

# Association between cumulative exposure to different lipid parameters and risk of newly developed carotid plaque

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## ABSTRACT

**Background and purpose** Both the magnitude and cumulative exposure of atherogenic lipoproteins have an impact on the atherosclerosis risk, and the exploration focus has shifted from one single lipoprotein assessment to the cumulative exposure of lipoproteins. We aim to investigate the relationship between cumulative exposure to different lipid parameters and the risk of newly developed carotid plaque in this study.

**Methods** In the Asymptomatic Polyvascular Abnormalities Community study, 2947 participants were included with follow-up every 2 years from 2006 to 2012. Lipid parameters including total cholesterol (TC), triglycerides (TGs), low-density lipoprotein cholesterol (LDLC), high-density lipoprotein cholesterol (HDLC) and non-HDLC were measured. Cumulative exposure was calculated by adding the weighted sum of the difference between the measured value and the cut-off value of each parameter. Newly developed carotid plaques were identified by carotid ultrasound performed at the third and fourth follow-ups.

**Results** In the univariate analysis, non-HDLC burden had the highest ORs among the five lipid parameters for newly developed carotid plaque in each quartile, as 1.0 (reference), 1.35 (1.09–1.67), 1.68 (1.36–2.08) and 2.74 (2.22–3.38) from the lowest to the highest quartile. In the multivariate analysis and sensitivity analysis, we obtained similar results.

**Conclusions** TC burden, TG burden, LDLC burden and non-HDLC burden are all independent risk factors for newly developed carotid plaque, especially for the vulnerable plaques. Among lipid parameters, non-HDLC burden is an optimal predictor. Moreover, the predictive value remained significant for participants under the age of 65 years old or free of hypertension, diabetes mellitus and hyperlipidaemia.

## INTRODUCTION

China bears the largest stroke burden worldwide with a prevalence of 1596 per 100 000 people, and 77.8% is ischaemic stroke.<sup>1</sup> It was reported carotid plaque is a crucial cause of thromboembolism with an estimation of 40% among all atherosclerosis.<sup>2</sup> The heavy socioeconomic burden urges the need for risk factor controls to slow down the asymptomatic atherosclerosis progression at the early stage.

Hyperlipidaemia is an important risk factor for atherosclerosis and cardiovascular guidelines have specific recommendations for targeted lipid control levels on the one-time measurement. Recently, the *Journal of the American College of Cardiology* introduced a concept that both the magnitude and cumulative exposure duration to atherogenic lipoproteins have an impact on the cardiovascular disease risk, shifting the focus from one single assessment to the cumulative exposure of lipoproteins.<sup>3</sup> This hypothesis has been proved by the Mendelian randomisation studies that the genetic variants maintained an ideal level of apo-B containing lipoproteins all lifelong could effectively slow down the progression of atherosclerotic plaques,<sup>4–6</sup> while the clinical evidence is still absent.

Therefore, in this study, we aimed to investigate the predictive association between cumulative exposure to different lipid parameters and newly developed carotid plaque, especially the vulnerable plaque, in the Asymptomatic Polyvascular Abnormalities Community (APAC) prospective study.

## SUBJECTS AND METHODS

### Study population

The APAC study is a community-based, prospective and long-term observational study which has been described in detail previously.<sup>7</sup> As a subpopulation of Kailuan study,<sup>8</sup> a total of 5440 participants were enrolled from June 2006 to October 2007 when met the inclusion criteria: (1) older than 40 years old; (2) without previous cardiovascular or cerebrovascular diseases, including transient ischaemic attack, stroke and coronary disease at baseline. For this study, participants were eligible if they attended four consecutive examinations in 2006–2007 (exam 1), 2008–2009 (exam 2), 2010–2011 (exam 3) and 2012–2013 (exam 4). Finally, we included

2947 participants (1272 men and 1675 women) with complete information on questionnaire assessment, clinical evaluation, laboratory test every 2 years together with two times of carotid ultrasound on exam 3, and exam 4 in the current analyses.

### Lipid parameters measurement and lipid burden calculation

For each clinical examination, blood samples were drawn under fasting conditions and analysed within 4 hours using an autoanalyser (Hitachi 747; Hitachi, Tokyo, Japan) at the central laboratory of the Kailuan hospital. Total cholesterol (TC) was measured using the end-point test method. Low-density lipoprotein cholesterol (LDLC) and high-density lipoprotein cholesterol (HDLC) were measured using a direct test method and triglycerides (TGs) were measured using the glycerol phosphate oxidase (GPO) method (interassay coefficient of variation <10%; Mind bioengineering Co., Shanghai, China). Non-HDLC level is calculated routinely as total TC minus HDLC. We calculated the cumulative burden of TC, TG, LDLC or HDLC for each subject from baseline to the fourth examination ((mmol/L) \* year) based on ideal cut-off levels as follows: 5.2, 1.7, 1.8, 1.0 mmol/L.<sup>9 10</sup> The cumulative burden of TC was calculated as the weighted sum of the difference between the measured value and the cut-off value:

$$\text{TC burden}_{2006-2008} = [(TC_{2006} - 5.2) + (TC_{2008} - 5.2)] / 2 * \text{time}_{2006-2008}$$

$$\text{TC burden}_{2006-2012} = \text{TC burden}_{2006-2008} + \text{TC burden}_{2008-2010} + \text{TC burden}_{2010-2012}$$

TG burden and LDLC burden were calculated by the same method. For HDLC calculation, the subtraction was opposite as the decrease of HDLC is abnormal: HDLC burden<sub>2006-2008</sub> = [(1.0 - HDLC<sub>2006</sub>) + (1.0 - HDLC<sub>2008</sub>)] / 2 \* time<sub>2006-2008</sub>. For non-HDLC calculation, due to the lack of recommended target levels from any guidelines, we use the equation: non-HDLC burden<sub>2006-2008</sub> = (non-HDLC<sub>2006</sub> + non-HDLC<sub>2008</sub>) / 2 \* time<sub>2006-2008</sub>.

### Demographic, behavioural and clinical characteristics assessment

Baseline demographic characteristics were self-reported on a questionnaire at baseline including age, sex, physical activity, income status, medical history (including hypertension, diabetes mellitus (DM), hyperlipidaemia), smoking status, drinking status and current medication status. Blood pressure (BP) was measured by trained nurses on admission and body mass index (BMI) was calculated as body weight (kg) divided by the square of height (m<sup>2</sup>). The fasting blood glucose was measured with the hexokinase/glucose-6-phosphate dehydrogenase method and uric acid (UA) was determined with the uricase-peroxidase method.

### Newly developed carotid plaque assessment

Newly developed carotid plaque was defined as the first occurrence of carotid plaque in exam 4, either the stable or vulnerable plaque. High-resolution B-mode

ultrasounds (Philips iU-22 ultrasound system, Philips Medical Systems, Bothell, Washington, USA) with a 5–12 MHz linear array transducer were used to detect plaques bilaterally on three segments: the common carotid artery, the bifurcation and the internal carotid artery. An atherosclerotic plaque was defined as a focal structure encroaching into the arterial lumen of 0.5 mm or 50% of the surrounding intima-media thickness value, or thicker than 1.5 mm as measured from the intima-lumen interface to the media-adventitia interface.<sup>11</sup> The plaque vulnerability is determined based on morphological ultrasound characteristics, including the presence of surface irregularity or ulceration, or anaechogenic plaque, or heterogeneous plaque as previously described.<sup>12 13</sup>

### Statistical analysis

Continuous variables were described by medians and IQR because of skewed distributions, and categorical variables were presented as counts and percentages. The non-parametric Wilcoxon or Kruskal-Wallis test was used to compare group differences for continuous variables, and the  $\chi^2$  test was used for categorical variables.

The associations of cumulative exposure to different lipid parameters and newly developed carotid plaque, especially the vulnerable plaque, were assessed by logistic regression after adjusting for different cardiovascular risk factors. The TC burden, TG burden, LDLC burden, HDLC burden and non-HDLC burden from 2006 to 2012 were all divided into four groups according to their quartiles, and the lowest quartile was defined as the reference group. Both univariate and multivariate analyses were expressed by ORs and 95% CI. Sensitivity analysis was performed to test whether the results would change after excluding participants aged over 65 years old or with a history of hypertension, DM and hyperlipidaemia.

Overall, a two-sided value of  $p < 0.05$  was considered statistically significant. All statistical analyses were performed by SAS software, V.9.1 (SAS Institute, Cary, North Carolina, USA).

## RESULTS

### Baseline characteristics

Of the 2947 participants enrolled in our study, 55.04% (1622/2947) with pre-existing or non-existing carotid plaque, 44.96% of participants (1325/2947) were diagnosed as newly formed carotid plaque. Among them, 56.53% (749/1325) were stable plaque and 43.47% (576/1325) were vulnerable plaque. Those with a newly developed carotid plaque were more likely to be older and women; had slightly higher BP, BMI, UA, TC, TG, non-HDLC; had higher proportions of the current smoker, history of DM, hypertension, hypercholesterolaemia and current medication in use ( $p < 0.001$ , table 1).

### Correlation between different lipids burden and newly formed carotid plaque

In the univariate analysis, the associations between each lipid burden and newly developed carotid plaque were all

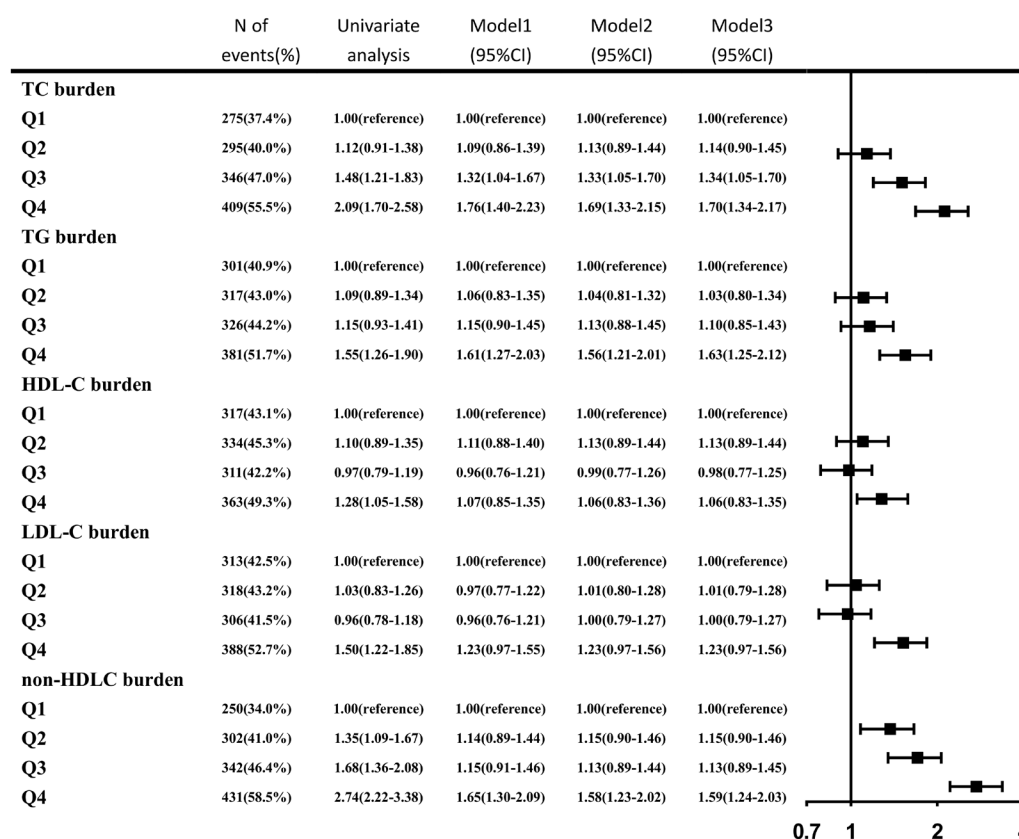
**Table 1** Baseline characteristics

	Pre-existing or non-existing carotid plaque	Newly developed carotid plaque		P value
		Stable plaque	Vulnerable plaque	
N	1622	749	576	
Age, years	46.72 (43.28–52.94)	54.60 (48.02–62.96)	59.97 (51.25–70.90)	<0.001
Male, %	810 (49.94)	285 (38.05)	177 (30.73)	<0.001
SBP, mm Hg	120.0 (110.0–130.0)	130.0 (119.3–140.0)	130.0 (120.0–147.0)	<0.001
DBP, mm Hg	80.0 (70.7–85.0)	80.0 (78.7–90.0)	80.0 (77.7–90.0)	<0.001
BMI, kg/m <sup>2</sup>	24.42 (22.37–26.75)	24.95 (22.90–27.31)	24.84 (22.77–27.12)	<0.001
FBG, mg/dL	5.09 (4.64–5.60)	5.10 (4.61–5.78)	5.09 (4.63–5.70)	0.448
Uric acid, μmol/L	262.0 (214.0–319.0)	294.0 (240.0–356.0)	299.5 (248.0–363.5)	<0.001
TC, mg/dL	4.82 (4.20–5.41)	5.01 (4.38–5.62)	5.09 (4.63–5.70)	<0.001
TG, mg/dL	1.19 (0.84–1.74)	1.30 (0.91–2.04)	1.35 (0.95–1.94)	<0.001
HDLC, mg/dL	1.53 (1.32–1.77)	1.49 (1.28–1.76)	1.49 (1.30–1.73)	0.137
LDLC, mg/dL	2.30 (1.85–2.70)	2.24 (1.81–2.74)	2.31 (1.83–2.80)	0.459
non-HDLC, mg/dL	3.26 (2.70–3.87)	3.49 (2.82–4.09)	3.52 (2.90–4.13)	<0.001
Physical activity				<0.001
None	162 (9.99)	116 (15.49)	134 (23.26)	
Seldom	1301 (80.21)	507 (67.69)	337 (58.51)	
Always	159 (9.80)	126 (16.82)	105 (18.23)	
Income status				<0.001
<600	450 (27.74)	244 (32.58)	235 (40.80)	
600–800	900 (55.49)	353 (47.13)	255 (44.27)	
800–1000	136 (8.38)	73 (9.75)	39 (6.77)	
>1000	136 (8.38)	79 (10.55)	47 (8.16)	
Current smoker, n (%)	395 (24.35)	228 (30.44)	170 (29.51)	<0.001
Current drinker, n (%)	574 (35.39)	271 (36.18)	192 (33.33)	0.281
Medical history				
Diabetes mellitus	22 (1.36)	36 (4.81)	30 (5.21)	<0.001
Hypertension	115 (7.09)	122 (16.29)	100 (17.36)	<0.001
Hypercholesterolaemia	80 (4.93)	85 (11.35)	60 (10.42)	<0.001
Antihypertensive medication, n (%)	93 (5.73)	108 (14.42)	94 (16.32)	<0.001
Antidiabetic medication, n (%)	17 (1.05)	30 (4.01)	26 (4.51)	<0.001
Lipid-lowering medication, n (%)	9 (0.55)	14 (1.87)	10 (1.74)	<0.001

BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

significant ( $p < 0.05$ ). Non-HDLC burden had the highest OR value for newly developed carotid plaque in each quartile, as 1.0 (reference), 1.35 (1.09–1.67), 1.68 (1.36–2.08) and 2.74 (2.22–3.38) from the lowest to the highest quartile ( $p < 0.001$ ). In the multivariate analysis, the statistical significance of the HDLC burden disappeared after adjustment for age, sex, smoking status, drinking status, BMI, hypertension, DM, hypercholesterolaemia, physical activity, income status, antihypertensive medication, antidiabetic medication and lipid-lowering medication. The rest four lipid burdens were still positively associated with newly developed carotid plaque after adjusting for potential covariates (figure 1).

With further examination of the relationship between each lipid burden and newly developed vulnerable carotid plaque, similar results were obtained. Non-HDLC burden was superior to the other four lipid burdens, having the highest OR value as 1.0 (reference), 1.36 (1.11–1.67), 1.67 (1.26–2.05), 2.53 (2.07–3.09) in each quartile ( $p < 0.001$ ). After adjustment for potential covariates, the significance remained except for HDL-C burden (figure 2). Besides, sensitivity analysis coincided with these results among participants under the age of 65 years or free of hypertension, DM and hyperlipidaemia, additional information is given in table 2.



**Figure 1** ORs for newly developed carotid plaque for various level of lipid burdens. 95% CI; model 1: adjusted for age, sex; model 2: add smoker, drinker, body mass index, diabetes mellitus, hypertension, hypercholesterolaemia, physical activity, income status to model 1; model 3: add antihypertensive medication, antidiabetic medication, lipid-lowering medication to model 2. HDLC, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

## DISCUSSION

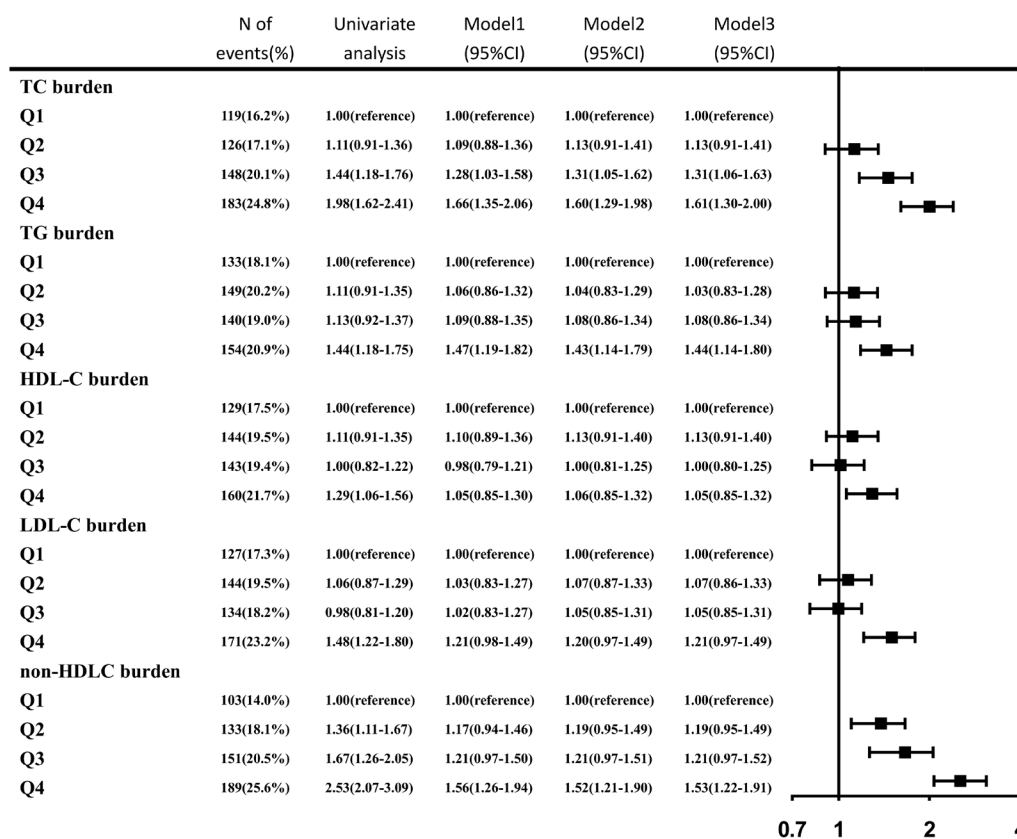
In this study, among the five lipid parameters, non-HDLC burden, calculated as the weighted sum of average non-HDLC in the four examinations from 2006 to 2012, was the superior independent predictor for newly developed carotid plaque, especially for the vulnerable plaques. The significance remained in participants under the age of 65 years or free of hypertension, DM and hyperlipidaemia.

Previous studies revealed the association between different lipid parameters and carotid plaque.<sup>14-18</sup> The cross-sectional study based on one single time-point measurement could not indicate causality. Atherosclerotic plaques grow over time as additional lipoprotein particles retain, and the size of plaque is determined by both the magnitude and cumulative exposure to the lipids. Major guidelines endorse one single assessment of lipid parameters<sup>19,20</sup>; it could not be expected to adequately reflect the dynamic change. There were studies focused on cumulative exposure to other atherosclerotic risk factors, such as C-reactive protein and resting heart rate.<sup>21,22</sup> Thus, we aim to evaluate the cumulative exposure to lipid over time derived from multiple measurements to predict newly developed carotid plaque, which might be a better

method to quantify the relationship between different lipid parameters and asymptomatic carotid plaques.

When TG levels are higher than 2.3 mmol/L, non-HDLC surpass LDL-C being the optimal representative for all atherogenic lipoproteins.<sup>9</sup> In the series of APAC study, the predictive value of non-HDLC was not better than LDL-C on extracranial internal carotid stenosis, which could be partially attributed to the small percentage of participants with hypertriglyceridaemia.<sup>23</sup> The data are limited to validate the predictive values of different lipid parameters for early-stage asymptomatic atherosclerosis before developing into ischaemic cardiovascular disease or stroke. Our study suggests the predictive value of non-HDLC burden is superior to LDL-C burden on newly developed carotid plaque. Atherosclerosis is a progressive process, from the normal arterial intima, to the fatty streak, fibrous plaque, atherosclerotic plaque and eventually to plaque disruption.<sup>24</sup> As newly developed carotid plaque could not quantitatively reflect the atherosclerosis degree, our study further investigated the relationship between cumulative exposure to different lipid parameters and newly developed vulnerable carotid plaque, which indicates a more severe degree of atherosclerosis





**Figure 2** ORs for newly developed vulnerable carotid plaque for various level of lipid burdens. 95% CI; model 1: adjusted for age, sex; model 2: add smoker, drinker, body mass index, diabetes mellitus, hypertension, hypercholesterolaemia, physical activity, income status to model 1; model 3: add antihypertensive medication, antidiabetic medication, lipid-lowering medication to model 2. HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

progression. The study highlights the need of taking cumulative exposure into account rather than a single risk factor measurement. When the atherosclerotic lipoproteins accumulate to a certain extent, the plaque rupture probability increases. Individualised lipid-lowering therapy should be administrated to slow down the plaque progression speed. Aggressive treatment is recommended to patients with high lipids burden.

It is noteworthy that the recommended levels of TC, TG, LDLC and HDLC are under 5.2, 1.7, 2.6, 1.0 mmol/L in the Third Report of the National Cholesterol Education Program.<sup>9</sup> The cut-off value of LDLC was set at 1.8 mmol/L instead of 2.6 mmol/L, as the 2019 European guideline highlighted a more aggressive control of LDLC to achieve a significant reduction in the risk of stroke.<sup>10 25</sup> The cumulative exposure to increased TC, TG, LDLC, HDLC and total non-HDLC over 6 years could not fully reflect the lipid burden of lifelong health. Therefore, we conducted a sensitivity analysis excluding participants over 65 years old to minimise the age-related growth of carotid plaque attributed to lipids deposition.<sup>26</sup> Hypertension, DM and hyperlipidaemia are recognised risk factors for atherosclerosis,<sup>27</sup> sensitivity analysis was performed and the same results were obtained that the

non-HDLC burden was concentration dependently associated with newly developed carotid plaque.

Our study has some limitations. As cumulative exposure is also relevant to non-lipid risk factors, the ideal expression of cardiovascular risk theoretically would be an integration of cumulative exposure to all-risk covariates, such as tobacco pack years, drinking years and environmental pollution factors. Second, both carotid plaque and vulnerable carotid plaque are semiquantitative endpoint events. The size, area or numbers of carotid plaque should also be taken into consideration when seeking for the relationship between cumulative exposure to lipid parameters and early-stage asymptomatic atherosclerosis. Although we collected the information in ultrasonography, further research is needed to provide insight into the relationship.

## CONCLUSIONS

In conclusion, TC burden, TG burden, LDLC burden and non-HDLC burden are all independent risk factors for newly developed carotid plaque, especially the vulnerable plaque. Among them, non-HDLC burden is the optimal predictor. The predictive value remained in participants

**Table 2** ORs for newly developed carotid plaque for various level of lipid burdens in sensitivity analysis

	Newly developed carotid plaque		Newly developed vulnerable carotid plaque	
	Model 4 (95% CI)	Model 5 (95% CI)	Model 4 (95% CI)	Model 5 (95% CI)
<b>TC burden</b>				
Q1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2	1.12 (0.87 to 1.44)	1.09 (0.84 to 1.41)	1.12 (0.88 to 1.42)	1.08 (0.85 to 1.37)
Q3	1.31 (1.01 to 1.68)	1.30 (1.00 to 1.68)	1.31 (1.03 to 1.67)	1.28 (1.01 to 1.63)
Q4	1.67 (1.29 to 2.15)	1.54 (1.18 to 2.00)	1.68 (1.32 to 2.14)	1.49 (1.17 to 1.89)
P for trend	<0.001	0.003	<0.001	<0.001
Continuous scale	1.03 (1.01 to 1.05)	1.03 (1.01 to 1.04)	1.03 (1.02 to 1.05)	1.03 (1.01 to 1.04)
<b>TG burden</b>				
Q1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2	1.04 (0.81 to 1.35)	1.05 (0.81 to 1.37)	1.05 (0.82 to 1.34)	1.03 (0.82 to 1.31)
Q3	1.09 (0.84 to 1.43)	1.15 (0.88 to 1.49)	1.09 (0.85 to 1.40)	1.14 (0.90 to 1.45)
Q4	1.65 (1.26 to 2.16)	1.64 (1.24 to 2.16)	1.56 (1.21 to 2.01)	1.51 (1.18 to 1.95)
P for trend	0.020	0.017	0.015	0.010
Continuous scale	1.01 (1.00 to 1.03)	1.02 (1.00 to 1.03)	1.01 (1.00 to 1.02)	1.02 (1.00 to 1.03)
<b>HDLC burden</b>				
Q1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2	1.16 (0.90 to 1.48)	1.20 (0.92 to 1.56)	1.21 (0.95 to 1.54)	1.23 (0.97 to 1.57)
Q3	0.96 (0.74 to 1.24)	1.01 (0.77 to 1.32)	1.03 (0.81 to 1.31)	1.09 (0.85 to 1.39)
Q4	1.09 (0.84 to 1.41)	1.17 (0.89 to 1.53)	1.12 (0.87 to 1.43)	1.17 (0.91 to 1.50)
P for trend	0.454	0.166	0.433	0.182
Continuous scale	1.02 (0.97 to 1.07)	1.04 (0.99 to 1.09)	1.02 (0.97 to 1.07)	1.03 (0.99 to 1.08)
<b>LDLC burden</b>				
Q1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2	0.98 (0.76 to 1.26)	1.04 (0.80 to 1.35)	1.03 (0.81 to 1.31)	1.10 (0.87 to 1.40)
Q3	0.98 (0.77 to 1.26)	0.94 (0.73 to 1.23)	1.02 (0.80 to 1.29)	1.04 (0.82 to 1.33)
Q4	1.20 (0.93 to 1.54)	1.30 (1.00 to 1.69)	1.19 (0.94 to 1.51)	1.31 (1.03 to 1.67)
P for trend	0.016	0.006	0.009	0.001
Continuous scale	1.03 (1.01 to 1.05)	1.04 (1.01 to 1.06)	1.03 (1.01 to 1.05)	1.04 (1.01 to 1.06)
<b>Non-HDLC burden</b>				
Q1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2	1.21 (0.94 to 1.56)	1.12 (0.87 to 1.45)	1.26 (0.99 to 1.60)	1.17 (0.92 to 1.48)
Q3	1.18 (0.91 to 1.52)	1.15 (0.88 to 1.49)	1.21 (0.95 to 1.55)	1.16 (0.91 to 1.47)
Q4	1.56 (1.20 to 2.03)	1.53 (1.17 to 2.01)	1.60 (1.24 to 2.05)	1.53 (1.20 to 1.96)
P for trend	0.005	0.008	<0.001	<0.001
Continuous scale	1.02 (1.01 to 1.04)	1.02 (1.01 to 1.04)	1.02 (1.01 to 1.04)	1.03 (1.01 to 1.04)

Model 4: model 3 excluding subjects with age  $\geq 65$  years.

Model 5: model 3 excluding subjects with history of hypertensive, diabetes mellitus, hyperlipidaemia.

HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

under the age of 65 years old or free of hypertension, DM and hyperlipidaemia.

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**Contributors** JW and YW performed the experiments, interpreted the results of statistical analysis, and drafted the manuscript. AW and JX performed data analysis. KK and JX commented on the drafts. XZ revised the manuscript for intellectual

content. All authors read and approved the final manuscript, and agreed to be accountable for all aspects of the work.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** The study was conducted in accordance with the guidelines from the Helsinki Declaration and approved by the Ethics Committees of the Kailuan General Hospital and Beijing Tiantan Hospital. The Kailuan study, as the original population of APAC study, was registered at the International Clinical Trials Registry Platform with study identifying number ChiCTR-TNRC-11001489. Written informed consent was obtained from all participants.

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**Data availability statement** Data are available to researchers on request for purpose of reproducing the results or replicating the procedure by directly contacting the corresponding author.

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