Original Article

Synergistic Association of Serum Albumin and Globulin with Coronary Heart Disease

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Aim: Serum albumin and globulin have important roles in atherosclerosis development; however, separate studies exploring the relationship between albumin or globulin and coronary heart disease (CHD) have been conducted. We explored whether there was a synergistic effect of albumin and globulin on the presence of CHD.

Methods: A total of 395 patients aged 50-74 years with angiographically documented CHD were recruited, and 596 age- and sex-matched controls without CHD were randomly selected from the general population. The association of albumin and globulin with CHD was analyzed using conditional logistic regression after adjusting for traditional CHD risk factors.

Results: Mean values of serum albumin and globulin were significantly lower in cases than in controls ($p < 0.001$). In the fully adjusted model, compared with participants whose albumin (≥ 47.3 g/L) and globulin (≥ 25.6 g/L) levels were both higher than the median levels in these participants, the odds ratio for CHD was 1.59 ($p = 0.048$) for participants with higher albumin (≥ 47.3 g/L) but lower globulin (< 25.6 g/L), 2.79 ($p < 0.001$) for participants with lower albumin (< 47.3 g/L) but higher globulin (≥ 25.6 g/L), and 16.03 ($p < 0.001$) for participants with lower levels of both albumin (< 47.3 g/L) and globulin (< 25.6 g/L).

Conclusions: Low serum albumin and globulin are independently associated with CHD. The synergistic association of both low albumin and low globulin with CHD is greater than either one alone. The synergistic effect deserves further investigation.

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Key words; Coronary heart disease, Albumin, Globulin, Case-control study

Introduction

Serum total protein is composed of albumin and globulin. Albumin is the most abundant protein in the intravascular compartment and plays an important part in vascular protection as an antioxidant¹⁻³. Globulin is a key component of antibodies⁴. Population-based studies have suggested an association between

low serum albumin and a high risk of coronary heart disease (CHD)⁵⁻¹⁷. The association between globulin and CHD is less well known, although studies have suggested that the immune system has an important role in the occurrence and development of atherosclerotic cardiovascular disease^{18, 19}. No studies have simultaneously explored the relationship between serum albumin and globulin levels and CHD.

Aim

The aim of the present study was to explore the association of low serum albumin, low globulin, and the synergistic effect of low levels of both protein components with the presence of CHD.

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Methods

The study protocol was reviewed and approved by the Ethics Committee of Beijing An Zhen Hospital (Beijing, China). Written informed consent was obtained from all participants.

Participants

Three hundred and ninety-five patients with arteriographically documented CHD (349 cases of angina pectoris and 46 cases of acute myocardial infarction (AMI)) aged 50-74 years were consecutively enrolled from the Department of Cardiology of Beijing An Zhen Hospital from April 2008 to May 2009 when they were admitted to hospital. Coronary angiography was undertaken using the Judkins technique. CHD was defined as $\geq 50\%$ stenosis of any epicardial coronary artery. CHD patients with cardiogenic shock, severe heart failure, severe ventricular arrhythmias, and other severe comorbidities (malignant tumors, chronic disease of the liver/kidney) were excluded. Controls were selected from the 5402 participants who had been recruited from six provinces in China using stratified random sampling for each sex and a 10-year age group in the Chinese Multi-provincial Cohort Study, and who had attended the examination for assessments of the risk factors of CHD from 2008 to 2009. The response in that examination was 80%. After the exclusion of CHD (defined on the basis of symptoms, history, and electrocardiography), chronic disease of the liver/kidney or a history of infectious diseases in the past week, 2250 participants were eligible for random sampling as controls. Although the number of eligible controls was sufficient for 2:1 frequency matching to cases in each age group and sex group, we used a ratio of 1.5:1 to get the maximum number of controls and to ensure randomization. Controls were then randomly selected in each age group and sex group according to the ratio. In total, 596 controls were selected.

Measurements

A standardized questionnaire was used to collect information regarding demographic characteristics, risk factors of CHD, comorbidities, and medications in cases and controls. In controls, height, weight, and blood pressure were measured during the interview. The mean blood pressure was calculated by two measurements of blood pressure from participants in a seated position using standard techniques after a 5-min rest.

Blood samples were obtained from all participants after an overnight fast. In cases, the first fasting

blood sample after hospitalization and before coronary arteriography was obtained for biochemical tests (97.8% in the first 24 h after CHD onset). Levels of serum triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), glucose, high-sensitivity C-reactive protein (Hs-CRP), total protein, and albumin were measured. The level of serum total protein was determined using the biuret reaction (DiaSys Diagnostic Systems, Shanghai, China). Coefficients of variation (CV) of the intra-assay of low level, mid-level and high level of total protein were 1.88%, 1.68%, and 1.59%, respectively, and inaccuracy was 0.24%, 0.17%, and 0.10%, respectively. The level of serum albumin was determined by the bromocresol green method (DiaSys Diagnostic Systems). CVs of the intra-assay of low level, mid-level and high level of albumin were 2.01%, 2.27%, and 1.70%, respectively, and inaccuracy was 0.79%, 0.55%, and 0.87%, respectively. The level of globulin was calculated by subtracting the albumin level from the total protein level. Levels of TG, TC, and LDL-C were determined using an enzymatic method (Human Diagnostics, Wiesbaden, Germany). CVs of the intra-assay of low level, mid-level and high level of TG were 3.16%, 3.62% and 1.76%, respectively, and inaccuracy was 1.00%, 2.50%, and 0.43%, respectively. CVs of the intra-assay of low level, mid-level and high level of TC were 1.69%, 1.66%, and 1.58%, respectively, and inaccuracy was 1.15%, 0.21%, and 0.14%, respectively. CVs of the intra-assay of low level, mid-level and high level of LDL-C were 2.49%, 2.23% and 2.37%, respectively, and inaccuracy was 0.68%, 0.54%, and 0.58%, respectively. The level of HDL-C was determined directly using the phosphotungstic acid/magnesium chloride precipitation method (Human Diagnostics). CVs of the intra-assay of low level, mid-level and high level of HDL-C were 1.88%, 1.73%, and 1.41%, respectively, and inaccuracy was 1.14%, 0.67%, and 1.46%, respectively. Blood glucose was determined using the hexokinase method (Human Diagnostics). Hs-CRP levels were determined using a particle-enhanced immunoturbidimetric method (DiaSys Diagnostic Systems, Holzheim, Germany). CVs of the intra-assay for low level, mid-level and high level of Hs-CRP were 3.37%, 1.11%, and 2.58%, respectively, and inaccuracy was 1.12%, 0.83%, and 1.20%, respectively. The tests described above were carried out with a Hitachi 7600 automatic biochemistry analyzer (Hitachi, Tokyo, Japan) and an assay with an identical batch number in the Clinical Laboratory of Beijing An Zhen Hospital that passed the external quality assessment of the National Center

for Clinical Laboratory, Beijing, China.

Definition and Assessment of Risk Factors

Diabetes mellitus (DM) was defined as fasting blood glucose ≥ 126 mg/dL (7.0 mmol/L) or with a previous clinical diagnosis²⁰. Dyslipidemia was defined as LDL-C ≥ 3.37 mmol/L or a history of dyslipidemia with statin therapy²¹. Obesity was defined as a body mass index (BMI) ≥ 28 kg/m²²². Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or patients on antihypertensive medications²³. Hs-CRP levels were stratified according to guidelines set by the Centers for Disease Control and Prevention, as well as the American Heart Association (<1.0 , 1.0 - 3.0 , and >3.0 mg/L)²⁴. Active smoking was defined as having smoked at least one cigarette per day for ≥ 1 year. Alcohol consumption was defined according to the frequency of alcohol consumption. Participants who drank at least once a week were classified as “drinkers” and those who consumed alcohol less than once a week or subjects who abstained from drinking alcohol were classified as “non-drinkers”. The educational level was divided into elementary school or no education, middle or high school, and college or university or higher. The monthly income per capita was defined as the mean monthly total household income in the preceding year divided by the number of family numbers. Monthly income per capita was divided into $<2,000$ RMB (1 RMB=0.157 US dollar), 2,000-3,000 RMB, and more than 3,000 RMB.

Statistical Analyses

In describing the study population, normally distributed continuous variables were presented as the mean $\pm$ standard deviation. Variables with a skewed distribution were presented as medians and interquartile ranges. Mean values of normally distributed variables were compared using Student's *t*-test. Levels of TG and Hs-CRP were compared using the Mann-Whitney *U* test because of its skewed distribution. Categorical variables were presented as percentages and compared using the chi-square test. The odds ratio (OR) and 95% confidence interval (CI) from conditional logistic regression analyses were measures of the association of serum albumin and globulin with CHD after adjusting for DM, hypertension, dyslipidemia, BMI level, log-transformed hs-CRP level, alcohol consumption, and smoking status. The effect of globulin level on the association of albumin with CHD was first assessed by entering albumin $\times$ globulin interaction terms, and testing for multiplicative statistical interaction. A subsequent conditional logistic

model of interaction estimated the associations of all combinations of low and high levels of albumin and low and high levels of globulin (above or below the median (47.3 g/L for albumin and 25.6 g/L for globulin) of participants) with CHD. $P < 0.05$ (two-sided) was considered significant. Conditional logistic regression analyses were performed using SAS software (Version 9.2; SAS Institute Inc., Cary, NC, USA). All other statistical analyses were carried out using SPSS software (Version 13.0; SPSS, Chicago, IL, USA).

Results

Characteristics of Participants

A total of 991 participants were enrolled in this study: 395 cases (280 males and 115 females) and 596 controls (422 males and 174 females). Sixty-eight percent of the cases had a prior history of CHD. The distribution of serum albumin and globulin levels in cases and controls is shown in **Fig. 1A** and **B**. Mean age, blood glucose level, and percentage of males were not significantly different between the two groups (**Table 1**). The prevalence of smoking, obesity, hypertension, DM, and dyslipidemia was significantly higher in cases than controls ($p < 0.001$). Because the prevalence of the use of antihypertensive drugs and statins was higher in cases than in controls, blood pressure, TC, and LDL-C were lower in cases than in controls ($p < 0.001$). Mean values of TG, Hs-CRP, BMI, and waist circumference were higher in cases than controls.

Levels of Serum Albumin and Globulin in Cases and Controls

Levels of albumin and globulin were higher in controls than in cases ($p < 0.001$). A difference was observed in each stratum of sex, age, DM, obesity, hypertension, dyslipidemia, Hs-CRP level and medication use (**Table 2**).

Mean values of serum albumin were not significantly different between subgroups of different sexes with or without DM, obesity, and hypertension. The mean level of albumin decreased with age in cases and controls, but the mean albumin level in the oldest controls was higher than the mean albumin level in the youngest cases. The albumin level was slightly higher in participants with dyslipidemia than in those without dyslipidemia in both groups. Within cases, the level of albumin decreased with Hs-CRP level ($p = 0.004$), and the mean level of albumin was significantly lower in AMI patients than in patients with angina pectoris ($p = 0.003$).

In cases and controls, the mean level of serum

Fig. 1.

A: Proportion of serum albumin level in cases and controls, B: Proportion of serum globulin level in cases and controls.

globulin was higher in women than in men; in non-smokers than in smokers; and in non-drinkers than in drinkers. The globulin level increased with age and Hs-CRP level in both groups, but the mean globulin level in the youngest controls exceeded the mean value in the oldest cases, and the mean globulin level in controls with Hs-CRP < 1.0 mg/L also exceeded the mean value in cases with Hs-CRP > 3.0 mg/L (**Table 2**); however, the serum globulin level was not affected by DM, hypertension, dyslipidemia, and types of CHD. The mean level of albumin and globulin was not significantly different between participants who were or

were not using antihypertensive drugs, hypoglycemic drugs, and statins.

Association of Serum Levels of Albumin and Globulin with CHD

The results of univariate conditional logistic regression analysis showed that the OR for CHD was 1.25 (95% CI 1.20-1.30) for each g/L decrease in albumin level and 1.12 (95% CI 1.09-1.16) for each g/L decrease in globulin level. After adjustment for DM, hypertension, dyslipidemia, BMI, HDL-C, log-transformed hs-CRP level, alcohol consumption, and

Table 1. Characteristics of cases and controls

Variable	Cases (<i>n</i> =395)	Controls (<i>n</i> =596)	<i>p</i>
Age (years)	60.3 ± 5.9	60.4 ± 6.0	0.737
Systolic blood pressure (mmHg)	127.7 ± 15.9	140.6 ± 20.4	<0.001
Diastolic blood pressure (mmHg)	76.6 ± 8.2	85.1 ± 10.7	<0.001
Blood glucose (mmol/L)	5.9 ± 1.6	6.0 ± 1.4	0.751
TC (mmol/L)	4.27 ± 1.09	5.35 ± 0.96	<0.001
TG (mmol/L)	1.52 (1.16, 2.24) [†]	1.43 (1.03, 2.01) [†]	0.005 [‡]
LDL-C (mmol/L)	2.81 ± 0.96	3.38 ± 0.84	<0.001
HDL-C (mmol/L)	1.14 ± 0.98	1.31 ± 0.28	<0.001
Hs-CRP (mg/L)	1.3 (0.6, 3.4) [†]	0.9 (0.5, 2.0) [†]	<0.001 [‡]
Body mass index (kg/m ²)	26.2 ± 3.1	25.0 ± 3.1	<0.001
Waist circumference (cm)	95.5 ± 8.9	85.9 ± 9.1	<0.001
Male (%)	70.9	70.8	0.978
Smoking (%)	35.2	26.0	0.002
Alcohol consumption (%)	17.6	23.0	0.041
Obesity (%)	27.6	16.0	<0.001
Hypertension (%)	71.9	61.7	0.001
Diabetes mellitus (%)	30.9	17.7	<0.001
Dyslipidemia (%)	73.4	53.9	<0.001
Current use of antihypertensive drugs (%)	71.4	31.4	<0.001
Current use of hypoglycemic drugs (%)	14.4	8.6	0.004
Current use of statins (%)	58.5	3.5	<0.001

TC, total cholesterol; TG, total triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Hs-CRP, High-sensitivity C-reactive protein

[†]Median (25th percentile, 75th percentile), [‡]Compared by the Mann-Whitney *U* test.

smoking status, lower serum albumin and globulin levels had an independent correlation with the presence of CHD (OR for albumin, 1.32; OR for globulin, 1.20; all *p* < 0.001; **Table 3**).

Because there are no established cutoff values for serum albumin and globulin to identify an increased risk of CHD, different cutoffs were tested, including quartiles (albumin: 50.5 g/L, 47.3 g/L, and 44.2 g/L; globulin: 29.4 g/L, 25.6 g/L, and 22.2 g/L), tertiles (albumin: 49.4 g/L and 45.5 g/L; globulin: 28.0 g/L and 23.4 g/L), median (albumin: 47.3 g/L and globulin: 25.6 g/L), mid-value of normal range (albumin: 47.5 g/L and globulin: 25.0 g/L), and mean value (albumin: 47.4 g/L and globulin: 25.8 g/L). Lower serum albumin or globulin was consistently associated with higher odds of CHD in all analyses (all *p* < 0.001).

Synergistic Effect of Albumin and Globulin on CHD

When the levels of serum albumin and globulin were included in the multiple conditional logistic regression model as interaction terms, albumin and globulin had a synergistic effect on increasing the odds of having CHD (*p* for interaction < 0.001). In the

conditional logistic model adjusting for all traditional risk factors and dividing participants into four groups (high albumin + high globulin; high albumin + low globulin; low albumin + high globulin; and low albumin + low globulin) according to the median values of albumin and globulin levels of the participants, compared with those with high albumin and high globulin, only low albumin was significantly associated with CHD, and a synergistic effect of albumin and globulin on CHD was found when both albumin and globulin were low (OR = 16.03; 95% CI 9.66-26.59; **Table 4**).

The socioeconomic status may affect the association of CHD with albumin and globulin. Further analysis was conducted by taking monthly income and education level into account. The synergistic effect of albumin and globulin on CHD remained significant (OR = 18.37; 95% CI 10.48-32.18, *p* < 0.001), as well as the effects of DM, hypertension, dyslipidemia, smoking, alcohol consumption, BMI, monthly income and education level.

Considering that the potential acute inflammatory response due to the onset of AMI may decrease the serum albumin level, we excluded 46 AMI patients

Table 2. Serum albumin and globulin levels in different groups

Variable		Serum albumin level (g/L)			Serum globulin level (g/L)		
		Cases	Controls	$p^{\ddagger}$	Cases	Controls	$p^{\ddagger}$
Total		45.2 ± 4.2	48.9 ± 4.1	< 0.001	24.4 ± 4.4	26.8 ± 4.9	< 0.001
Sex	Male	45.2 ± 4.0	48.9 ± 4.0	< 0.001	23.7 ± 4.4	26.2 ± 5.0	< 0.001
	Female	45.4 ± 4.8	48.7 ± 4.2	< 0.001	26.0 ± 4.2	28.2 ± 4.6	< 0.001
	$p^{\dagger}$	0.576	0.553		< 0.001	< 0.001	
Age (years)	50-54	46.0 ± 3.6	49.6 ± 3.7	< 0.001	23.9 ± 4.2	25.9 ± 4.7	0.003
	55-59	45.5 ± 3.7	50.2 ± 3.9	< 0.001	23.0 ± 4.1	25.8 ± 4.4	< 0.001
	60-64	45.2 ± 5.3	48.1 ± 4.2	< 0.001	25.3 ± 4.8	27.4 ± 5.6	0.005
	65-69	44.6 ± 4.3	47.7 ± 4.0	< 0.001	25.4 ± 4.4	27.8 ± 4.8	< 0.001
	70-74	44.2 ± 2.9	47.7 ± 3.7	0.001	25.4 ± 3.6	28.5 ± 5.0	0.021
	$p^{\dagger}$	0.040	< 0.001		0.015	< 0.001	
Smoking	No	45.5 ± 4.4	48.7 ± 4.1	< 0.001	25.1 ± 4.6	27.4 ± 4.9	< 0.001
	Yes	44.8 ± 4.0	49.5 ± 3.8	< 0.001	23.2 ± 3.9	24.9 ± 4.5	0.001
	$p^{\dagger}$	0.164	0.035		< 0.001	< 0.001	
Alcohol consumption	No	45.3 ± 4.2	48.7 ± 4.0	< 0.001	24.5 ± 4.2	27.3 ± 4.7	< 0.001
	Yes	45.4 ± 3.6	49.8 ± 3.9	< 0.001	23.4 ± 4.2	24.5 ± 4.6	0.083
	$p^{\dagger}$	0.919	0.003		0.045	< 0.001	
Diabetes mellitus	No	45.2 ± 4.0	48.9 ± 4.2	< 0.001	24.4 ± 4.3	26.6 ± 5.0	< 0.001
	Yes	45.4 ± 4.7	49.2 ± 4.1	< 0.001	24.4 ± 4.7	26.9 ± 5.2	0.001
	$p^{\dagger}$	0.752	0.514		0.927	0.548	
Obesity	No	45.2 ± 4.2	48.9 ± 4.1	< 0.001	24.2 ± 4.5	26.5 ± 5.0	< 0.001
	Yes	45.3 ± 4.4	49.2 ± 4.2	< 0.001	25.0 ± 4.3	27.7 ± 5.0	< 0.001
	$p^{\dagger}$	0.946	0.504		0.105	0.040	
Hypertension	No	44.8 ± 4.4	49.0 ± 4.1	< 0.001	24.5 ± 4.9	26.6 ± 4.8	< 0.001
	Yes	45.4 ± 4.2	48.8 ± 4.1	< 0.001	24.4 ± 4.3	26.8 ± 5.1	< 0.001
	$p^{\dagger}$	0.173	0.527		0.869	0.603	
Dyslipidemia	No	45.1 ± 4.6	48.5 ± 4.2	< 0.001	23.9 ± 4.1	26.6 ± 5.2	< 0.001
	Yes	45.3 ± 4.1	49.3 ± 4.0	< 0.001	24.6 ± 4.5	26.8 ± 4.9	< 0.001
	$p^{\dagger}$	0.603	0.032		0.168	0.646	
Hs-CRP level (mg/L)	< 1.0	45.9 ± 4.1	49.0 ± 3.8	< 0.001	23.5 ± 4.1	25.7 ± 4.4	< 0.001
	1.0-3.0	45.5 ± 3.8	48.9 ± 4.5	< 0.001	24.6 ± 4.1	27.2 ± 5.5	< 0.001
	> 3.0	44.5 ± 4.2	49.7 ± 4.1	< 0.001	25.3 ± 4.4	27.7 ± 4.6	< 0.001
	$p^{\dagger}$	0.004	0.156		< 0.001	< 0.001	
Use of antihypertensive drugs (%)	No	45.1 ± 3.9	49.0 ± 4.1	< 0.001	24.5 ± 4.2	26.5 ± 4.8	< 0.001
	Yes	45.3 ± 4.4	48.6 ± 4.1	< 0.001	24.4 ± 4.5	27.3 ± 5.1	< 0.001
	$p^{\dagger}$	0.624	0.193		0.806	0.060	
Use of hypoglycemic drugs (%)	No	45.3 ± 4.1	48.9 ± 4.1	< 0.001	24.3 ± 4.3	26.8 ± 5.0	< 0.001
	Yes	45.2 ± 5.0	49.1 ± 3.8	< 0.001	25.1 ± 5.1	27.0 ± 4.4	0.044
	$p^{\dagger}$	0.949	0.710		0.193	0.744	
Use of statins (%)	No	45.6 ± 4.4	48.9 ± 4.0	< 0.001	24.5 ± 4.1	26.7 ± 5.0	< 0.001
	Yes	45.0 ± 4.1	48.7 ± 4.8	< 0.001	24.3 ± 4.6	27.6 ± 3.2	0.002
	$p^{\dagger}$	0.200	0.848		0.661	0.435	
CHD type	Angina pectoris	45.5 ± 4.1	—	—	24.4 ± 4.4	—	—
	AMI	43.5 ± 4.7	—	—	24.8 ± 4.9	—	—
	$p^{\dagger}$	0.003			0.548		

Hs-CRP, high-sensitivity C-reactive protein; CHD, coronary heart disease; AMI, acute myocardial infarction

 † Comparison between subgroups within cases or controls, ‡ Comparison of the mean level between cases and controls.

Table 3. Multiple conditional logistic regression analysis of the association of albumin and globulin with CHD

Variable	β	OR (95% CI)	<i>p</i>
Diabetes	0.703	2.02 (1.36, 2.99)	<0.001
Hypertension	0.288	1.33 (0.92, 1.93)	0.127
Dyslipidemia	1.056	2.87 (2.02, 4.09)	<0.001
Smoking	0.445	1.56 (1.04, 2.35)	0.033
Alcohol consumption	-0.595	0.55 (0.35, 0.87)	0.011
BMI (kg/m ²)	0.119	1.13 (1.06, 1.19)	<0.001
HDL-C (mmol/L)	-0.218	0.80 (0.63, 1.02)	0.073
Lg_hsCRP	0.464	1.59 (1.15, 2.21)	0.006
Albumin level (g/L)	0.277	1.32 (1.26, 1.38)	<0.001
Globulin level (g/L)	0.184	1.20 (1.15, 1.25)	<0.001

CHD, coronary heart disease; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; Lg_hsCRP, log-transformed high-sensitivity C-reactive protein level (mg/L); OR, odds ratio; 95% CI, 95% confidence interval

The model was adjusted for diabetes mellitus, hypertension, dyslipidemia, BMI, HDL-C, Lg_hsCRP, alcohol consumption, smoking status, and albumin and globulin.

in cases and their corresponding controls. Similar results were obtained.

Discussion

We found that the levels of serum albumin and globulin were both associated with CHD, independent of traditional CHD risk factors such as DM, hypertension, dyslipidemia, BMI, HDL-C, Hs-CRP, alcohol consumption, smoking status, monthly income and education level. The strongest association with CHD was the combination of low albumin and low globulin.

Authors of several prospective studies have found an association of low serum albumin with the risk of future CHD, but whether such a relationship is confounded by sex, age, blood pressure, blood lipids and other factors is not well established^{7-17, 25, 26}. One study found that older persons with a relatively low serum albumin level, even within the normal range, might be at increased risk of incident CHD; however, in that study, blood samples were collected when participants were in a non-fasting state¹⁶. The Framingham Offspring Study, which had a mean follow-up of 21.9 years and 280 cases of myocardial infarction in 5124 participants, found that lower serum albumin appeared to be associated with an increased risk of CHD, though the certainty of the association was compromised by a lack of statistical power¹⁵. Most of these studies were conducted in Caucasians and, until the present study, no study has examined the association of protein components with CHD in Asians.

The mechanism underlying the associations observed among albumin, globulin and CHD remains unknown. One possibility is that higher levels of albumin and globulin are protective against CHD. The antioxidant activity of albumin may play a part: serum albumin molecules have the highest sulfhydryl content in the human body, and the antioxidant activity of albumin may come from oxidation of the albumin thiol to sulfenic acid³. The antioxidant properties of serum albumin may also result from their ligand-binding capacity. Albumin contains a type of high-affinity site for copper²⁷. Free copper can react with hydrogen peroxide, leading to the formation of deleterious hydroxyl radicals released from the Fenton reaction, and sequestration of copper ions by albumin can prevent this reaction²⁸. Indirect antioxidant activity of albumin comes from its ability to bind and transport bilirubin, which has been shown to act as an inhibitor of lipid peroxidation²⁹. Albumin also can bind homocysteine, resulting in a decreased level of serum homocysteine, which is a risk factor for atherosclerosis³⁰.

The results of basic scientific research suggest that globulins contain anti-atherosclerotic components (e.g., γ -globulin). Nicoletti *et al.* found that injection with γ -globulin could inhibit the progression of atherosclerosis during the fatty streak phase and plaque phase in apoE knockout mice³¹. Another experimental study in Japan found that treatment with γ -globulin, even at a later stage of atherosclerosis, could suppress lesion development³². A basic science study found that γ -globulin, lipids and some cells can move from circulating blood into the arterial

Table 4. Synergistic effects of serum albumin and globulin on CHD from conditional logistic regression

Variable	β	OR (95% CI)	<i>p</i>
Diabetes	0.580	1.79 (1.24, 2.58)	0.002
Hypertension	0.391	1.48 (1.04, 2.11)	0.030
Dyslipidemia	1.051	2.86 (2.04, 4.01)	<.0001
Smoking	0.600	1.82 (1.23, 2.69)	0.003
Alcohol consumption	-0.618	0.54 (0.35, 0.84)	0.006
BMI (kg/m ²)	0.109	1.12 (1.06, 1.18)	<.0001
HDL-C (mmol/L)	-0.274	0.76 (0.59, 0.97)	0.029
Lg_hsCRP	0.266	1.31 (0.96, 1.77)	0.088
Strata of albumin and globulin level [‡]			
Albumin $\geq$ 47.3 g/L + globulin $\geq$ 25.6 g/L	0	1 [†]	—
Albumin $\geq$ 47.3 g/L + globulin < 25.6 g/L	0.462	1.59 (1.00, 2.51)	0.048
Albumin < 47.3 g/L + globulin $\geq$ 25.6 g/L	1.026	2.79 (1.78, 4.39)	<.0001
Albumin < 47.3 g/L + globulin < 25.6 g/L	2.774	16.03 (9.66, 26.59)	<.0001

CHD, coronary heart disease; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; Lg_hsCRP, log-transformed high-sensitivity C-reactive protein level (mg/L); OR, odds ratio; 95% CI, 95% confidence interval

[†]Reference group.

[‡]The median of albumin and globulin levels in these study participants was used as the cutoff.

The model was adjusted for diabetes mellitus, hypertension, dyslipidemia, BMI, HDL-C, Lg_hsCRP, alcohol consumption, smoking status, and strata of albumin and globulin levels.

wall through localized structural defects of the arterial wall, which initiated localized lesions of atherosclerosis³³). The serum globulins in the present study comprised all four types (α 1, α 2, β , and γ globulins). Whether the correlation between globulin and CHD seen in the present study was largely driven by the anti-atherosclerotic effect of γ -globulin deserves further investigation.

Several factors may affect the serum levels of albumin and globulin. We found that the level of serum globulin was higher in women than that in men in both cases and controls. This difference might be explained by the different patterns of circulating proteins of humans between men and women³⁴). The present study and a former population study found that a fall in serum albumin was associated with aging³⁵). This might be because younger subjects had a better nutritional state than older cases.

We found a correlation among serum albumin (in cases), globulin (in cases and controls) and Hs-CRP levels, which might be due to an inflammatory reaction. Serum albumin is a type of negative acute-phase protein whose levels decrease during inflammatory reactions³⁶). Levels of α 1 globulins (α 1-antitrypsin, thyroid-binding globulin, and transcortin) and α 2 globulins (ceruloplasmin, α 2-macroglobulin, and haptoglobin) are also increased in acute inflammation³⁷).

We found that the serum globulin level was lower in smokers than in non-smokers in cases and

controls. Gofin *et al.* also observed this phenomenon³⁸). Other researchers have reported that the levels of immunoglobulin (IgA, IgC, IgG and IgM) were significantly lower in smokers than in non-smokers, but the mechanism was not clear^{39, 40}). Some researchers have suggested that tobacco smoking seems to decrease the humoral immune response, resulting in suppressed formation of antibodies to inhaled antigens⁴⁰).

The serum globulin level was lower in alcohol consumers than in non-drinkers; the potential mechanism needs further investigation. Our results also suggested that alcohol consumption might have a cardioprotective effect. One meta-analysis showed that light-to-moderate alcohol consumption (5-25 g/day) was significantly associated with a lower incidence of cardiovascular and all-cause mortality⁴¹). Drinking was defined only by the frequency of alcohol consumption in the present study, so the cardioprotective effects of alcohol here might have resulted from light-to-moderate consumption of alcohol.

The level of albumin decreases after inflammation, usually reaching the lowest value one week later^{12, 36, 42}). Within subgroups, the albumin level was significantly lower in the AMI subgroup than in the angina pectoris subgroup. To avoid the potential influence of a transient decrease in serum albumin due to the inflammatory response, we excluded 46 AMI patients and their corresponding controls and reana-

lyzed the data (349 cases and 527 controls). Similar results were obtained.

There are several limitations in this study. First, as a case-control study, we could investigate only the cross-sectional association of albumin and globulin with CHD, and could not conclude whether albumin and globulin are “innocent bystanders” in the CHD disease process, or whether low albumin or globulin precedes or follows CHD in the causal pathway. Prospective and mechanistic experimental studies are required to further elucidate the relationship between low serum albumin or globulin and CHD, and why the synergistic effect of low levels of both albumin and globulin exceeds the CHD association found with either protein component alone. Secondly, the cases in this study were sampled from a hospital, while the controls were sampled from a sample of the general population. The first record of blood pressure and lipid level collected for all CHD cases from medical records might not represent the usual blood pressure and lipid levels of those cases because the CHD cases might have received immediate treatment, such as statins, before their hospitalization; therefore, we used hypertension and dyslipidemia instead of blood pressure and lipid levels in our analyses, which may have resulted in a residual confounding effect. Third, the blood samples of 2.2% cases were obtained during 24 to 48 hours after CHD onset; however, such a small proportion of cases should have little effect on the results. A previous study showed that the albumin level did not decrease significantly until one week after an acute stimulus³⁶. Finally, we only collected the data on the frequency of alcohol consumption. The absence of information about the volume of alcohol consumption was another limitation of the present study.

In conclusion, in this case-control study, low serum albumin and low globulin were independently associated with CHD. Low albumin and low globulin together had a synergistic effect in increasing the odds of having CHD after adjustment for traditional risk factors. The possible predictive value of albumin and globulin for CHD risk and the potential mechanism of the association of low albumin and low globulin with CHD deserve further investigation.

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Conflict of Interests

The authors declare that there are no conflicts of interests.

References

- 1) Halliwell B: Albumin--an important extracellular antioxidant? *Biochem Pharmacol*, 1988; 37: 569-571
- 2) Roche M, Rondeau P, Singh NR, Tarnus E, Bourdon E: The antioxidant properties of serum albumin. *FEBS Lett*, 2008; 582: 1783-1787
- 3) Turell L, Carballal S, Botti H, Radi R, Alvarez B: Oxidation of the albumin thiol to sulfenic acid and its implications in the intravascular compartment. *Braz J Med Biol Res*, 2009; 42: 305-311
- 4) Walker WA: Immunology. *Curr Opin Gastroenterol*, 2002; 18: 688-690
- 5) Atukorala TM, Gunarathne PH, Ekanayake RA: Total cholesterol: albumin ratio as an alternative indicator of risk of cardiovascular disease. *Ceylon Med J*, 1986; 31: 161-164
- 6) Phillips A, Shaper AG, Whincup PH: Association between serum albumin and mortality from cardiovascular disease, cancer, and other causes. *Lancet*, 1989; 2: 1434-1436
- 7) Gillum RF, Makuc DM: Serum albumin, coronary heart disease, and death. *Am Heart J*, 1992; 123: 507-513
- 8) Stehouwer CD, Nauta JJ, Zeldenrust GC, Hackeng WH, Donker AJ, den Ottolander GJ: Urinary albumin excretion, cardiovascular disease, and endothelial dysfunction in non-insulin-dependent diabetes mellitus. *Lancet*, 1992; 340: 319-323
- 9) Folsom AR, Ma J, Eckfeldt JH, Nieto FJ, Metcalf PA, Barnes RW: Low serum albumin. Association with diabetes mellitus and other cardiovascular risk factors but not with prevalent cardiovascular disease or carotid artery intima-media thickness. The Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Ann Epidemiol*, 1995; 5: 186-191
- 10) Corti MC, Salive ME, Guralnik JM: Serum albumin and physical function as predictors of coronary heart disease mortality and incidence in older persons. *J Clin Epidemiol*, 1996; 49: 519-526

- 11) Weijenberg MP, Feskens EJ, Souverein JH, Kromhout D: Serum albumin, coronary heart disease risk, and mortality in an elderly cohort. *Epidemiology*, 1997; 8: 87-92
- 12) Danesh J, Collins R, Appleby P, Peto R: Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *JAMA*, 1998; 279: 1477-1482
- 13) Gillum RF: Assessment of serum albumin concentration as a risk factor for stroke and coronary disease in African Americans and whites. *J Natl Med Assoc*, 2000; 92: 3-9
- 14) Nelson JJ, Liao D, Sharrett AR, Folsom AR, Chambless LE, Shahar E, Szklo M, Eckfeldt J, Heiss G: Serum albumin level as a predictor of incident coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) study. *Am J Epidemiol*, 2000; 151: 468-477
- 15) Djousse L, Rothman KJ, Cupples LA, Levy D, Ellison RC: Serum albumin and risk of myocardial infarction and all-cause mortality in the Framingham Offspring Study. *Circulation*, 2002; 106: 2919-2924
- 16) Schalk BW, Visser M, Bremmer MA, Penninx BW, Bouter LM, Deeg DJ: Change of serum albumin and risk of cardiovascular disease and all-cause mortality: Longitudinal Aging Study Amsterdam. *Am J Epidemiol*, 2006; 164: 969-977
- 17) Deng C, Shen L: Serum albumin in patients with acute myocardial infarction and its effect on in-hospital prognosis. *Beijing Medical Journal*, 2006; 28: 331-333
- 18) Binder CJ, Chang MK, Shaw PX, Miller YI, Hartvigsen K, Dewan A, Witztum JL: Innate and acquired immunity in atherogenesis. *Nat Med*, 2002; 8: 1218-1226
- 19) Okazaki T, Tanaka Y, Nishio R, Mitsuiye T, Mizoguchi A, Wang J, Ishida M, Hiai H, Matsumori A, Minato N, Honjo T: Autoantibodies against cardiac troponin I are responsible for dilated cardiomyopathy in PD-1-deficient mice. *Nat Med*, 2003; 9: 1477-1483
- 20) Genuth S, Alberti KG, Bennett P, Buse J, DeFronzo R, Kahn R, Kitzmiller J, Knowler WC, Lebovitz H, Lernmark A, Nathan D, Palmer J, Rizza R, Saudek C, Shaw J, Steffes M, Stern M, Tuomilehto J, Zimmet P: Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care*, 2003; 26: 3160-3167
- 21) Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ: A summary of implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Arterioscler Thromb Vasc Biol*, 2004; 24: 1329-1330
- 22) Chen C, Lu FC: The guidelines for prevention and control of overweight and obesity in Chinese adults. *Biomed Environ Sci*, 2004; 17 Suppl: 1-36
- 23) Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*, 2003; 289: 2560-2572
- 24) Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, 3rd, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC Jr, Taubert K, Tracy RP, Vinicor F: Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*, 2003; 107: 499-511
- 25) Ljungman S, Wikstrand J, Hartford M, Berglund G: Urinary albumin excretion--a predictor of risk of cardiovascular disease. A prospective 10-year follow-up of middle-aged nondiabetic normal and hypertensive men. *Am J Hypertens*, 1996; 9: 770-778
- 26) Savage S, Estacio RO, Jeffers B, Schrier RW: Urinary albumin excretion as a predictor of diabetic retinopathy, neuropathy, and cardiovascular disease in NIDDM. *Diabetes Care*, 1996; 19: 1243-1248
- 27) Laussac JP, Sarkar B: Characterization of the copper(II)- and nickel(II)-transport site of human serum albumin. Studies of copper(II) and nickel(II) binding to peptide 1-24 of human serum albumin by ¹³C and ¹H NMR spectroscopy. *Biochemistry*, 1984; 23: 2832-2838
- 28) Simpson JA, Cheeseman KH, Smith SE, Dean RT: Free-radical generation by copper ions and hydrogen peroxide. Stimulation by Hepes buffer. *Biochem J*, 1988; 254: 519-523
- 29) Neuzil J, Stocker R: Bilirubin attenuates radical-mediated damage to serum albumin. *FEBS Lett*, 1993; 331: 281-284
- 30) Papatheodorou L, Weiss N: Vascular oxidant stress and inflammation in hyperhomocysteinemia. *Antioxid Redox Signal*, 2007; 9: 1941-1958
- 31) Nicoletti A, Kaveri S, Caligiuri G, Bariety J, Hansson GK: Immunoglobulin treatment reduces atherosclerosis in apo E knockout mice. *J Clin Invest*, 1998; 102: 910-918
- 32) Okabe TA, Kishimoto C, Shimada K, Murayama T, Yokode M, Kita T: Effects of late administration of immunoglobulin on experimental atherosclerosis in apolipoprotein E-deficient mice. *Circ J*, 2005; 69: 1543-1546
- 33) Sims FH, Gavin JB, Edgar S, Koelmeyer T: Diffusion of gamma globulin into the arterial wall identifies localized entry of lipid and cells in atherosclerosis. *Coron Artery Dis*, 2001; 12: 21-30
- 34) Gersten DM, Khirabadi BS, Kurian P, Ledley RS, Mahany T, Ramey ER, Ramwell PW: Albumin obscures sex differences in blood protein patterns of rats and humans. *Biochem J*, 1980; 191: 869-872
- 35) Gom I, Fukushima H, Shiraki M, Miwa Y, Ando T, Takai K, Moriaki H: Relationship between serum albumin level and aging in community-dwelling self-supported elderly population. *J Nutr Sci Vitaminol (Tokyo)*, 2007; 53: 37-42
- 36) Gabay C, Kushner I: Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med*, 1999; 340: 448-454
- 37) O'Connell TX, Horita TJ, Kasravi B: Understanding and interpreting serum protein electrophoresis. *Am Fam Physician*, 2005; 71: 105-112
- 38) Gofin J, Kark JD, Halfon ST, Friedlander Y, Stein Y: Cigarette smoking and its relation to anthropometric characteristics and biochemical variables in Jerusalem 17-year-olds and adults. *Isr J Med Sci*, 1982; 18: 1233-1241
- 39) Gerrard JW, Heiner DC, Ko CG, Mink J, Meyers A,

- Dosman JA: Immunoglobulin levels in smokers and non-smokers. *Ann Allergy*, 1980; 44: 261-262
- 40) Andersen P, Pedersen OF, Bach B, Bonde GJ: Serum antibodies and immunoglobulins in smokers and nonsmokers. *Clin Exp Immunol*, 1982; 47: 467-473
- 41) Costanzo S, Di Castelnuovo A, Donati MB, Iacoviello L, de Gaetano G: Alcohol consumption and mortality in patients with cardiovascular disease: a meta-analysis. *J Am Coll Cardiol*, 2010; 55: 1339-1347
- 42) Fleck A: Clinical and nutritional aspects of changes in acute-phase proteins during inflammation. *Proc Nutr Soc*, 1989; 48: 347-354

Appendix Table 1. Multiple logistic regression analysis of the association of albumin and globulin with CHD (using quartile as cutoff)

Variable	β	OR (95%CI)	<i>p</i> value
Diabetes mellitus	0.677	1.97 (1.33, 2.91)	< 0.001
Hypertension	0.305	1.36 (0.94, 1.96)	0.106
Dyslipidemia	1.101	3.01 (2.12, 4.27)	< 0.001
Smoking	0.485	1.63 (1.08, 2.44)	0.020
Alcohol consumption	-0.569	0.57 (0.36, 0.89)	0.015
BMI (kg/m ²)	0.116	1.12 (1.06, 1.19)	< 0.001
HDL-C (mmol/L)	-0.203	0.82 (0.64, 1.04)	0.097
Lg_hsCRP	0.460	1.58 (1.14, 2.20)	0.006
Albumin level (g/L)			
≥ 50.5	0	1 [†]	—
47.3-50.4	1.464	4.32 (2.62, 7.14)	< 0.001
44.2-47.2	2.220	9.21 (5.57, 15.21)	< 0.001
≤ 44.1	3.127	22.81 (13.44, 38.71)	< 0.001
Globulin level (g/L)			
≥ 29.4	0	1 [†]	—
25.6-29.3	0.996	2.71 (1.68, 4.38)	< 0.001
22.2-25.5	1.668	5.30 (3.21, 8.76)	< 0.001
≤ 22.1	2.163	8.70 (5.14, 14.73)	< 0.001

CHD, coronary heart disease; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; Lg_hsCRP, log-transformed high-sensitivity C-reactive protein level (mg/L); OR, odds ratio; 95%CI, 95% confidence interval[†], Reference group.

The model was adjusted for diabetes mellitus, hypertension, dyslipidemia, BMI, HDL-C, Lg_hsCRP, alcohol consumption, smoking status, albumin and globulin.

Appendix Table 2. Multiple logistic regression analysis of the association of albumin and globulin with CHD (using tertile as cutoff)

Variable	β	OR (95%CI)	<i>p</i> value
Diabetes mellitus	0.664	1.94 (1.33, 2.85)	< 0.001
Hypertension	0.213	1.24 (0.86, 1.78)	0.249
Dyslipidemia	1.075	2.93 (2.08, 4.14)	< 0.001
Smoking	0.511	1.67 (1.12, 2.49)	0.013
Alcohol consumption	-0.614	0.54 (0.34, 0.85)	0.008
BMI (kg/m ²)	0.117	1.12 (1.06, 1.19)	< 0.001
HDL-C (mmol/L)	-0.239	0.79 (0.62, 1.00)	0.046
Lg_hsCRP	0.527	1.69 (1.23, 2.33)	0.001
Albumin level (g/L)			
≥ 49.4	0	1 [†]	—
45.5-49.3	1.687	5.40 (3.53, 8.26)	< 0.001
≤ 45.4	2.584	13.25 (8.52, 20.61)	< 0.001
Globulin level (g/L)			
≥ 28.0	0	1 [†]	—
23.4-27.9	1.219	3.39 (2.22, 5.17)	< 0.001
≤ 23.3	1.996	7.36 (4.65, 11.65)	< 0.001

CHD, coronary heart disease; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; Lg_hsCRP, log-transformed high-sensitivity C-reactive protein level (mg/L); OR, odds ratio; 95%CI, 95% confidence interval[†], Reference group.

The model was adjusted for diabetes mellitus, hypertension, dyslipidemia, BMI, HDL-C, Lg_hsCRP, alcohol consumption, smoking status, albumin and globulin.

Appendix Table 3. Multiple logistic regression analysis of the association of albumin and globulin with CHD (using median as cutoff)

Variable	β	OR (95%CI)	<i>p</i> value
Diabetes mellitus	0.602	1.83 (1.27, 2.63)	0.001
Hypertension	0.357	1.43 (1.01, 2.02)	0.044
Dyslipidemia	0.978	2.66 (1.92, 3.69)	< 0.001
Smoking	0.650	1.92 (1.31, 2.81)	< 0.001
Alcohol consumption	-0.612	0.54 (0.35, 0.84)	0.006
BMI (kg/m ²)	0.111	1.12 (1.06, 1.18)	< 0.001
HDL-C (mmol/L)	-0.274	0.76 (0.60, 0.97)	0.027
Lg_hsCRP	0.264	1.30 (0.96, 1.76)	0.086
Albumin level (g/L)			
≥ 47.3	0	1 [†]	-
< 47.3	1.703	5.49 (3.96, 7.61)	< 0.001
Globulin level (g/L)			
≥ 25.6	0	1 [†]	-
< 25.6	1.133	3.10 (2.23, 4.33)	< 0.001

CHD, coronary heart disease; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; Lg_hsCRP, log-transformed high-sensitivity C-reactive protein level (mg/L); OR, odds ratio; 95%CI, 95% confidence interval[†], Reference group.

The model was adjusted for diabetes mellitus, hypertension, dyslipidemia, BMI, HDL-C, Lg_hsCRP, alcohol consumption, smoking status, albumin and globulin.

Appendix Table 4. Multiple logistic regression analysis of the association of albumin and globulin with CHD (using the mid-value of normal range as cutoff)

Variable	β	OR (95%CI)	<i>p</i> value
Diabetes mellitus	0.685	1.98 (1.40, 2.82)	< 0.001
Hypertension	0.339	1.40 (1.01, 1.96)	0.046
Dyslipidemia	0.959	2.61 (1.90, 3.58)	< 0.001
Smoking	0.605	1.83 (1.27, 2.65)	0.001
Alcohol consumption	-0.699	0.50 (0.33, 0.75)	0.001
BMI (kg/m ²)	0.094	1.10 (1.04, 1.16)	< 0.001
HDL-C (mmol/L)	-0.282	0.75 (0.58, 0.97)	0.030
Lg_hsCRP	0.376	1.46 (1.09, 1.95)	0.012
Albumin level (g/L)			
≥ 47.5	0	1 [†]	-
< 47.5	1.711	5.53 (3.46, 8.86)	< 0.001
Globulin level (g/L)			
≥ 25.0	0	1 [†]	-
< 25.0	0.985	2.68 (1.95, 3.68)	< 0.001

CHD, coronary heart disease; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; Lg_hsCRP, log-transformed high-sensitivity C-reactive protein level (mg/L); OR, odds ratio; 95%CI, 95% confidence interval[†], Reference group.

The model was adjusted for diabetes mellitus, hypertension, dyslipidemia, BMI, HDL-C, Lg_hsCRP, alcohol consumption, smoking status, albumin and globulin.

Appendix Table 5. Multiple logistic regression analysis of the association of albumin and globulin with CHD (using the mean as cutoff)

Variable	β	OR (95%CI)	<i>p</i> value
Diabetes mellitus	0.551	1.74 (1.2, 2.51)	0.004
Hypertension	0.339	1.40 (0.99, 2.00)	0.059
Dyslipidemia	1.051	2.86 (2.04, 4.00)	< 0.001
Smoking	0.586	1.80 (1.22, 2.65)	0.003
Alcohol consumption	-0.551	0.58 (0.37, 0.90)	0.014
BMI (kg/m ²)	0.108	1.11 (1.06, 1.18)	< 0.001
HDL-C (mmol/L)	-0.243	0.78 (0.62, 1.00)	0.047
Lg_hsCRP	0.300	1.35 (0.99, 1.83)	0.055
Albumin level (g/L)			
≥ 47.4	0	1 [†]	–
< 47.4	1.906	6.72 (4.80, 9.42)	< 0.001
Globulin level (g/L)			
≥ 25.8	0	1 [†]	–
< 25.8	1.170	3.22 (2.29, 4.53)	< 0.001

CHD, coronary heart disease; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; Lg_hsCRP, log-transformed high-sensitivity C-reactive protein level (mg/L); OR, odds ratio; 95%CI, 95% confidence interval[†], Reference group.

The model was adjusted for diabetes mellitus, hypertension, dyslipidemia, BMI, HDL-C, Lg_hsCRP, alcohol consumption, smoking status, albumin and globulin.