Original Article

Association between Serum Alkaline Phosphatase and Carotid Atherosclerosis in a Chinese Population: A Community-based Cross-sectional Study

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Abstract

Objective This study aimed to investigate the relationship between alkaline phosphatase (ALP) and common carotid intima media thickness (IMT), carotid plaque, and extracranial carotid artery stenosis (ECAS).

Methods A total of 3,237 participants aged ≥ 40 years were recruited from Jidong community in 2013-2014. Participants were divided into five quintile groups based on their serum ALP levels. Carotid atherosclerosis was assessed using ultrasound. Abnormal IMT, carotid plaque, and ECAS were defined as IMT > 0.9 mm, IMT > 1.5 mm, and ≥ 50% stenosis in at least one extracranial carotid artery, respectively.

Results Common carotid IMT values and the prevalence of carotid plaque increased across serum ALP quintiles. Higher ALP quintiles were correlated with an increased risk of abnormal IMT [fourth quintile: odds ratio (*OR*) 1.78, 95% confidence interval (*CI*) 1.13-2.82, *P* = 0.0135; fifth quintile: *OR* = 1.82, 95% *CI*: 1.15-2.87, *P* = 0.0110] and ECAS compared to the lowest quintile (fifth quintile: *OR* = 1.47, 95% *CI*: 1.09-1.97, *P* = 0.0106). The association between ALP and prevalence of carotid plaque became insignificant after adjustment for confounders.

Conclusion Serum ALP levels were independently associated with abnormal common carotid IMT and ECAS. These conclusions need to be further corroborated in future prospective cohort studies.

Key words: Alkaline phosphatase; Atherosclerosis; Intima media thickness; Carotid plaque; Extracranial carotid artery stenosis

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INTRODUCTION

Various circulating markers of liver function have been shown to be associated with cardiovascular risk[1]. For instance, epidemiological studies have indicated that circulating alkaline phosphatase (ALP), an important enzyme primarily present in the liver and bone[2], is positively correlated with increased risk of cardiovascular events and mortality in patients with chronic kidney disease, as well as in the general population[3-5]. Elevated ALP is an independent prognostic factor for long-term functional outcomes after acute cerebral infarction[6]. Serum ALP is also a predictor of mortality, myocardial infarction, and stent thrombosis in patients with drug-eluting stents[7].

Carotid intima media thickness (IMT) is a valid and reproducible modality to assess subclinical

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carotid atherosclerosis in clinical practice. Extensive evidence has indicated that IMT is a marker of atherosclerosis and could be used to predict future adverse cardiovascular events[8-11]. However, a meta-analysis of 11 population-based studies found that carotid plaque had a significantly higher diagnostic accuracy than IMT for predicting future myocardial infarction[12]. Thus, a combination of carotid plaque detection and IMT measurement could be a more accurate diagnostic tool than either of the measurements alone to screen for coronary artery disease[13]. According to the European guidelines for preventing cardiovascular diseases, both increased IMT and carotid plaque can cause vascular organ damage[14,15]. While the relationship between ALP and IMT has been investigated, the findings remain inconclusive[16-18]. As these previous studies included specific populations, such as children with end-stage renal disease or African men with hypertension, their findings cannot be generalized.

This cross-sectional study aimed to determine the relationship between serum ALP levels and carotid atherosclerosis, including carotid IMT, carotid plaque, and extracranial carotid artery stenosis (ECAS), in a community-based general population.

MATERIAL AND METHODS

Study Population

This prospective cohort study was conducted in Jidong community, located in Tangshan, Hebei Province, China. This community primarily comprises employees who work at Jidong Oilfield Industry, and their families[19]. All residents aged over 18 years from this community were invited to participate in this cohort study. The response rate was 90.4% (9,078/10,043).

This cross-sectional study used baseline data obtained from the cohort study in 2013-2014. Carotid ultrasound was performed only in participants who were aged at least 40 years in the Jidong study. Participants with any of the following conditions or who underwent any of the following procedures were excluded from this cross-sectional study: (1) carotid angioplasty/stenting; (2) carotid endarterectomy; (3) active liver diseases; (4) cirrhosis; (5) bone fracture or bone diseases (e.g. Paget's disease); (6) malignant tumor; (7) hyperparathyroidism; (8) end-stage renal disease requiring dialysis; and (9) pregnancy. The study protocol was approved by the Medical Ethics Committee of Jidong Oilfield. This study was conducted in accordance with the Declaration of Helsinki, and all participants signed informed consent for participation.

Covariate Analysis

All participants were interviewed by well-trained physicians at Jidong Hospital. The demographic data, lifestyle-related information, and medical histories of the participants were collected using standardized questionnaires. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Blood pressure was measured by well-trained physicians using a standard mercury sphygmomanometer while the participants were in a seated position and after at least 5 minutes of rest. Hypertension was defined as systolic blood pressure (SBP) > 140 mmHg or diastolic blood pressure (DBP) > 90 mmHg, being prescribed anti-hypertensive medication, or any prior diagnosis of hypertension. Diabetes was defined as fasting plasma glucose ≥ 7.0 mmol/L, being prescribed diabetes medication, or any prior diagnosis of diabetes. Heavy alcoholism was defined as consumption of more than 5 standard units (1 standard unit contains approximately 14 grams) of alcohol per day.

A fasting venous blood sample (more than 8 h of fasting) was drawn from each participant. Fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and creatinine levels were determined by standard methods using UniCel DxC 600 Synchron (Beckman Coulter, Inc., Brea, CA, USA). Estimated glomerular filtration rate (eGFR) was calculated using the EPI-CKD creatinine equation[20].

Serum ALP activity was measured using the 2-amino-2-methyl-I-propanol (AMP)-buffed method (Kehua Bio-Engineering, Shanghai, China). The coefficient of variation for ALP measurement was 4.6%. Participants were divided into five quintile groups according to their serum ALP levels (U/L): quintile 1, 26-54; quintile 2, 55-63; quintile 3, 64-73; quintile 4, 74-86; and quintile 5, 87-209.

Assessment of Carotid Artery Atherosclerosis

Each participant underwent carotid artery ultrasonography using a high-resolution B-mode tomographic ultrasound system (ACUSON X300, Siemens, Cologne, Germany) with a 10-MHz

linear-array transducer. IMT was measured at the far wall of the common carotid artery proximal to the bifurcation in the longitudinal view, following a plaque-free segment of ≥ 10 mm in length with a clearly identified double-line pattern. Mean IMT values obtained using the edge detection system were analyzed across the entire segment. Plaques were defined as either focal structures encroaching the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value, or > 1.5 mm in thickness, as measured from the intima-lumen interface to the media–adventitia interface[21]. Abnormal IMT was defined as IMT > 0.9 mm[21]. Extracranial carotid arteries included the common carotid arteries, carotid bifurcation, the internal carotid artery, and the external carotid artery. ECAS was defined as ≥ 50% stenosis in at least one extracranial carotid artery[22]. All measurements were performed by two independent sonographers who were blinded to the clinical information of the participants. The inter-observer and intra-observer variability of IMT assessment among 30 volunteers showed a coefficient of variation of 12.5% and 8.1%, respectively.

Statistical Analyses

Categorical variables are presented as a percentage, and continuous variables are shown as means ± standardized deviation (SD). Participant characteristics, IMT, and carotid plaque were compared across ALP quintile groups using either the Chi square test for categorical variables or ANOVA for continuous variables. Logistic regression analysis was used to estimate the risk of abnormal IMT, carotid plaque, and ECAS across the ALP quintiles (with the lowest quintile serving as the reference) by calculating the odds ratios (*OR*s) and 95% confidence intervals (*CI*s). Adjustments were made for the following variables: age, sex, BMI, hypertension, diabetes mellitus, eGFR, myocardial infarction, stroke, smoking, alcohol drinking, lipid profile (TC, TG, LDL-C, and HDL-C), education level, family income, and statin therapy. In addition, subgroup analyses were conducted to determine the effects of age, sex, renal function, nonalcoholic fatty liver disease (NAFLD), and metabolic syndrome on the risk of abnormal IMT, after adjusting for all of the above-mentioned variables. Metabolic syndrome was defined as the presence of three or more of the following factors: (1) waist circumference ≥ 80 cm in women and ≥ 90 cm in men; (2) fasting serum HDL-C < 1.29 mmol/L in women and < 1.04 mmol/L in men; (3) fasting serum TG ≥ 1.69 mmol/L; (4) BP ≥ 130/85 mmHg or consumption of regular antihypertensive medications; and (5) FBG ≥ 5.6 mmol/L or already being treatment for diabetes[23,24]. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Demographic and Clinical Characteristics of the Study Population According to APL Quintiles

A total of 3,237 participants fulfilled the eligibility criteria and were included in the analyses (Figure 1). The mean age of the eligible participants (48.7% male) was 53.5 ± 8.6 years, and the mean ALP level was 71.39 ± 20.35 U/L. The characteristics of the eligible participants and the excluded population are presented in Supplementary Table S1 (available in www.besjournal.com). All participants were divided into quintile groups according to their serum ALP levels, and the demographic data and cardiovascular risk factors were compared across the five quintile groups, as presented in Table 1. Participants in the higher ALP quintiles were older, had a higher BMI, and were more likely to have hypertension, diabetes mellitus, and stroke (all $P < 0.05$). From the lowest to the highest quintile, TC, LDL-C, and TG levels increased, while eGFR and HDL-C levels decreased (all $P < 0.05$).

Association between Serum ALP Levels and Common Carotid IMT

The mean common carotid IMT values across the ALP quintiles are presented in Table 2. Both sides of the common carotid IMT increased gradually from the lowest to the highest quintiles. Compared with the first quartile (the reference category), the *OR*s (95% *CI*s) for abnormal common carotid IMT were 2.14 (1.38-3.32), 2.34 (1.52-3.59), 3.24 (2.14-4.93), and 3.45 (2.27-5.23) for the second, third, fourth, and fifth quintile, respectively (all $P < 0.0001$). After adjusting for confounders, the *OR*s for abnormal common carotid IMT in the fourth and fifth quintile were 1.78 (95% *CI* 1.13-2.82, $P = 0.0135$) and 1.82 (95% *CI*: 1.15-2.87, $P = 0.0110$), respectively (Table 3). In the subgroup analysis, the risk of abnormal IMT per ALP quintile did not differ with respect to sex, age, eGFR, NAFLD, and metabolic syndrome (Supplementary Table S2 available in www.besjournal.com).

Table 1. Demographic and Baseline Clinical Characteristics of the Study Population According to ALP Quintiles

ALP Quintiles	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* Value
Number of subjects, *n*	646	628	690	643	630	/
ALP level, U/L	47.28 ± 5.59	59.17 ± 2.50	68.62 ± 2.95	79.76 ± 3.79	102.78 ± 15.94	/
Age, year	49.49 ± 7.84	52.84 ± 8.27	53.81 ± 8.19	55.15 ± 8.70	56.50 ± 8.22	< 0.0001
Male, %	230 (35.60)	329 (52.39)	377 (54.64)	333 (51.79)	307 (48.73)	< 0.0001
BMI, kg/m^2	23.94 ± 3.19	24.87 ± 3.24	25.17 ± 3.05	25.27 ± 3.10	25.61 ± 3.36	< 0.0001
Hypertension, %	96 (14.86)	119 (18.95)	161 (23.33)	171 (26.59)	213 (33.81)	< 0.0001
Diabetes, %	31 (4.80)	47 (7.48)	47 (6.81)	64 (9.95)	80 (12.70)	< 0.0001
eGFR, $mL \cdot min^{-1}$ 1.73 m^{-2}	90.91 ± 12.75	89.13 ± 11.99	87.86 ± 12.73	87.00 ± 13.34	85.92 ± 13.54	< 0.0001
Myocardial infarction, %	1 (0.15)	7 (1.11)	9 (1.30)	0 (0.00)	6 (0.95)	0.0014
Stroke, %	6 (0.93)	17 (2.71)	24 (3.48)	18 (2.80)	22 (3.49)	0.0279
Current smoker, %	97 (15.02)	146 (23.25)	185 (26.81)	163 (25.35)	182 (28.89)	< 0.0001
Heavy alcoholism, %	3 (0.46)	6 (0.96)	9 (1.30)	4 (0.62)	4 (0.63)	0.4370
Total cholesterol, mmol/L	4.52 ± 0.80	4.62 ± 0.85	4.71 ± 0.90	4.85 ± 0.85	4.84 ± 1.03	< 0.0001
LDL-C, mmol/L	2.49 ± 0.56	2.58 ± 0.60	2.67 ± 0.62	2.75 ± 0.58	2.74 ± 0.61	< 0.0001
TG, mmol/L	1.35 ± 0.98	1.65 ± 1.42	1.70 ± 1.16	1.89 ± 1.60	2.06 ± 1.77	< 0.0001
HDL-C, mmol/L	1.28 ± 0.29	1.21 ± 0.26	1.20 ± 0.28	1.19 ± 0.27	1.16 ± 0.25	< 0.0001
Statin therapy, %	10 (1.55)	7 (1.11)	12 (1.74)	9 (1.40)	18 (2.86)	0.1558
Education level						< 0.0001
Illiteracy/primary/middle school	122 (18.89)	183 (29.14)	214 (31.01)	255 (39.66)	261 (41.43)	
High school	221 (34.21)	191 (30.41)	222 (32.17)	206 (32.04)	209 (33.17)	
College/University	303 (46.90)	254 (40.45)	254 (36.81)	182 (28.30)	160 (25.40)	
Income, CNY						< 0.0001
≤ 3,000	267 (41.33)	297 (47.29)	350 (50.72)	356 (55.37)	335 (53.17)	
3,001-5,000	336 (52.01)	286 (45.54)	301 (43.62)	265 (41.21)	254 (40.32)	
> 5,000	43 (6.66)	45 (7.17)	39 (5.65)	22 (3.42)	41 (6.51)	

Note. ALP: alkaline phosphatase; BMI: body mass index; eGFR: estimated glomerular filtration rate; LDL-C: low-density lipoprotein cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol.

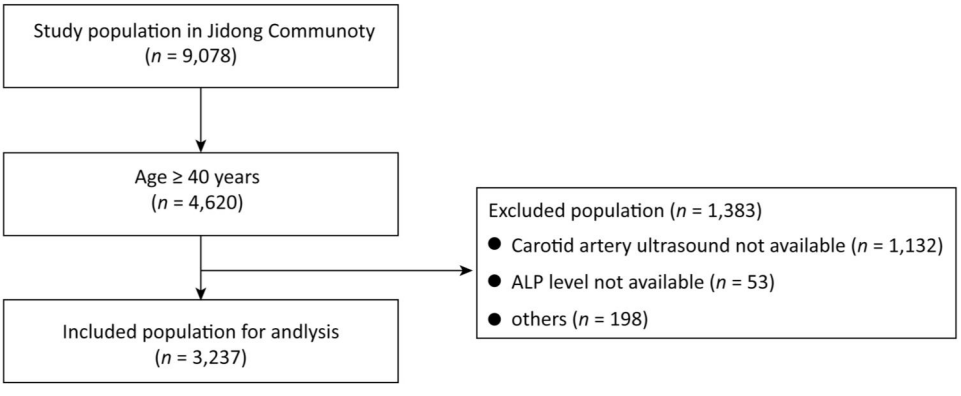

Figure 1. Flow chart of study enrollment. ALP: alkaline phosphatase.

Association between Serum ALP Levels, and Carotid Plaque and ECAS

We examined the correlation of serum ALP levels with carotid plaque and ECAS. As shown in Table 2, the prevalence of carotid plaques increased gradually from the lowest to the highest quintile (from 6.19% to 16.19% on the left side and from 4.49% to 13.65% on the right side, all $P < 0.0001$). The unadjusted risks of carotid plaques were significantly elevated in the higher quintiles, compared to the reference (the lowest quintile). However, after adjusting for confounding covariates, the association between carotid plaques and ALP quintiles was no longer significant (Table 3). Therefore, our data indicate that there is no significant link between ALP levels and carotid plaques.

Using the first ALP quintile as the reference, we found that the *OR*s for ECAS in the second, third, fourth, and fifth quintile were 1.77 (95% *CI*: 1.34-2.33), 1.65 (95% *CI*: 1.25-2.18), 1.880 (95% *CI*: 1.43-2.48), and 2.47 (95% *CI*: 1.88-3.23), respectively. In addition, the *OR* for ECAS in the fifth quintile was 1.47 (95% *CI*: 1.09-1.97, $P = 0.0106$) after adjusting for age, sex, BMI, hypertension, diabetes mellitus, eGFR, myocardial infarction, stroke, smoking, alcohol drinking, lipid profile, education level, family income, and statin therapy (Table 4).

Table 2. Comparison of Common Carotid IMT and Carotid Plaque Across different ALP Levels

ALP Quintiles	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* Value
Left						
Mean common carotid IMT, mm	0.69 ± 0.13	0.73 ± 0.16	0.74 ± 0.20	0.76 ± 0.16	0.78 ± 0.18	< 0.0001
Carotid plaque, %	40 (6.19)	67 (10.67)	70 (10.14)	83 (12.91)	102 (16.19)	< 0.0001
Right						
Mean common carotid IMT, mm	0.68 ± 0.13	0.72 ± 0.16	0.73 ± 0.18	0.76 ± 0.20	0.76 ± 0.16	< 0.0001
Carotid plaque, %	29 (4.49)	60 (9.55)	69 (10.00)	78 (12.13)	86 (13.65)	< 0.0001

Note. IMT: Intima media thickness; ALP: alkaline phosphatase.

Table 3. Risk of Abnormal Common Carotid IMT or Carotid Plaque Across ALP Quintiles

ALP	Unadjusted			Adjusted		
	OR	95% *CI*	*P* value	*OR*	95% *CI*	*P* value
Mean common carotid IMT > 0.9 mm						
Quintile 1	reference	-	-	-	-	-
Quintile 2	2.14	1.38-3.32	0.0007	1.53	0.95-2.47	0.0812
Quintile 3	2.34	1.52-3.59	0.0001	1.47	0.92-2.34	0.1085
Quintile 4	3.24	2.14-4.93	< 0.0001	1.78	1.13-2.82	**0.0135**
Quintile 5	3.45	2.27-5.23	< 0.0001	1.82	1.15-2.87	**0.0110**
Carotid plaques						
Quintile 1	reference	-	-	-	-	-
Quintile 2	1.90	1.34-2.68	0.0003	1.28	0.87-1.88	0.2072
Quintile 3	1.92	1.37-2.70	0.0002	1.12	0.77-1.64	0.5438
Quintile 4	2.45	1.75-3.41	< 0.0001	1.23	0.84-1.78	0.2895
Quintile 5	2.77	1.99-3.85	< 0.0001	1.27	0.88-1.85	0.2071

Note. The lowest quintile (quintile 5) was used as the reference. IMT: Intima media thickness; ALP: alkaline phosphatase; *OR*: odds ratio; *CI*: confidence interval.

Table 4. Risk of ECAS Across different ALP Quintiles

ALP	Unadjusted			Adjusted		
	OR	95% *CI*	*P* value	*OR*	95% *CI*	*P* value
Quintile 1	reference	-	-	reference	-	-
Quintile 2	1.77	1.34-2.33	< 0.0001	1.30	0.96-1.74	0.0864
Quintile 3	1.65	1.25-2.18	0.0004	1.11	0.83-1.49	0.4896
Quintile 4	1.88	1.43-2.48	< 0.0001	1.20	0.90-1.62	0.2180
Quintile 5	2.47	1.88-3.23	< 0.0001	1.47	1.09-1.97	0.0106

Note. ALP: alkaline phosphatase; *OR*: odds ratio; *CI*: confidence interval; ECAS: extracranial carotid artery stenosis.

DISCUSSION

In this largest cross-sectional study regarding the relationship between serum ALP levels and carotid atherosclerosis, we found that compared to the lowest ALP quintile, elevated ALP levels are associated with higher common carotid IMT values and higher risk of ECAS.

Previously, a meta-analysis of 24 trials including 147,634 participants identified a linear correlation of serum ALP levels with the risk of cardiovascular events and mortality[25]. However, the relationship between ALP and subclinical atherosclerosis, particularly carotid atherosclerosis, remains ambiguous. A case-control study comparing 56 obese adolescents and 58 controls found a positive correlation between ALP and carotid IMT using univariate analysis[16]. However, after adjusting for confounding factors, ALP, as well as other liver enzymes, were no longer associated with carotid IMT[16]. In contrast, another cross-sectional study comprising 79 African men with hypertension demonstrated that carotid IMT positively correlated with ALP after adjusting for covariates[17]. Although the exact reasons underpinning these discrepant findings are unclear, it is highly likely that the small sample size and the difference in study populations affected the outcomes. Our study was a community-based study with a large sample size, which allowed us to draw solid conclusions regarding the correlation between serum ALP and subclinical atherosclerosis.

Vascular calcification and inflammation are the two major probable mechanisms linking circulating ALP levels to cardiovascular mortality[26]. Several epidemiological studies have shown that C-reactive protein modulates the relationship between serum ALP and cardiovascular events[27,28]. *In vitro* studies have also demonstrated associations between ALP and mediators of inflammation (especially tumor necrosis factor) in different cell lines[29-31]. Moreover, serum ALP levels were shown to be correlated with endothelial dysfunction in patients with hypertension[32]. Another study found that overexpression of tissue non-specific ALP in endothelial cells could promote pathophysiological vascular calcification[33]. Collectively, these findings indicate that serum ALP levels are correlated with systemic inflammation, endothelial dysfunction, and vascular calcification.

It is well established that compared to healthy individuals, individuals with NAFLD have a higher risk of cardiovascular events. Thus, NAFLD has been considered an independent risk factor for cardiovascular disease[34,35]. Similar to the case for multiple liver markers, elevated ALP levels could be caused by NAFLD. However, our subgroup analyses indicated that the associations between ALP and IMT were similar in participants with and without NAFLD. In contrast, the association between ALP and cardiovascular disease was robust in patients with chronic kidney disease[26], which may be attributed to the role of ALP in skeletal mineralization. In our study, the ALP-linked risks of carotid atherosclerosis were independent of renal function and consistent across different eGFR subgroups[26].

Vitamin D deficiency is a common reason for elevated ALP. Epidemiological studies demonstrate an unequivocal association between vitamin D deficiency, and cardiovascular morbidity and mortality[36]. Further research has indicated that vitamin D is associated with the development and progression of atherosclerotic cardiovascular disease, including response to oxidative stress[37] vascular smooth muscle function[38], endothelial function[39], renin-angiotensin-aldosterone system activation[40], and insulin metabolism[41]. Thus, vitamin D could be a potential confounder for the effect of ALP on carotid atherosclerosis. However, recent vitamin D supplement trials failed to show clear improvements in blood pressure, insulin sensitivity, and lipid parameters[42], as well as cardiovascular disease[43].

Our study has several limitations. First, this was a cross-sectional study that failed to determine the cause-effect association between ALP and carotid atherosclerosis. Second, although we adjusted for several traditional risk factors, it is highly likely that residual confounders such as vitamin D and systemic inflammation still exist. Third, this was a community-based study, and thus, it is unclear whether our findings can be extrapolated to the general population.

CONCLUSIONS

In conclusion, we found a positive correlation between serum ALP levels and common carotid IMT in a Chinese population, which was independent of traditional cardiovascular risk factors. Higher ALP levels were also associated with increased risk of ECAS. However, these conclusions need to be further corroborated in future prospective cohort studies.

CONTRIBUTIONS

YE Yi Cong designed the research/study and wrote the manuscript, LIU Hua Min performed the research/study, and ZHOU Yong and ZENG Yong collected and analyzed the data.

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Supplementary Table S1. Comparison of Characteristics between Included and Excluded Participants

Characteristics	Included Population	Excluded Population	*P* Value
Number	3,237	1,383	< 0.0001
Age, year	53.55 ± 8.58	51.89 ± 8.70	< 0.0001
Male, %	1,576 (48.69)	736 (53.22)	0.0048
BMI, kg/m^2	24.97 ± 3.24	25.07 ± 3.53	0.5446
Hypertension, %	760 (23.48)	289 (20.90)	0.0550
Diabetes, %	269 (8.31)	107 (7.74)	0.5139
eGFR, $mL \cdot min^{-1}$ 1.73 m^{-2}	88.18 ± 12.99	90.02 ± 13.28	< 0.0001
Myocardial infarction, %	23 (0.71)	17 (1.23)	0.0814
Stroke, %	87 (2.69)	29 (2.10)	0.2398
Current smoker, %	773 (23.88)	391 (28.27)	0.0016
Heavy alcoholism, %	26 (0.80)	15 (1.08)	0.3503
Total cholesterol, mmol/L	4.71 ± 0.90	4.67 ± 0.91	0.1162
LDL-C, mmol/L	2.65 ± 0.60	2.62 ± 0.63	0.0988
TG, mmol/L	1.73 ± 1.43	1.72 ± 1.48	0.8393
HDL-C, mmol/L	1.21 ± 0.27	1.20 ± 0.28	0.4096
Statins therapy, %	56 (1.73)	16 (1.16)	0.1498
Education level			0.0004
Illiteracy/primary/middle school	1,035 (31.97)	377 (27.26)	
High school	1,049 (32.41)	436 (31.53)	
College/University	1,153 (35.62)	570 (41.21)	
Income,			0.0083
≤3,000	1,605 (49.58)	659 (47.65)	
3,001-5,000	1,442 (44.55)	609 (44.03)	
> 5,000	190 (5.87)	115 (8.32)	
ALP level, U/L	71.39 ± 20.35	70.30 ± 24.06	0.0493

Note. ALP: alkaline phosphatase; BMI: body mass index; eGFR: estimated glomerular filtration rate; LDL-C: low density lipoprotein cholesterol; TG: triglyceride; HDL-C: high density lipoprotein cholesterol.

Supplementary Table 2. Adjusted risks of abnormal common carotid IMT per ALP quintile across different subgroups

	Adjusted Odd Ratios	95% Confidence Interval	*P* for Interaction
Sex			0.1644
Male	1.09	0.97-1.21	
Female	1.26	1.05-1.51	
Age			0.3846
< 65 years	1.14	1.03-1.26	
≥ 65 years	1.23	1.00-1.51	
Estimated glomerular filtration rate (eGFR)			0.8495
< 50th	1.08	0.96-1.22	
≥ 50th	1.19	1.03-1.38	
Nonalcoholic fatty liver disease (NAFLD)			0.8362
Yes	1.13	1.00-1.27	
No	1.14	0.98-1.33	
Metabolic syndrome			0.2544
Yes	1.10	0.97-1.25	
No	1.14	0.99-1.32	