

Original Article



C-reactive Protein Level, Apolipoprotein B-to-apolipoprotein A-1 Ratio, and Risks of Ischemic Stroke and Coronary Heart Disease among Inner Mongolians in China*

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Abstract

Objective We aimed to investigate the cumulative effect of high CRP level and apolipoprotein B-to-apolipoprotein A-1 (ApoB/ApoA-1) ratio on the incidence of ischemic stroke (IS) or coronary heart disease (CHD) in a Mongolian population in China.

Methods From June 2003 to July 2012, 2589 Mongolian participants were followed up for IS and CHD events based on baseline investigation. All the participants were divided into four subgroups according to C-reactive protein (CRP) level and ApoB/ApoA-1 ratio. Cox proportional hazard models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the IS and CHD events in all the subgroups.

Results The HRs (95% CI) for IS and CHD were 1.33 (0.84-2.12), 1.14 (0.69-1.88), and 1.91 (1.17-3.11) in the 'low CRP level with high ApoB/ApoA-1', 'high CRP level with low ApoB/ApoA-1', and 'high CRP level with high ApoB/ApoA-1' subgroups, respectively, in comparison with the 'low CRP level with low ApoB/ApoA-1' subgroup. The risks of IS and CHD events was highest in the 'high CRP level with high ApoB/ApoA-1' subgroup, with statistical significance.

Conclusion High CRP level with high ApoB/ApoA-1 ratio was associated with the highest risks of IS and CHD in the Mongolian population. This study suggests that the combination of high CRP and ApoB/ApoA-1 ratio may improve the assessment of future risk of developing IS and CHD in the general population.

Key words: C-reactive protein; Apolipoprotein B-to-apolipoprotein A-1 ratio; Ischemic stroke; Coronary heart disease

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INTRODUCTION

In China, 3.14 million deaths were attributed to cardiovascular disease (CVD) in 2010 alone, with coronary heart disease (CHD) and ischemic stroke (IS) accounting for 30.25% and 19.44% of CVD deaths, respectively^[1]. Both IS and CHD are ischemic vascular disorders, while atherosclerosis is the main pathological basis of IS and CHD.

Both inflammation and hyperlipidemia play major roles in atherothrombosis^[2]. C-reactive protein (CRP) is an easily measurable and reliable biomarker of inflammatory status. Previous studies^[3], but not all^[4-6], have shown that increased CRP level significantly increases the risk of IS and CHD. Meanwhile, several studies have shown that the lipid-associated proteins, particularly the apolipoprotein B-to-apolipoprotein A-1 (ApoB/ApoA-1) ratio, which indicates the balance between atherogenic and anti-atherosclerotic particles, are more effective predictors of cardiovascular risk than the other cholesterol^[7-9]. High ApoB/ApoA-1 ratio has been demonstrated to increase the risk of IS and CHD^[10-12].

Recently, a few studies found an indication of the synergistic effects of inflammation and dyslipidemia on the risk of developing CVD^[13-14]. Hence, we hypothesized a co-effect between the inflammatory biomarkers CRP and dyslipidemia, especially high ApoB/ApoA-1 ratio, on the incidences of IS and CHD. However, the relationship of high CRP and ApoB/ApoA-1 ratio to the risk of developing IS and CHD in Mongolians has not been reported yet. We therefore examined the cumulative effect of high CRP and ApoB/ApoA-1 ratio on the risk of developing IS and CHD in a Mongolian population from Inner Mongolia, China.

METHODS

Study Subjects

This prospective cohort study was conducted from June 2003 to July 2012 in Inner Mongolia, an autonomous region in Northern China. The participant selection and data collection were based on previously reported methods^[15]. The study participants were recruited from 32 villages in Kezuohou Banner (county) and Naiman Banner in Inner Mongolia, China. Most of the local residents were Mongolians who had lived in their villages for

many generations and maintained their traditional diet and lifestyle. Among 3457 Mongolian residents aged ≥ 20 years who were living in these villages, 2589 were selected to participate in this study. None of the participants had chronic kidney disease, malignant tumor, thyroid disease or adrenalopathy, or acute infectious disease. This study was approved by the Soochow University Ethics Committee in China. Written informed consent was obtained from all the participants.

Data Collection

Baseline information on demographic characteristics, lifestyle-related risk factors, history of disease, and family history of CVD was collected by trained investigators by using a standardized questionnaire. Alcohol consumption was defined as consuming an average of 25 g of alcohol per day for ≥ 1 year during the past years, from any type of alcoholic beverage. Height, body weight, and waist circumference were measured by using the standard methods. Body mass index (BMI) was calculated as weight in kilograms divided by height in square meters. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured on the right arm by using a mercury sphygmomanometer, according to a standard protocol in the sitting position^[16]. The first and fifth Korotkoff sounds were recorded as SBP and DBP, respectively. The mean of three BP measurements was calculated for the data analysis. Hypertension was defined as a SBP of ≥ 140 mm Hg and/or a DBP of ≥ 90 mm Hg, and/or use of antihypertensive medication within the previous 2 weeks.

Fasting blood samples were collected from each participant in the morning. Plasma and serum samples were frozen at -80°C until laboratory testing. Fasting plasma glucose (FPG) level was measured by using a modified hexokinase enzymatic method^[17]. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels were measured enzymatically on a Beckman Synchrony CX5 Delta Clinical System (Beckman Coulter, Fullerton, California, USA) with commercial reagents^[18]. Low-density lipoprotein cholesterol (LDL-C) levels were calculated by using the Friedwald equation for participants who had triglyceride levels of < 400 mg/dL^[19]. Serum CRP, ApoB, and ApoA-1 levels were determined by using an immunoturbidimetric assay on a Beckman SynchronCX5 Delta Clinical System with commercial reagents.

Follow-up and Outcome Assessment

All the participants were followed up from June 2003 to July 2012. The incidences of IS and CHD during the follow-up period were the primary study outcomes. Participants who did not experience IS or a CHD, who died from other causes, or who were lost to follow-up were defined as censored. If the participants were interviewed and found to have IS or CHD, the IS and CHD incidence data were defined as the end point data. Data were censored at the time of contact if the participant was reached and was found to have had no IS or CHD and on the day we last contacted the participant if the participant was lost to follow-up. For those who died from other causes, data were censored at the time of death indicated in the medical records. Since 2004, household surveys of all the participants were conducted every 2 years on average to determine the incidences of new IS and CHD events. If the participants were unable to communicate or had died, trained investigators interviewed the participants’ relatives. If the participants reported occurrence of IS or CHD during the period since the last survey, the staff reviewed the hospital records, including outpatient or inpatient records and the discharge summary. CHD was diagnosed based on symptoms, electrocardiographic changes, cardiac enzymes, and autopsy findings, according to the criteria of the World Health Organization MONICA project^[20]. Stroke was defined as sudden onset of neurological symptoms lasting ≥24 h and positive findings on cranial computed tomography or magnetic resonance imaging^[21]. Participants diagnosed as having IS or CHD at the hospital were considered to have the outcome of interest in this study.

Statistical Analyses

Statistical data on the participants’ baseline characteristics were calculated separately for the two groups with and without study outcomes. Mean (standard deviation) or median (interquartile ranges) values were used to describe normally distributed or not normally distributed continuous variables, and frequencies were used to describe categorical variables. Differences between the two groups were tested by using *t* test for normally distributed continuous variables, the Wilcoxon rank-sum test for variables that followed a skewed distribution, and the chi-squared test for categorical variables. Serum CRP levels were log transformed because of

skewness before the statistical analysis. CRP level was included as 2 categories as follows: low CRP [log CRP <1.06 mg/L (bottom 3 quartiles)] and high CRP [log CRP ≥1.06 mg/L (upper quartile)]. The ApoB/ApoA-1 ratio was entered as a categorical variable with 2 levels [low ApoB/ApoA-1 <0.505 (bottom 3 quartiles) and high ApoB/ApoA-1 ≥0.505 (upper quartile)]. Multivariate Cox proportional hazard models were used to determine the hazard ratios (HRs) for IS and CHD associated with high CRP level and ApoB/ApoA-1 ratio, respectively, adjusting for age, sex, BMI, smoking, drinking, blood glucose level, hypertension, and lipid levels.

Then, the participants were divided into four subgroups as follows: low CRP level with low ApoB/ApoA-1, low CRP with high ApoB/ApoA-1, high CRP with low ApoB/ApoA-1, and high CRP with high ApoB/ApoA-1. The Kaplan-Meier curves were used to estimate the cumulative incidence of events for the four subgroups, and the cumulative incidences of events were compared among the four groups by using the log-rank test. Furthermore, we used the Cox proportional hazard models to compute HRs for IS and CHD across the four subgroups, adjusting for age, sex, BMI, smoking, drinking, blood glucose level, hypertension, and lipid levels. All *P* values were two-tailed. A *P* value of <0.05 was considered statistically significant. The statistical analyses were performed by using the SAS statistical package version 9.3 (SAS institute, Cary, NC).

RESULTS

The study included 2589 participants who were followed up for a mean period 9.2 years. Six participants were lost to follow up, resulting in a follow-up rate of 99.8%. Among the 2589 participants, 53 were excluded because of lack of data on CRP, ApoB, or ApoA-1 level. Finally, 2536 participants were included in the analysis. After 23,114 person-years of follow-up, 151 IS or CHD events occurred. The cumulative incidence of IS and CHD events was 5.95%, and the incidence density was 653 per 100,000 person-years.

Table 1 presents a comparison of basic characteristics between the subjects with and those without outcome. The participants who developed IS or CHD during the 9.2 years of follow-up were older, more often male, smokers, and more likely to have a family history of CVD, hypertension, high FPG level, and TC level. In addition, they had significantly higher CRP levels, ApoB levels, and ApoB/ApoA-1

ratios ($P<0.05$). However, no significant difference in drinking habits, BMI, TG level, and ApoA-1 level were found between the two groups. Multivariate adjusted HRs for the association of CRP level and ApoB/ApoA-1 ratio and risk of developing IS and CHD are shown in Table 2. In crude models, high CRP level and ApoB/ApoA-1 ratio were significantly associated with the risk of IS or CHD, respectively. After further adjustment for age, sex, drinking, smoking, hypertension, FPG level, BMI, lipid levels, family history of CVD, CRP level, and ApoB/ApoA-1 ratio, CRP level was not significantly associated with the incidences of IS and CHD, regardless of whether it was treated as a continuous or categorical variable.

Only high ApoB/ApoA-1 ratio remained marginally significant [HR (95% confidence interval, CI), 1.45 (1.00-2.08)] as a categorical variable.

Pearson correlation analysis revealed a significant linear relationship between CRP level and ApoB/ApoA-1 ratio. As shown in Figure 1, ApoB/ApoA-1 ratio positively correlated to log-transformed CRP level, with a significant coefficient of 0.269 ($P<0.01$).

The participants were further divided into 4 groups according to CRP levels and ApoB/ApoA-1 ratio. Figure 2 shows that the cumulative incidences of IS and CHD were 4.30%, 6.56%, 8.00%, and 11.97% in the ‘low CRP level with low ApoB/ApoA-1’,

Table 1. Characteristics of the Participants Who Developed and Did not Develop IS or CHD

Variable	Did not Develop IS and CHD N=2385	Developed IS or CHD N=151	P Value
Age	45.77±12.08	57.69±11.31	<0.001
Gender, %			
Male	959 (40.21)	78 (51.66)	
Female	1426 (59.79)	73 (48.34)	0.006
Drinking, %	786 (32.96)	60 (39.74)	0.087
Smoking, %	1037 (43.48)	87 (57.62)	<0.001
Family history of CVD, %			
No family history	1985 (88.26)	100 (70.42)	
Family history	286 (11.99)	43 (28.48)	<0.001
BMI, kg/m ²	22.25±3.46	22.29±3.88	0.909
Hypertension, %	845 (35.43)	103 (68.21)	<0.001
Fasting glucose, mmol/L	4.96±1.19	5.30±1.51	<0.001
Total cholesterol, mmol/L	3.73±1.13	3.94±1.15	0.028
Triglycerides, mmol/L	1.26±1.29	1.29±1.11	0.788
Log CRP, mg/L	0.77 (0.59-1.05)	0.88 (0.70-1.21)	<0.001
ApoA-1, g/L	1.43 (1.20-1.74)	1.41 (1.25-1.82)	0.588
ApoB, g/L	0.60 (0.45-0.78)	0.68 (0.51-0.87)	<0.001
ApoB/ApoA-1	0.40 (0.32-0.50)	0.47 (0.36-0.57)	<0.001

Table 2. Hazard Ratios and 95% Confidence Intervals of IS and CHD Associated with CRP and ApoB/ApoA-1 Ratio

Item	Unadjusted		Adjusted Age and Gender		Adjusted Multiple Factors [*]	
	HR	95% CI	HR	95% CI	HR	95% CI
Low CRP	1		1		1	
High CRP	1.77	1.27-2.46	1.46	1.04-2.03	1.2	0.82-1.76
Log CRP (per 1 unit)	2.37	1.52-3.69	1.74	1.11-2.72	1.41	0.84-2.38
Low ApoB/ApoA-1	1		1		1	
High ApoB/ApoA-1	2.07	1.49-2.87	1.56	1.12-2.16	1.45	1.00-2.08
ApoB/ApoA-1 (per 1 unit)	2.87	1.74-4.74	1.97	1.07-3.62	1.9	0.93-3.89

Note. ^{*}Adjusted for age, gender, drinking, smoking, hypertension, blood glucose, body mass index, lipids, family history of CVD, CRP, and ApoB/ApoA-1 ratio.

‘high CRP level with low ApoB/ApoA-1’, ‘low CRP level with high ApoB/ApoA-1’, and ‘high CRP level with high ApoB/ApoA-1’ groups, respectively ($P<0.001$). The cumulative incidence of IS and CHD was highest in the ‘high CRP level with high ApoB/ApoA-1’ group. After 23,114 person-years of follow-up, 76 IS and 75 CHD events occurred. The multivariate adjusted HRs (95% CI) were 2.04 (0.97-4.27) and 1.93 (1.00-3.70) for IS and CHD, respectively. The participants with high CRP levels and high ApoB/ApoA-1 had marginally significant risk of developing IS or CHD after adjustment for multivariable, compared with those with low CRP levels and low ApoB/ApoA-1. Table 3 shows that the participants with low CRP levels and high ApoB/ApoA-1 (HR, 1.33; 95% CI, 0.84-2.12) or high

CRP levels and low ApoB/ApoA-1 (HR, 1.14; 95% CI, 0.69-1.88) had no significant risk of developing IS and CHD after adjustment for multivariable, compared with those with low CRP levels and low ApoB/ApoA-1. However, the participants with high CRP levels and high ApoB/ApoA-1 had a significantly increased risk of developing IS and CHD. The corresponding age/sex- and multivariable-adjusted HRs (95% CI) were 2.03 (1.32-3.12) and 1.91 (1.17-3.11), respectively. The ‘high CRP level with high ApoB/ApoA-1’ subgroup still had the highest risk of developing IS and CHD. Significant interactions of CRP \times ApoB/ApoA-1 on the risk of developing IS and CHD were observed in the multivariate analysis (HR, 1.69; 95% CI, 1.10-2.61).

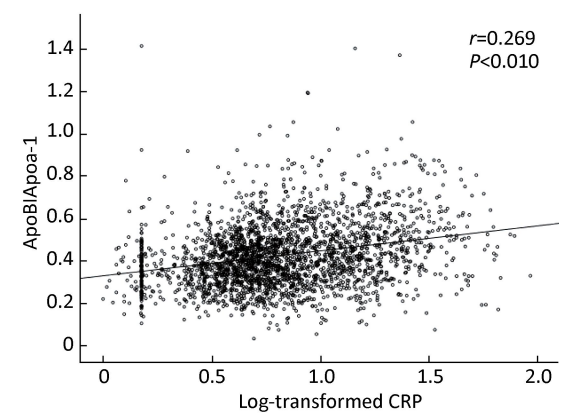


Figure 1. Scatterplot showing a significant and positive correlation of log-transformed CRP to ApoB/ApoA-1.

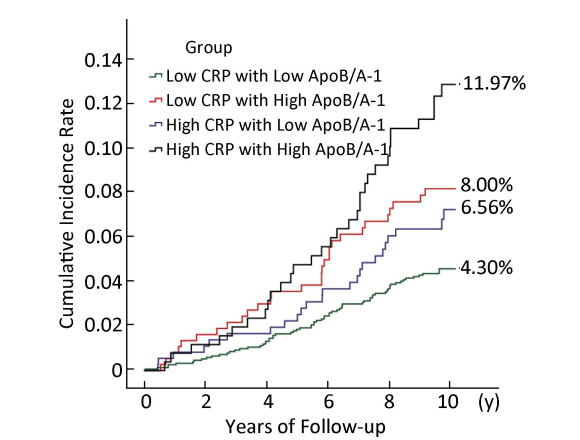


Figure 2. Cumulative incidence curve of IS and CHD according to CRP level with ApoB/ApoA-1 level.

Table 3. Adjusted Hazard Ratio for IS and CHD Incidence According to CRP with ApoB/ApoA-1 Lever							
Item	Events	Unadjusted		Adjusted Age and Gender		Adjusted Multiple Factors [*]	
		HR	95% CI	HR	95% CI	HR	95% CI
Low CRP	66	1		1		1	
Low ApoB/ApoA-1							
Low CRP	30	1.9	1.23-2.94	1.36	0.87-2.12	1.33	0.84-2.12
High ApoB/ApoA-1							
High CRP	24	1.54	0.96-2.46	1.24	0.78-1.98	1.14	0.69-1.88
Low ApoB/ApoA-1							
High CRP	31	2.81	1.83-4.31	2.03	1.32-3.12	1.91	1.17-3.11
High ApoB/ApoA-1							
CRP \times ApoB/ApoA-1		2.29	1.54-3.40	1.81	1.22-2.70	1.69	1.10-2.61

Note. ^{*} Adjusted for age, gender, drinking, smoking, hypertension, blood glucose, body mass index and lipids.

DISCUSSION

In this cohort study, we found that higher ApoB/ApoA-1 ratios were associated with increased incidence of IS and CHD events among the Inner Mongolian population. Notably, such association remained marginally significant after adjustment for age, sex, drinking, smoking, hypertension, FPG level, BMI, lipid levels, family history of CVD, and CRP. Some studies have shown that high ApoB/ApoA-1 ratios may increase the risk of developing IS and CHD^[10-12]. The results of the Apolipoprotein-Related Mortality Risk Study, a large prospective population-based study, indicated that high ApoB/ApoA-1 ratio was strongly and positively related to increased risk of fatal myocardial infarction in both men and women^[7]. As we have known, ApoB is the major apolipoprotein in all potentially atherogenic lipoprotein particles and ApoA-1 manifests several anti-atherogenic effects. An elevated ApoB/ApoA-1 ratio reflects an adverse imbalance between atherogenic and anti-atherogenic lipoprotein particles, which may result in enhanced atherosclerotic burden^[9,22]. ApoB/ApoA-1 ratio, as a predictor of CVD risk, was superior to any other conventional lipid index^[9,23-25]. Our findings also suggest that the ApoB/ApoA-1 ratio at baseline may be a predictor of future IS or CHD events.

Inflammation has been shown to be the primary key to the time course of atherosclerosis. CRP expression has been found to activate a number of processes involved in inflammatory reactions^[26-27]. Large population-based studies suggested that CRP plays a role in predicting cardiovascular events^[28-31]. For example, in the study of Cushman et al.^[29], the relative risk (RR) (95% CI) of CHD with increased CRP level was 1.45 (1.14-1.86) in the elderly population. The Framingham Heart Study^[28] showed that the HR for total CVD with log (CRP) was 1.26 (1.12-1.40) and the HR for CHD was 1.34 (1.14-1.58). However, in the Health, Aging, and Body Composition (Health ABC) study^[32], the RR of stroke or CHD associated with the top-tertile CRP levels was 1.20 (0.83-1.75) compared with the bottom-tertile CRP levels. In the Rotterdam study^[6], HR was 1.38 (0.98-1.94), showing a relatively weak association. In our study, the HR for IS or CHD with high CRP levels was 1.23 (0.84-1.80) among the Mongolian population. Although we observed a weak association between high CRP level and the incidence of IS or CHD, we found that the

participants with both high CRP level and ApoB/ApoA-1 ratio had the highest cumulative incidence of IS and CHD. These participants also had the highest risk of developing IS and CHD among the various groups, with statistical significance and independent of other classic risk factors.

Both inflammation and hyperlipidemia play major roles in atherothrombosis^[2]. In our study, the results of the Spearman correlation analysis demonstrated that ApoB/ApoA-1 ratio was significantly related to CRP level ($P < 0.01$), which was similar to the results in the study of Xu et al.^[33] Several studies have shown that hyperlipidemia seem to promote inflammation and then aggravate the progression of ischemic lesions^[34]. Meanwhile, treatment with statins was reported to possibly prevent coronary events among individuals with relatively low lipid levels and high CRP levels^[35]. Inflammation, as assessed based on hs-CRP level, and hyperlipidemia appear to play key roles in the development of cerebrovascular atherosclerosis and IS, consistent with their well-known roles in the pathophysiological mechanisms of coronary atherosclerosis and CHD^[36]. Holme et al suggested indications, but without clear evidence, that inflammation and dyslipidemia act synergistically on the risk of developing major cardiovascular events^[13]. Our findings seem to indicate a cumulative effect of high CRP level and high ApoB/ApoA-1 ratio on incidences of IS and CHD. Our finding was similar to that of Hristova et al.^[14], which suggested that the synergistic effects between ApoB and CRP levels might increase the risk of developing IS and CHD. The mechanisms underlying this phenomenon may be that the coexistence of increased CRP level with high ApoB/ApoA-1 ratio may accelerate the atherosclerotic process, which increases the risks of IS and CHD incidence in the future. Our study findings suggest that combined use of the two indexes-high CRP level and ApoB/ApoA-1 ratio-may improve the assessment of risks of IS and CHD in the general population in the future. Therefore, examination for CRP level and ApoB/ApoA-1 ratio at the same time and combined use of these two indexes may be considered as good screening methods for people at high risk of developing CVDs, including IS and CHD.

Our study has several strengths worth mentioning. The study participants were homogeneous regarding their genetic background and environmental exposures, and the study data were collected with rigid quality control. In addition,

important covariables were measured and controlled in the analysis. The relatively long observation period and high follow-up rate enabled us to identify a less biased association between exposure variables and outcome events. The limitations of our study included the following: First, the ApoA-1 and ApoB and CRP levels were measured only once at baseline; therefore, intraindividual variation during the follow-up could not be assessed. Second, we did not collect data on the use of certain kinds of drugs that can lower CRP levels, such as statins. However, as well known, people from relatively isolated areas who have high lipid levels almost always do not use these medications because they have a low knowledge rate about hyperlipidemia. Third, about 25% of the baseline population did not participate in the study, which might have introduced some selection bias. However, this bias is minimal because it is unlikely that the participants decided not to participate because of their CRP levels or ApoB/ApoA-1 ratios.

In conclusion, our study indicated that high ApoB/ApoA-1 ratio was an independent risk factor of IS and CHD, and high CRP level with high ApoB/ApoA-1 ratio conferred the highest risks of IS and CHD in the Mongolian population. This study suggests that combined use of high CRP level and high ApoB/ApoA-1 ratio may improve the assessment of the risks of IS and CHD in the general population in the future.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

AUTHORS CONTRIBUTIONS

TIAN Yun Fan and ZHOU Yi Peng collected and researched data, and wrote the manuscript. ZHONG Chong Ke, BUREN Ba Tu, and XU Tian collected and researched data. LI Hong Mei, ZHANG Ming Zhi, and WANG Ai Li researched data. ZHANG Yong Hong designed the study, collected and researched data,

and revised the manuscript. ZHANG Yong Hong is the guarantor of this work and, as such, has full access to the data and takes responsibility for the accuracy of the data analysis.

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