may be useful as an independent protector against NAFLD.

Methods

Study population. In the current study, we included 2012 participants $\geq$40 years old who had their serum Lp-PLA_2 levels measured in the APAC (Asymptomatic Polyvascular Abnormalities in Community) study[29]. We further excluded the participants who had (1) no or incomplete NAFLD information (n = 36), (2) a history of cancer (n = 27), (3) excessive alcohol consumption (male $\geq$ 20 g/d, female $\geq$ 10 g/d) and a positive HbsAg test (n = 362). In total, 1587 individuals were included in this analysis (Fig. 3).

All participants underwent a standardized questionnaire survey, physical examinations and laboratory assessments conducted by 11 hospitals in the Kailuan community. The study was performed according to the Declaration of Helsinki guidelines and was approved by the Ethics Committees of Beijing Tiantan Hospital and Kailuan General Hospital. All subjects provided informed consent for participation in the study.

Lp-PLA_2 Assessment. Blood samples were drawn from the antecubital vein after an overnight fast and were collected in ethylene diamine tetraacetic acid (EDTA) tubes. The samples were stored at −80 °C for subsequent analyses after a centrifugation at least 10 min at 3000 r/min. The serum Lp-PLA_2 concentration was measured by enzyme-linked immunosorbent assays (ELISAs) according to the manufacturer's instructions[29]. The intra- and inter-assay coefficients of variation were <8% and <10%. To minimize the measurement error, the serum levels of Lp-PLA_2 were also assessed by professional technicians in Beijing Tiantan Hospital simultaneously. The participants were classified into 4 groups according to the quartile of Lp-PLA_2 concentration.

NAFLD Assessment. NAFLD examination was performed via abdominal ultrasonography by two experienced radiologists who were blinded to laboratory participants. Fatty liver was diagnosed by a high-resolution B-mode topographic ultrasound system with a 3.5 MHz probe (ACUSON × 300, Siemens, Germany). The fatty liver diagnosis was based on the presence of at least two of the following three clinical findings: (1) diffusely increased liver near field ultrasound echo ('bright liver'); (2) liver echo greater than kidney; (3) vascular blurring and the gradual attenuation of far field ultrasound echo. NAFLD was also categorized into three types: Light (5% < lipid content $\leq$ 10%), Moderate (10% < lipid content $\leq$ 25%), Heavy (25% < lipid content)[30,31].

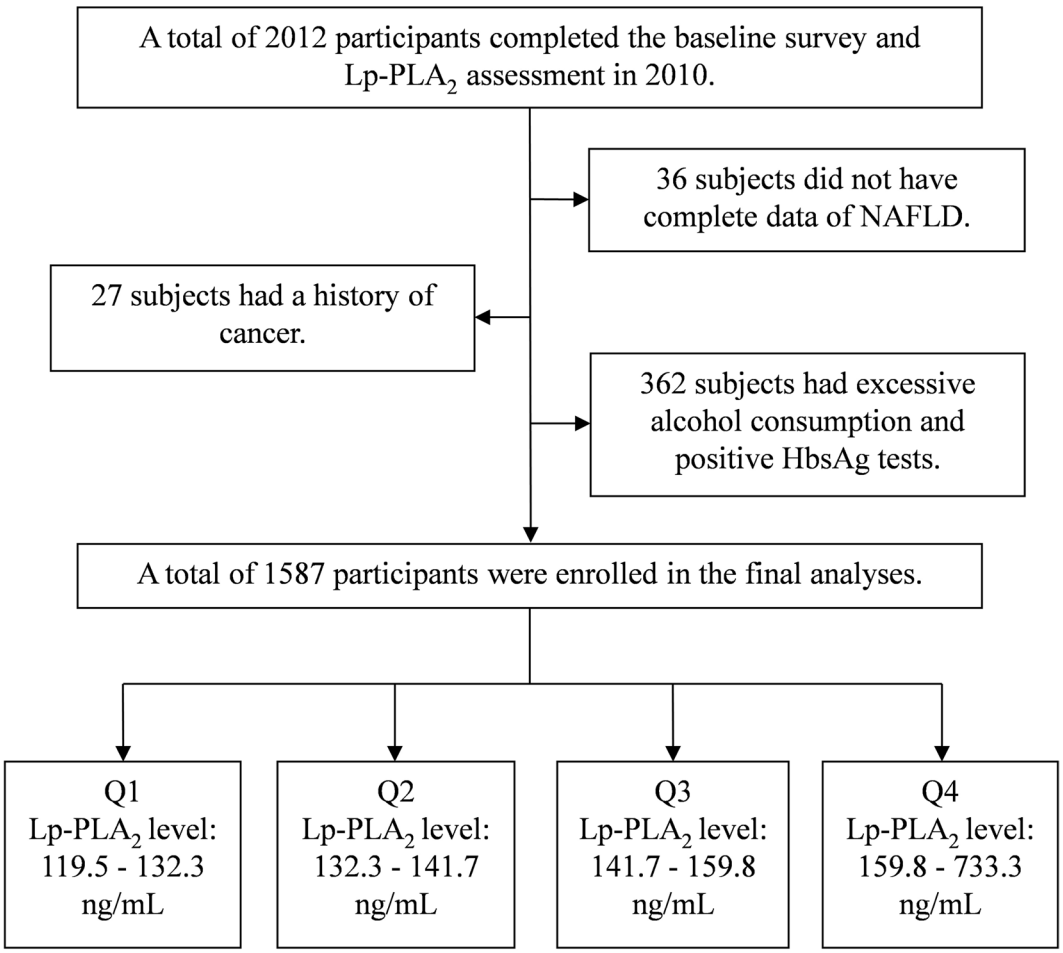

Figure 3. Flow chart of the study.

Assessment of demographic variables and potential covariates. Participants reported basic information by answering questionnaires including age, sex, lifestyle behaviours and medical history. Smoking was categorized as none or current smoking on the basis of the self-report. Physical activity was evaluated from subject responses, and the subjects were categorized as inactive, moderate and active. Education level was classified as illiterate or primary, middle/high school or college and above.

All participants were measured by standing in light clothing without shoes and hats. Body weight was measured to the nearest 0.1 kg with the use of calibrated platform scales, and height was measured to the nearest 0.1 cm with the use of a tape ruler. Body mass index (BMI) was calculated as weight divided by the square of height.

Diseases history mainly included hypertension, diabetes and hyperlipidaemia. After a $\geq$5-min resting period, blood pressure was measured with a mercury sphygmomanometer twice at 5-min intervals on the left arm while the patient was in a seated position. The mean of 2 readings was used for analysis. A systolic blood pressure $\geq$140 mm Hg, diastolic blood pressure $\geq$90 mm Hg or a history of hypertension was defined as hypertension. Diabetes was defined as a fasting blood glucose concentration $>$7.0 mmol/L or a medical history of diabetes. The total cholesterol (TC) level was measured with the use of an enzymatic colorimetric method, and high-density lipoprotein cholesterol (HDL) and low-density lipoprotein cholesterol (LDL) levels were measured by direct tests (Mind Bioengineering Co. Ltd). Triglyceride (TG) and alanine aminotransferase (ALT) levels were also measured. Hyperlipidaemia was defined as a history of hyperlipidaemia, TC $\geq$ 5.7 mmol/L, TG $\geq$ 1.7 mmol/L, or the current use of lipid-lowering drugs. An autoanalyser (Hitachi 747; Hitachi) was used to analyse all plasma samples at the central laboratory of Kailuan General Hospital.

Statistical analyses. Continuous variables are shown as the means $\pm$ standard deviation (ME $\pm$ SD) and were compared using an analysis of variance (ANOVA) or a t-test. Categorical variables are presented as frequencies (percentage) and were compared using the Chi-squared test. Multivariate logistic regression was used to evaluate the relationship between Lp-PLA2 concentration and NAFLD by calculating the odds ratio (OR) and 95% confidence interval (CI). Moreover, the association between Lp-PLA_2 and different levels of NAFLD was analysed by logistic regression. Potential confounders such as age, sex, BMI, smoking, physical activity, education level, ALT, diabetes, hypertension and hyperlipidaemia were adjusted in statistical analyses. Statistical analysis was performed using SAS software, version 9.3 (SAS Institute Inc., Cary, NC, USA). $P < 0.05$ was regarded as significant for 2-sided tests.

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Author Contributions

Z.L., L.Y. and Y.Z. conceived and designed the research Y.Z., Z.G. and L.C. contributed to the acquisition of data Z.L. and H.L. analyzed and interpreted the data Z.L. and H.L. were primarily responsible for writing the paper. All authors revised the manuscripts for important intellectual content.

Additional Information

Competing Interests: The authors declare no competing interests.

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