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Joint and Temporal Relationships of Systemic Inflammation and Atherogenic Dyslipidemia with Risk of Cardiometabolic Disease: A Longitudinal Cohort Study

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Purpose: We sought to investigate the joint association of systemic inflammation and atherogenic dyslipidemia with cardiometabolic disease (CMD) and whether the temporal relationship between them is associated with risk of CMD.

Patients and Methods: This prospective cohort study included 78,206 participants without history of cardiovascular disease and diabetes mellitus at study entry in 2006. Systemic inflammation and atherogenic dyslipidemia were evaluated by C-reactive protein (CRP) and atherogenic index of plasma (AIP), respectively. Participants were categorized into six groups according to their CRP level (<1, 1–3, or ≥3 mg/L) and AIP level (<0.1 or ≥0.1). We used Cox proportional hazard regression to calculate the hazard ratios and 95% confidence intervals (CI) for incident CMD. The temporal relationship between increased CRP and elevated AIP and the association of this temporal relationship with subsequent CMD risk were assessed by cross-lagged analysis and mediation analysis in the 53,713 participants who attended the resurvey in 2010.

Results: Increased CRP and elevated AIP were additively associated with a higher risk of CMD, where participants with a CRP of ≥3 mg/L and an AIP of ≥0.1 had 64% higher risk compared with those with low CRP and AIP values (adjusted HR: 1.64, 95% CI, 1.55–1.74). In the cross-lagged analysis, the standard regression coefficient from baseline CRP to follow-up AIP was 0.069 (95% CI, 0.061–0.077), which was greater than that from baseline AIP to follow-up CRP 0.014 (95% CI, 0.005–0.023). Furthermore, in the mediation analysis, 21.52% (95% CI 17.71–25.34) of the total association between CRP and incident CMD was mediated through AIP.

Conclusion: Systemic inflammation and atherogenic dyslipidemia were jointly associated with increased risk of CMD. Systemic inflammation might precede atherogenic dyslipidemia, and atherogenic dyslipidemia partly mediated the association between systemic inflammation and incident CMD.

Keywords: systemic inflammation, atherogenic dyslipidemia, cardiometabolic disease, cohort study

Introduction

Cardiometabolic disease (CMD), which includes cardiovascular disease and type 2 diabetes mellitus (T2DM),[1,2] is a leading cause of morbidity and mortality and constitutes a significant social and financial burden for individuals and health care systems.[3] Systemic inflammation is a strong predictor of development of cardiovascular disease[4] and T2DM.[5,6] Furthermore, atherogenic dyslipidemia, which was characterized as elevated triglycerides and low high-density lipoprotein cholesterol (HDLC), has been demonstrated to be associated with remnant atherogenic risk[7,8] and

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insulin resistance.[9] Recently, increasing attention has been attached on the contributions of inflammation and elevated low-density lipoprotein cholesterol (LDLC) to the risk of cardiovascular events.[10–12] However, data are limited with respect to the long-term (≥ 15 years) risk associated with inflammation and atherogenic dyslipidemia in combination. Because focusing on LDLC reduction alone will unlikely eliminate all lipid-related cardiometabolic outcomes,[9] we must understand the relative effect of inflammation and atherogenic dyslipidemia as important sources of residual cardiometabolic risk.

Basic studies have found that inflammation and atherogenic dyslipidemia have a bidirectional causal relationship.[13] Elevated concentrations of triglyceride-rich lipoproteins induce inflammation through upregulation of proinflammatory genes encoding cytokines, which reversely leads to dysfunctional triglyceride clearance through inhibiting lipoprotein lipase,[13,14] decreased level of HDLC, and abnormality of HDLC composition and function.[15] Although the mechanism of the relationship between systemic inflammation and atherogenic dyslipidemia is partially clarified, few studies have investigated the temporal pattern of systemic inflammation and atherogenic dyslipidemia in population and how this bidirectional crosstalk accelerates the progression of cardiovascular and glucose metabolism disorders. Insight into the combined association and temporal orders of systemic inflammation and atherogenic dyslipidemia with development of CMD could provide important information for an effective clinical assessment, development, and application of interventions.

Based on previous findings, we hypothesized that systemic inflammation and atherogenic dyslipidemia jointly contribute to increased risk of cardiometabolic outcomes, and one of them plays a mediator role in the disease progression in a population setting. We, therefore, aimed to examine the joint association of systemic inflammation and atherogenic dyslipidemia with incident CMD; to investigate the temporal relationship of systemic inflammation and atherogenic dyslipidemia using cross-lagged analysis; and to study whether and how the temporal relation pattern of systemic inflammation and atherogenic dyslipidemia influence future risk of CMD using mediation analysis.

Materials and Methods

Study Population

The Kailuan study has a community-based prospective cohort design and aims to determine the risk factors for common noncommunicable diseases, as described elsewhere.[16,17] Briefly, in 2006 to 2007, 101,510 participants were recruited from the Kailuan community in Tangshan, China. All participants completed a questionnaire interview to collect information on demographic characteristics, medical comorbidities, medication history, and lifestyle factors. All participants attended for clinical examinations and laboratory tests and have been followed biennially to update their data.

For the purposes of this study, the following exclusion criteria were applied for the 101,510 participants screened in 2006: non-attendance at follow-up visits; missing data on triglyceride, HDLC, and C-reactive protein (CRP); having history of coronary artery disease, stroke, atrial fibrillation, heart failure, and T2DM. Those who had CRP ≥10 mg/L were excluded to minimize the confounding of acute infection or inflammatory response.[18] Finally, data of 78,206 participants were included in the analysis for the joint association of systemic inflammation and atherogenic dyslipidemia with CMD (Figure 1). For examination of the temporal relationship between systemic inflammation and atherogenic dyslipidemia and its association with the risk of CMD, we further excluded those who had missing data on CRP, triglyceride, and HDLC at the 2010 visit, those who had a CRP of ≥10 mg/L at the 2010 visit, and those who developed CMD before the 2010 visit, leaving data for 53,713 participants for analysis (Figure 1).

Assessments of Variables

In the current study, we assessed systemic inflammation with CRP and assessed atherogenic dyslipidemia with atherogenic index of plasma (AIP). AIP was defined as Log (triglyceride / HDLC)[19] and has been widely used to evaluate the level of atherogenic dyslipidemia in previous studies.[20–22] Fasting blood samples were collected after at least 8 hours of fasting, and transfused into vacuum tubes containing ethylene diamine tetra-acetic acid. Concentrations of CRP, triglyceride, HDLC, LDLC, fasting blood glucose (FBG), and creatinine were measured using an auto-analyzer (Hitachi 747, Hitachi, Tokyo, Japan) at the central laboratory of the Kailuan General Hospital. CRP was measured using

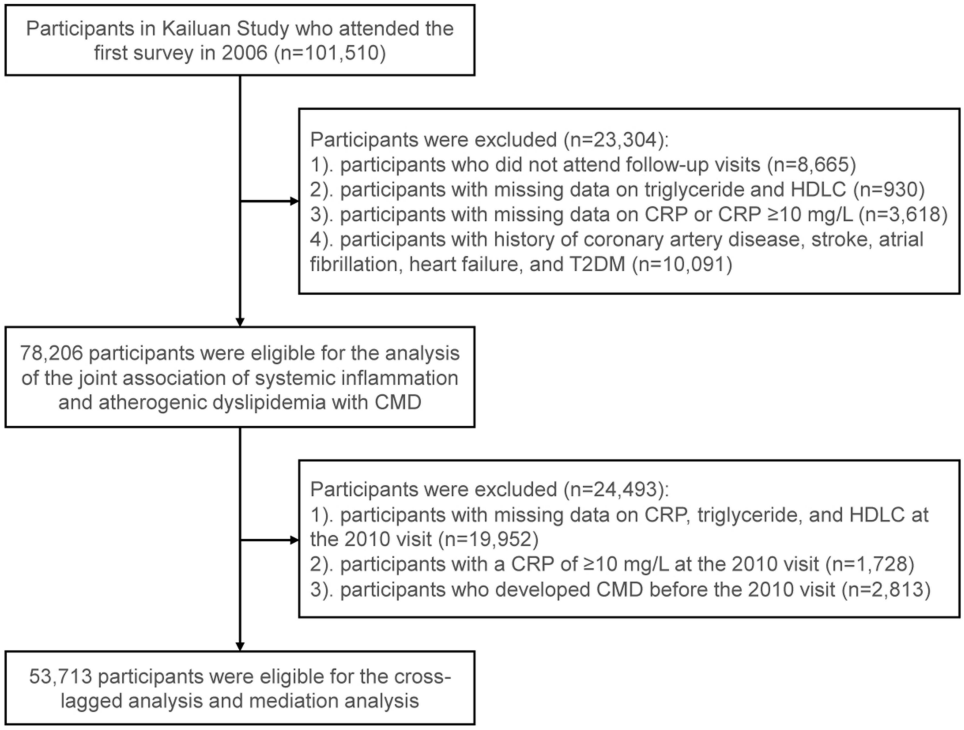

Figure 1 The flowchart of the eligibility of participants included in the present study.
Abbreviations: CMD, cardiometabolic disease; CRP, C-reactive protein; HDLC, high density lipoprotein cholesterol; T2DM, type 2 diabetes mellitus.

the high-sensitivity particle-enhanced immunonephelometric assay. Triglyceride, HDLC, and LDLC were measured using the enzymatic colorimetric method. FBG was measured using the hexokinase/glucose-6-phosphate dehydrogenase method. Creatinine was measured using the sarcosine oxidase assay method. Estimated glomerular filtration rate (eGFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.[23]

Information on demographic characteristics, including age, sex, educational level, lifestyle factors (including physical activity, smoking status, alcohol consumption, salt intake, and sleep duration), use of medication (including antihypertensive, antidiabetic, and lipid-lowering agents), and family history of myocardial infarction, stroke, and diabetes mellitus, were collected via a standardized questionnaire at baseline in 2006 and at each follow-up survey. Sleep disorders were defined as sleep duration less than 7 hours or greater than 9 hours.[24] Anthropometric measurements (including height, weight, systolic blood pressure [SBP], diastolic blood pressure [DBP], and heart rate) were obtained by trained physicians or nurses. Body mass index (BMI) was calculated as weight (kilograms) divided by the square of height (meters). Blood pressure was measured using a mercury sphygmomanometer after the participant had rested in a sitting position for at least 5 minutes. Two blood pressure readings separated by a 5-minute interval were obtained. A third reading would be taken if the difference between the two readings was ≥5 mmHg. The average of multiple measurements was used for analysis. Heart rate was measured using a 12-lead electrocardiogram that was recorded with the participant in a supine position.

Assessment of Incident CMD

The primary outcome was the first occurrence of CMD (including cardiovascular disease [myocardial infarction, coronary revascularization, ischemic stroke, hemorrhagic stroke, and heart failure] and T2DM). Information on incident CMD was collected from the Municipal Social Insurance Institution database, hospital discharge registers, and questionnaire interviews and laboratory tests performed at the follow-up visits. A panel of three physicians reviewed the medical records and confirmed diagnoses of myocardial infarction, coronary revascularization, stroke, and heart failure. Myocardial infarction was defined based on clinical symptoms, cardiac enzyme levels, and electrocardiographic results following the criteria of the World Health Organization's Multinational Monitoring of Trends and Determinants in Cardiovascular Disease.[25] Coronary revascularization was defined as a medical record of percutaneous coronary intervention or coronary artery bypass grafting. Stroke was

defined based on clinical symptoms, neurological signs, and neuroimages from computed tomography or magnetic resonance scans following the World Health Organization criteria.[26] Heart failure was defined based on clinical symptoms, cardiac function classified as New York Heart Association grade II, III, IV or Killip grade II, III, IV, and a left ventricular ejection fraction of <50% according to the European Society of Cardiology guideline.[27] T2DM was defined as either FBG ≥7 mmol/L, use of antidiabetic medications (including oral antidiabetic agents and insulin), or self-reporting of physician-diagnosed T2DM. Information on deaths was obtained from provincial vital statistics offices. Participants were followed until the date of death or December 31, 2021, whichever came first.

Statistical Analysis

We categorized the study participants into six groups according to their baseline CRP level (<1 mg/L, 1–3 mg/L, ≥3 mg/L)[18] and AIP (<0.1, ≥0.1).[28] Continuous variables with a normal distribution are presented as the mean ± standard deviation and were compared using analysis of variance. Continuous variables with a skewed distribution are presented as the median (interquartile range) and were compared using the Kruskal–Wallis test. Categorical variables are presented as the number (percentage) and were compared using the chi-square test.

We used Cox proportional hazard regression models to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of risk of CMD across the CRP-AIP groups. Our models met the proportional assumption criteria according to Schoenfeld residuals. The multivariable models were adjusted for age, sex, BMI, SBP, DBP, heart rate, FBG, LDLC, eGFR, smoking status, alcohol consumption, physical activity, educational level, salt intake, sleep disorders, family history of myocardial infarction, stroke, and diabetes mellitus, and use of antihypertensive and lipid-lowering medications. Missing data on covariates were handled by multiple imputation. The following sensitivity analyses were conducted to test the robustness of the results: analysis taking into account the competing risk of death; exclusion of participants who had outcome events within the first 2 years of follow-up to minimize potential reverse causation; exclusion of participants who used lipid-lowering medications; time-dependent Cox regression analysis with CRP-AIP group as a time-dependent explanatory variable; calculating AIP cutoff using clinical cutoff values for TG (1.7 mmol/L) and HDLC (1.0 mmol/L) (AIP cutoff = 0.23);[29] and estimating AIP cutoff by the receiver operating characteristic (ROC) curve analysis (AIP cutoff = −0.06). To assess whether combined CRP and AIP assessment provides additional predictive value beyond traditional risk factors, we used Logistic regression to establish a predictive model for 10-year CMD risk including all well-recognized risk factors that included in our study and a model including CRP and AIP additionally. We compared the areas under curves (AUC) for ROC curve analyses between models with and without CRP and AIP and calculated the net reclassification index (NRI) to assess the improvement of risk prediction.

To examine the temporal relationship between CRP and AIP further, we performed cross-lagged analysis for the 53,713 participants who attended both the baseline visit in 2006 and the follow-up visit in 2010 and had complete CRP and AIP measurements. Cross-lagged path analysis was performed based on the causal relationship presented in Figure 2. The cross-lagged analysis calculated the standard regression coefficient of baseline CRP in 2006 on follow-up AIP in 2010 (β1) and the standard regression coefficient of baseline AIP in 2006 on follow-up CRP in 2010 (β2). The difference between β1 and β2 was examined using Fisher's Z-test. Further adjusted model was adjusted for the time interval between the two measurements and other potential confounders mentioned in the above Cox regression analysis. Sensitivity analyses were performed by excluding participants using lipid-lowering medications.

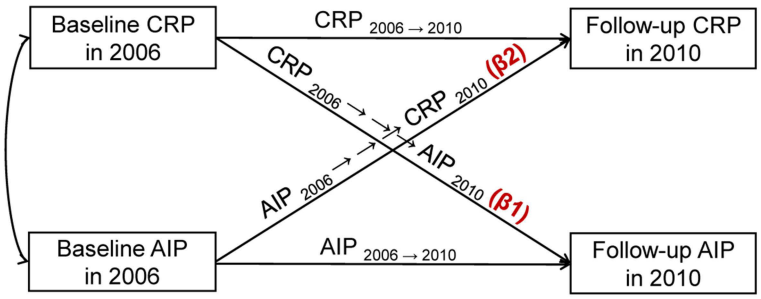

Figure 2 Cross-lagged analysis model about C-reactive protein (CRP) and atherogenic index of plasma (AIP) in 53,713 participants in the Kailuan Study. β1 and β2 indicate the standard regression coefficient.

After the temporal relationship between CRP and AIP had been identified, we conducted mediation analysis to explore the mediator in the association of CRP and AIP with the risk of CMD. The mediation analysis was conducted based on the variance-covariance matrix using the maximum likelihood method. This analysis calculated the total effect of the risk factor on the outcome (the sum of the direct and indirect effect), the direct effect (the effect without the impact of the mediator), and the indirect effect (the effect of the risk factor on the outcome attributable to the mediator). Further adjusted model included the potential confounders mentioned in the above Cox regression analysis. We performed several sensitivity analyses by excluding those who had outcome events within the first 2 years of follow-up and by excluding those who used lipid-lowering medications.

Given that both systemic inflammation level and lipid metabolism differ between women and men, we conducted subgroup analyses by sex in joint risk assessment, cross-lagged analysis, and mediation analysis.

Results

Baseline Characteristics

The baseline characteristics are presented according to CRP-AIP groups in Table 1. Compared with participants of other groups, those with a CRP of ≥1mg/L and an AIP of ≥0.1 were more likely to have a higher BMI, blood pressure, heart rate, to be on antihypertensive and lipid-lowering medications, and to have a family history of myocardial infarction and stroke.

Table 1 Baseline Characteristics of 78,206 Participants According to CRP-AIP Groups

Variables	CRP <1mg/L and AIP <0.1	CRP 1–3mg/L and AIP <0.1	CRP ≥3mg/L and AIP <0.1	CRP <1mg/L and AIP ≥0.1	CRP 1–3mg/L and AIP ≥0.1	CRP ≥3mg/L and AIP ≥0.1	*P* value
No. of participants	35,530	13,335	8130	11,585	6072	3554	
Age, y	50±12	51±12	54±12	49±11	50±11	53±12	<0.001
Men, No. (%)	27,206 (76.57)	10,173 (76.29)	6087 (74.87)	10,064 (86.87)	5024 (82.74)	2782 (78.28)	<0.001
CRP, mg/L	0.30 (0.13–0.57)	1.54 (1.20–2.10)	5.20 (3.80–7.29)	0.37 (0.17–0.62)	1.59 (1.23–2.10)	5.10 (3.78–7.10)	<0.001
AIP	−0.18 (−0.32–−0.06)	−0.15 (−0.28–−0.03)	−0.16 (−0.31–−0.04)	0.27 (0.17–0.41)	0.27 (0.17–0.42)	0.27 (0.17–0.40)	<0.001
BMI, kg/m^2	24.0±3.2	25.1±3.4	24.9±3.6	25.8±3.1	26.9±3.3	26.7±3.6	<0.001
SBP, mmHg	126±19	130±21	131±21	131±19	134±20	135±21	<0.001
DBP, mmHg	81±11	83±12	83±12	85±11	86±12	86±12	<0.001
Heart rate, beats/min	73±10	73±10	73±10	74±10	74±10	74±10	<0.001
FBG, mmol/L	5.05±0.65	5.09±0.69	4.98±0.74	5.16±0.70	5.21±0.72	5.15±0.76	<0.001
LDLC, mmol/L	2.34 (1.88–2.80)	2.40 (1.97–2.90)	2.19 (1.11–2.80)	2.34 (1.85–2.81)	2.40 (1.90–2.90)	2.19 (1.29–2.87)	<0.001
HDLC, mmol/L	1.61±0.38	1.60±0.37	1.63±0.42	1.37±0.36	1.35±0.34	1.37±0.34	<0.001
Triglyceride, mmol/L	1.02 (0.75–1.31)	1.10 (0.83–1.39)	1.07 (0.79–1.37)	2.55 (1.96–3.71)	2.52 (1.97–3.55)	2.56 (2.01–3.48)	<0.001
eGFR, mL/min/1.73m^2	83±19	82±19	84±19	81±20	81±20	82±21	<0.001
Smoking status, No. (%)							<0.001
Never	21,949 (61.78)	8109 (60.81)	5294 (65.12)	6224 (53.72)	3210 (52.87)	2131 (59.96)	
Past	1601 (4.51)	703 (5.27)	428 (5.26)	660 (5.70)	401 (6.60)	190 (5.35)	
Current	11,980 (33.72)	4523 (33.92)	2408 (29.62)	4701 (40.58)	2461 (40.53)	1233 (34.69)	
Ever-drinkers, No. (%)	14,430 (40.61)	5467 (41.00)	2878 (35.40)	5393 (46.55)	2915 (48.01)	1468 (41.31)	<0.001
Physical exercise, No. (%)							<0.001
Light	3242 (9.12)	1089 (8.17)	657 (8.08)	1220 (10.53)	584 (9.62)	289 (8.13)	
Moderate	27,322 (76.90)	9977 (74.82)	6346 (78.06)	8741 (75.45)	4417 (72.74)	2763 (77.74)	
Heavy	4966 (13.98)	2269 (17.02)	1127 (13.86)	1624 (14.02)	1071 (17.64)	502 (14.12)	
Salt intake, No. (%)							<0.001
Low	3215 (9.05)	1296 (9.72)	668 (8.22)	1098 (9.48)	563 (9.27)	282 (7.93)	
Moderate	28,769 (80.97)	10,570 (79.27)	6675 (82.10)	9149 (78.97)	4662 (76.78)	2878 (80.98)	
High	3546 (9.98)	1469 (11.02)	787 (9.68)	1338 (11.55)	847 (13.95)	394 (11.09)	
Higher education, No. (%)	2766 (7.78)	1029 (7.72)	576 (7.08)	718 (6.20)	468 (7.71)	249 (7.01)	<0.001
Sleep disorders, No. (%)	9968 (28.06)	3972 (29.79)	2143 (26.36)	3454 (29.81)	1909 (31.44)	956 (26.90)	<0.001
Antihypertensive drugs use, No. (%)	2044 (5.75)	1363 (10.22)	782 (9.62)	1039 (8.97)	959 (15.79)	517 (14.55)	<0.001
Lipid lowering drugs use, No. (%)	136 (0.38)	83 (0.62)	49 (0.60)	87 (0.75)	70 (1.15)	44 (1.24)	<0.001
Family history of MI, No. (%)	660 (1.86)	273 (2.05)	149 (1.83)	236 (2.04)	167 (2.75)	78 (2.19)	<0.001
Family history of Stroke, No. (%)	1501 (4.22)	633 (4.75)	307 (3.78)	488 (4.21)	342 (5.63)	178 (5.01)	<0.001
Family history of DM, No. (%)	1436 (4.04)	583 (4.37)	273 (3.36)	575 (4.96)	369 (6.08)	168 (4.73)	<0.001

Abbreviations: AIP, atherogenic index of plasma; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDLC, high density lipoprotein cholesterol; LDLC, low density lipoprotein cholesterol; MI, myocardial infarction; SBP, systolic blood pressure.

Risk of CMD According to CRP-AIP Group

During a median follow-up of 14.92 years, we documented 19,588 cases of CMD (including 9001 cases of cardiovascular disease and 12,629 cases of T2DM). After adjusting for potential confounders, increased CRP and elevated AIP were individually and cumulatively associated with increased risk of CMD. Compared with participants with a CRP of <1 mg/L and an AIP of <0.1, the adjusted HR (95% CI) for CMD was 1.18 (1.13–1.23) for those with a CRP of 1–3 mg/L and an AIP <0.1, 1.28 (1.22–1.35) for those with a CRP of ≥3 mg/L and an AIP of <0.1, 1.33 (1.27–1.38) for those with a CRP of <1 mg/L and an AIP ≥0.1, 1.53 (1.46–1.61) for those with a CRP of 1–3 mg/L and an AIP of ≥0.1, and 1.64 (1.55–1.74) for those with a CRP of ≥3 mg/L and an AIP of ≥0.1 (Table 2). Similar findings were observed in subanalyses for cardiovascular disease and T2DM (Table 2) and subgroup analyses in women and men (Supplementary Table S1). Sensitivity analyses taking into account the competing risk of death, excluding participants who had outcome events within the first 2 years of follow-up, excluding participants who used lipid-lowering medications, entering CRP-AIP group as a time-dependent explanatory variable, and using different AIP cutoffs for grouping yielded consistent results (Supplementary Tables S2–S4). The individual associations of CRP and AIP with risk of CMD were shown in Supplementary Tables S5 and S6. Adding CRP and AIP to a model containing conventional risk factors improved risk prediction for the 10-year cardiometabolic outcome (AUCs of ROC curves [95% CI]: 71.20 [70.70–71.69] vs 70.88 [70.39–71.37], P <0.001; NRI [95% CI]: 0.009 [0.004–0.011], P <0.001).

Cross-Lagged Analysis

The results of the cross-lagged path analysis of CRP and AIP are presented in Table 3. After adjustment for the time interval between the two measurements and other potential confounders, the standard regression coefficient from the baseline CRP to the follow-up AIP (β1=0.069, 95% CI: 0.061–0.077) was greater than that from the baseline AIP to the follow-up CRP (β2=0.014, 95% CI: 0.005–0.023), with P-value of <0.001 for the difference between β1 and β2. The variance of follow-up CRP and AIP (R^2) explained by baseline CRP and AIP were estimated at 0.0498 and 0.3171, respectively. This result suggested that the temporal relationship between increased CRP and future elevated AIP was

Table 2 Hazard Ratios (95% CI) for Incident CMD, Cardiovascular Disease, and T2DM According to CRP-AIP Groups

Outcomes	CRP-AIP Groups, HR (95% CI)					
	CRP <1mg/L and AIP <0.1	CRP 1–3mg/L and AIP <0.1	CRP ≥3mg/L and AIP <0.1	CRP <1mg/L and AIP ≥0.1	CRP 1–3mg/L and AIP ≥0.1	CRP ≥3mg/L and AIP ≥0.1
CMD						
Case/Total	6890/35,530	3355/13,335	2224/8130	3475/11,585	2247/6072	1397/3554
Incidence rate*	14.16 (13.83–14.50)	18.95 (18.32–19.60)	20.87 (20.02–21.75)	22.86 (22.11–23.64)	29.00 (27.82–30.22)	31.61 (29.99–33.31)
Model 1	1 (Reference)	1.30 (1.25–1.35)	1.33 (1.27–1.39)	1.61 (1.54–1.67)	2.02 (1.93–2.12)	2.08 (1.97–2.21)
Model 2	1 (Reference)	1.18 (1.13–1.23)	1.29 (1.23–1.35)	1.33 (1.28–1.39)	1.55 (1.48–1.63)	1.65 (1.56–1.75)
Model 3	1 (Reference)	1.18 (1.13–1.23)	1.28 (1.22–1.35)	1.33 (1.27–1.38)	1.53 (1.46–1.61)	1.64 (1.55–1.74)
Cardiovascular Disease						
Case/Total	3251/35,530	1649/13,335	1159/8130	1414/11,585	917/6072	611/3554
Incidence rate*	6.34 (6.12–6.56)	8.72 (8.31–9.16)	10.15 (9.58–10.75)	8.54 (8.11–9.00)	10.73 (10.06–11.45)	12.45 (11.50–13.47)
Model 1	1 (Reference)	1.30 (1.22–1.38)	1.32 (1.23–1.41)	1.35 (1.27–1.44)	1.66 (1.54–1.78)	1.72 (1.58–1.88)
Model 2	1 (Reference)	1.20 (1.13–1.28)	1.25 (1.17–1.34)	1.19 (1.12–1.27)	1.39 (1.29–1.49)	1.46 (1.33–1.59)
Model 3	1 (Reference)	1.19 (1.12–1.26)	1.24 (1.16–1.33)	1.19 (1.12–1.27)	1.35 (1.25–1.46)	1.43 (1.31–1.56)
T2DM						
Case/Total	4226/35,530	2054/13,335	1312/8130	2454/11,585	1616/6072	967/3554
Incidence rate*	11.72 (11.37–12.08)	15.45 (14.80–16.14)	16.11 (15.26–17.00)	21.18 (20.36–22.03)	26.60 (25.34–27.93)	27.30 (25.64–29.08)
Model 1	1 (Reference)	1.35 (1.28–1.42)	1.34 (1.26–1.42)	1.77 (1.69–1.86)	2.24 (2.12–2.38)	2.29 (2.13–2.45)
Model 2	1 (Reference)	1.19 (1.13–1.26)	1.28 (1.20–1.37)	1.38 (1.31–1.45)	1.58 (1.49–1.67)	1.67 (1.56–1.80)
Model 3	1 (Reference)	1.19 (1.13–1.25)	1.28 (1.20–1.36)	1.37 (1.30–1.44)	1.57 (1.48–1.67)	1.67 (1.55–1.79)

Notes: *Indicates per 1000 person-years. Model 1 was adjusted for age and sex; Model 2 was further adjusted for body mass index, systolic blood pressure, diastolic blood pressure, heart rate, fasting blood glucose, low-density lipoprotein cholesterol, estimated glomerular filtration rate, smoking status, alcohol consumption, physical activity, educational level, salt intake, sleep disorders, and family history of myocardial infarction, stroke, and diabetes mellitus; Model 3 was further adjusted for antihypertensive and lipid-lowering medications use.

Abbreviations: AIP, atherogenic index of plasma; CI, confidence interval; CMD, cardiometabolic disease; CRP, C-reactive protein; HR, hazard ratio; T2DM, type 2 diabetes mellitus.

Table 3 Cross-Lagged Standard Regression Coefficient of CRP and AIP Between 2006 and 2010 (n=53,713)

	R^2 of CRP	R^2 of AIP	CRP_{2006}–CRP_{2010}	AIP_{2006}–AIP_{2010}	CRP_{2006}–AIP_{2010} (β1)	AIP_{2006}–CRP_{2010} (β2)	*P* difference*
Model 1	0.0647	0.3763	0.246 (0.237–0.254)	0.604 (0.598–0.609)	0.080 (0.072–0.088)	0.054 (0.045–0.063)	<0.001
Model 2	0.0499	0.3184	0.223 (0.214–0.231)	0.558 (0.552–0.564)	0.069 (0.061–0.077)	0.014 (0.005–0.024)	<0.001
Model 3	0.0497	0.3172	0.222 (0.213–0.231)	0.557 (0.551–0.563)	0.069 (0.061–0.077)	0.014 (0.005–0.023)	<0.001
Model 4	0.0498	0.3171	0.222 (0.213–0.231)	0.557 (0.551–0.563)	0.069 (0.061–0.077)	0.014 (0.005–0.023)	<0.001

Notes: *Indicates the *P* value for the difference between β1 and β2. Model 1 was adjusted for age and sex; Model 2 was further adjusted for body mass index, systolic blood pressure, diastolic blood pressure, heart rate, fasting blood glucose, low-density lipoprotein cholesterol, estimated glomerular filtration rate, smoking status, alcohol consumption, physical activity, educational level, salt intake, sleep disorders, and family history of myocardial infarction, stroke, and diabetes mellitus; Model 3 was further adjusted for antihypertensive and lipid-lowering medications use; Model 4 was further adjusted for the time interval between the two measurements.
Abbreviations: AIP, atherogenic index of plasma; CRP, C-reactive protein.

significantly stronger than that between increased AIP and future elevated CRP. Consistent findings were showed in the sensitivity analysis that excluded participants using lipid-lowering medications (Supplementary Table S7) and subgroup analyses in women and men (Supplementary Table S8).

Mediation Analysis

The results of the mediation analysis are shown in Figure 3 and Supplementary Table S9. After adjusting for potential confounders, AIP mediated the association between CRP and the risks of CMD, cardiovascular disease, and T2DM. The total effect (HR_{total}) of CRP on incident CMD was 1.07 (95% CI 1.06–1.08). The indirect effect mediated by AIP ($HR_{indirect}$) was 1.01 (95% CI 1.01–1.02), with the percentage of mediation was 21.52 (95% CI 17.71–25.34). The results were similar for cardiovascular disease and T2DM, for which the respective mediation proportions were 15.04% (95% CI 9.71–20.37) for cardiovascular disease and 25.31% (95% CI 20.42–30.20) for T2DM. There was no material change in the mediation results after exclusion of participants with CMD events within the first 2 years of follow-up and those on lipid-lowering medications (Supplementary Table S9). Consistent findings were also observed in both women and men (Supplementary Table S10). Compared with the above findings, the mediation effect of CRP on the association of AIP with CMD risk was significantly lower (Supplementary Table S11).

Discussion

In this community-based cohort study, we prospectively examined the association of systemic inflammation and atherogenic dyslipidemia with the occurrence of CMD. Inflammation and atherogenic dyslipidemia were cumulatively associated with the risk of cardiovascular events and T2DM, and this finding persisted after adjustment for potential confounders and remained consistent among sensitivity analyses. Notably, we observed that increased systemic inflammation was associated with subsequent atherogenic dyslipidemia rather than the opposite direction, and the inflammation-related increase in risk of CMD seemed to be partially mediated through atherogenic dyslipidemia.

Several studies have reported the cumulative cardiovascular risk related to inflammation and cardiometabolic indicators. Both clinical trials and observational studies have shown that the risk of cardiovascular events is higher in individuals with elevated CRP and LDLC levels than in those with lower levels of these biomarkers.[10–12,30–32] Elevated CRP with low HDLC was also observed to be associated with poorer outcome in patients with ischemic stroke and coronary artery disease.[33,34] A cohort study in China suggested that elevated CRP and triglyceride-glucose index values cumulatively increased the risk of cardiovascular events in middle-aged and older individuals.[35] Currently, there are limited data on the combined influence of inflammation and atherogenic dyslipidemia on cardiometabolic risk, whereas our study provides new information that both increased systemic inflammation and atherogenic dyslipidemia individually and cumulatively promotes the development of CMD. More importantly, our study observed that increased inflammation might precede atherogenic dyslipidemia in a population setting and demonstrated the mediation effect of atherogenic dyslipidemia in the process of inflammation leading to cardiometabolic disorders. Lan et al examined the temporal relationship between inflammation and atherogenic dyslipidemia and found that the association between increased inflammation and future atherogenic dyslipidemia was stronger than the reverse.[36] However, the study population of this previous analysis did not exclude patients with CMD, thus the results could not represent the temporal relationship

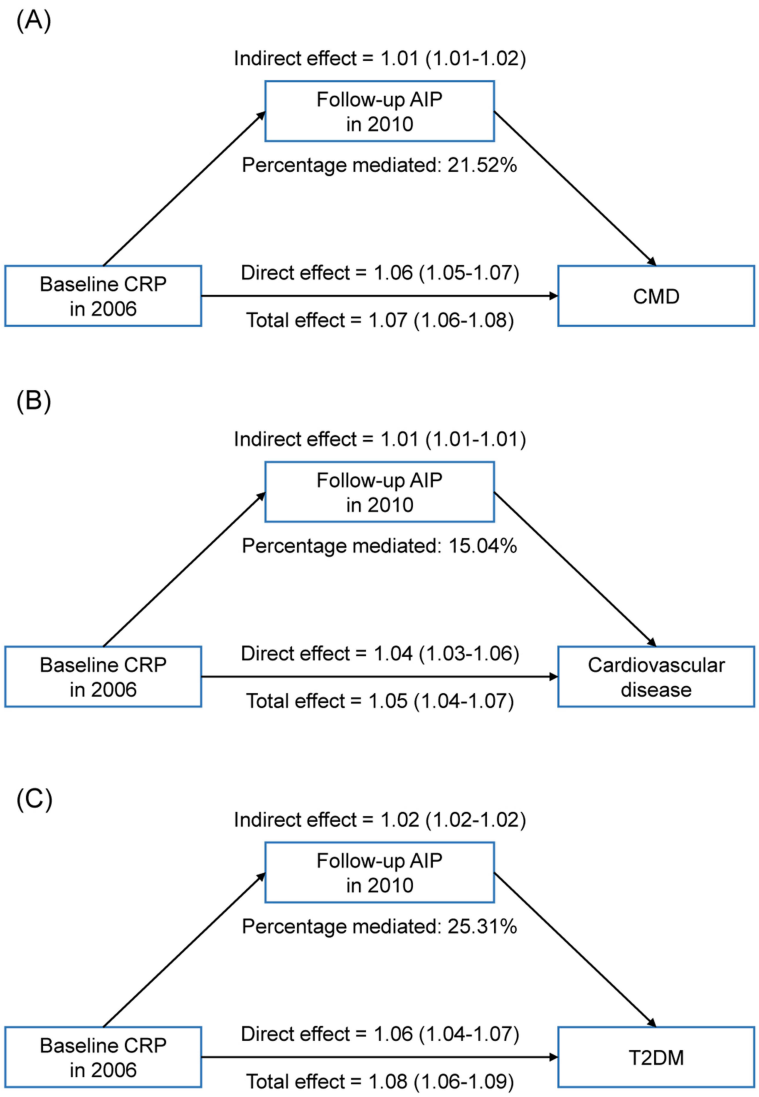

Figure 3 Mediation effect of follow-up atherogenic index of plasma (AIP) on the association between baseline C-reactive protein (CRP) and subsequent risk of (**A**) cardiometabolic disease (CMD), (**B**) cardiovascular disease, and (**C**) type 2 diabetes mellitus (T2DM). Models were adjusted for age, sex, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, fasting blood glucose, low-density lipoprotein cholesterol, estimated glomerular filtration rate, smoking status, alcohol consumption, physical activity, educational level, salt intake, sleep disorders, family history of myocardial infarction, stroke, and diabetes mellitus, and antihypertensive and lipid-lowering medications use.

between inflammation and atherogenic dyslipidemia before CMD onset. de Rooij et al reported that the association between inflammation and cardiometabolic risk was not mediated by insulin resistance.[37] But none of the previous studies examined the atherogenic dyslipidemia-mediated association between inflammation and CMD. Our findings extend the current knowledge by providing evidence regarding the role of atherogenic dyslipidemia in the pathological link between inflammation and cardiometabolic disorders.

Dysregulated lipid metabolism has been well-recognized as a cause of cardiovascular inflammation.[13] However, recent evidence suggests that immune status can also influence lipid metabolism, which may reveal a mechanism to explain our findings. Klingenberg et al found that the hepatic inflammation posed by impaired responses of regulatory T cells reduced the expression of sortilin-1 and upgraded lipoprotein lipase, hepatic lipase, and phospholipid transfer protein, resulting in atherogenic dyslipidemia.[38] Furthermore, inflammation can impair reverse cholesterol transport, attenuate the efflux function of HDLC, and alter the composition and antioxidative activity of HDLC.[15,39] Numerous inflammatory markers, including lipopolysaccharide, lipoteichoic acid, tumor necrosis factor, interleukin-1, and interleukin-6, can increase serum triglyceride levels.[40] Dysregulation of LIGHT expression on the T cells also result in

hypertriglyceridemia.[41] These inflammation-associated disorders of triglyceride and HDLC metabolism might be directly represented by atherogenic dyslipidemia. Furthermore, analysis of clinical trial data has demonstrated that inflammation reduces the beneficial effect of reduced-fat low-cholesterol diet on the lipid profile and increased serum triglyceride level, which might be another mechanism for inflammation-induced hypertriglyceridemia.[42] Hypertriglyceridemia causes overproduction and inefficient lipolysis of both very low-density lipoprotein and chylomicron. These lipoprotein particles lead to increased formation of triglyceride-rich lipoprotein remnants, which participate in the initiation and progression of atherosclerotic lesions.[43] Hypertriglyceridemia accompanied by low HDLC has been demonstrated to be a marker of insulin resistance.[44] Additionally, increased concentration of free fatty acids derived from elevated triglyceride may further deteriorate insulin sensitivity and increased diabetes risk.[44] Overall, these evidences suggest that inflammation can induce disorders of triglyceride-HDLC metabolism through multiple pathways and contribute to the development of atherosclerosis, metabolic dysfunction, and T2DM.

The findings of our study have important clinical implications. First, the observation that systemic inflammation and atherogenic dyslipidemia jointly contributes to incident CMD independent of LDLC highlighted the attention to the assessment of residual risk. In the current study, a single measurement of CRP and AIP strongly predicted cardiometabolic risk over a 15-year period. This provided reassurance for clinicians who do not routinely measure these biomarkers because of concerns with respect to variability over time. Second, our joint-effects and mediation-effects models provide epidemiologic evidence of the pathways underlying atherogenic diseases interact with each other to drive potentially cardiometabolic events. Clinical trials of canakinumab and colchicine have demonstrated that anti-inflammatory therapy can significantly reduce cardiovascular risk among patients receiving statins.[45,46] The current study reinforces the clinical concept that interventions addressing a diverse set of biologic targets is urgently needed for optimizing the prevention of cardiometabolic events. Third, our data offer a potential choice for primary and secondary prevention to patients with residual inflammatory risk and residual atherogenic risk who do not tolerate statin therapy. In addition, stringent intervention on atherogenic dyslipidemia may partially inhibit the progression of inflammation-related cardiometabolic events for those who has a poor response to anti-inflammatory treatment.

Strengths and Limitations

The strengths of our study include prospective cohort design, large sample size, long-term follow-up, high-quality data, central-laboratory blood test, and using longitudinal assessment of inflammation and atherogenic dyslipidemia to determine the association between their temporal relationship and cardiometabolic outcomes. Another major strength is that we adjusted a wide spectrum of confounding factors, including demographic characteristics, lifestyles, laboratory biomarkers, and medical conditions, which could greatly reduce unmeasured residual confounding. However, several limitations should be concerned. First, all of the study participants were from the Kailuan community, which may limit the generalizability of our findings to populations in other regions to some extent. Second, data on glycated hemoglobin and oral glucose tolerance test were not available, which may introduce some misclassification bias in the identification of T2DM events. Third, although our analyses had adjusted for a wide spectrum of confounders, confounding bias might still exist because there was a lack of data on several potential confounding factors that were related with inflammation and lipid metabolism, for instance, lipid intake and mental status. Fourth, this study was based on an observational design. Although the cross-lagged and mediation analyses are methodologically sound, the temporal and mediated inferences remain associative and the causality cannot be firmly established. Therefore, the results of our study should be interpreted with caution, further study on molecular mechanisms and clinical trial on anti-inflammatory treatment are required.

Conclusion

In this study, we found that systemic inflammation and atherogenic dyslipidemia were cumulatively associated with increased risk of CMD in general population. Systemic inflammation might precede the development of atherogenic dyslipidemia, and atherogenic dyslipidemia might play a mediating role in the progression from inflammation to CMD. Beyond implications for risk stratification, the findings of our study improve the understanding of the pathobiology and mechanisms of cardiometabolic disorders. In addition to focusing LDLC lowering, assessments and interventions on

inflammation and atherogenic dyslipidemia are promising means to reduce cardiometabolic risk. These data strongly support the need for efforts to extend strategies for the primary prevention of CMD by targeting dual pathways of inflammation and dyslipidemia.

Abbreviations

AIP, atherogenic index of plasma; AUC, area under curve; BMI, body mass index; CI, confidence interval; CMD, cardiometabolic disease; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDLC, high-density lipoprotein cholesterol; HR, hazard ratio; LDLC, low-density lipoprotein cholesterol; NRI, net reclassification index; ROC, receiver operating characteristic; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus.

Data Sharing Statement

The datasets generated during the current study are not publicly available due to privacy and ethical restrictions, but are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

The study was approved by the ethics committee of Kailuan General Hospital (reference number: 2006-5) and conducted in accordance with the Declaration of Helsinki. All study participants provided written informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors declare that they have no competing interests.

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