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ORIGINAL RESEARCH

# The Combination of Hyperuricemia and Elevated High-Sensitivity C-Reactive Protein Increased the Risk of Cardiac Conduction Block

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**Objective:** This study aimed to explore the impact of a combination of hyperuricemia (HUA) and excessive high-sensitivity C-reactive protein (hs-CRP) levels on the likelihood of developing cardiac conduction block (CCB). Additionally, it sought to assess whether the influence of uric acid (UA) on CCB is mediated by hs-CRP.

**Methods:** A prospective study was executed utilizing data from the Kailuan cohort, including 81,896 individuals initially free from CCB. The participants were categorized into four groups depending on the existence of HUA and low-grade inflammation (hs-CRP>3 mg/L). Cox regression analysis was employed to ascertain hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of incident CCB. A mediation analysis was performed to determine if hs-CRP functioned as a mediator in the connection between UA levels and the incidence of CCB.

**Results:** During a median observation period of 11.8 years, we identified 3160 cases of newly occurring CCB. Compared with the low UA/low CRP group, the combination of HUA and low-grade inflammation elevated the CCB risks (HR:1.56, 95% CI:1.22–1.99), atrioventricular block (AVB) (HR:1.88, 95% CI:1.27–2.77), and right bundle branch block (HR:1.47, 95% CI:1.02–2.12), respectively. Mediation analysis revealed that in the HUA group, compared with the non-HUA group, the risk of CCB elevated by 14.0%, with 10.3% of the increase mediated through hs-CRP.

**Conclusion:** HUA combined with elevated hs-CRP increased the risk of CCB, especially AVB. The connection between UA and the CCB risk was partly mediated by hs-CRP.

**Keywords:** hyperuricemia, inflammation, cardiac conduction block, combined exposure, risk factors, mediation

## Introduction

Cardiac conduction block (CCB) arises from conduction system malfunction and correlates with myocardial fibrosis.[1,2] It could manifest in any cardiac conduction system component. Increasing evidence suggested that even the first-degree atrioventricular block (AVB) was independently linked to worse cardiac prognosis.[3] Furthermore, the existence of bundle



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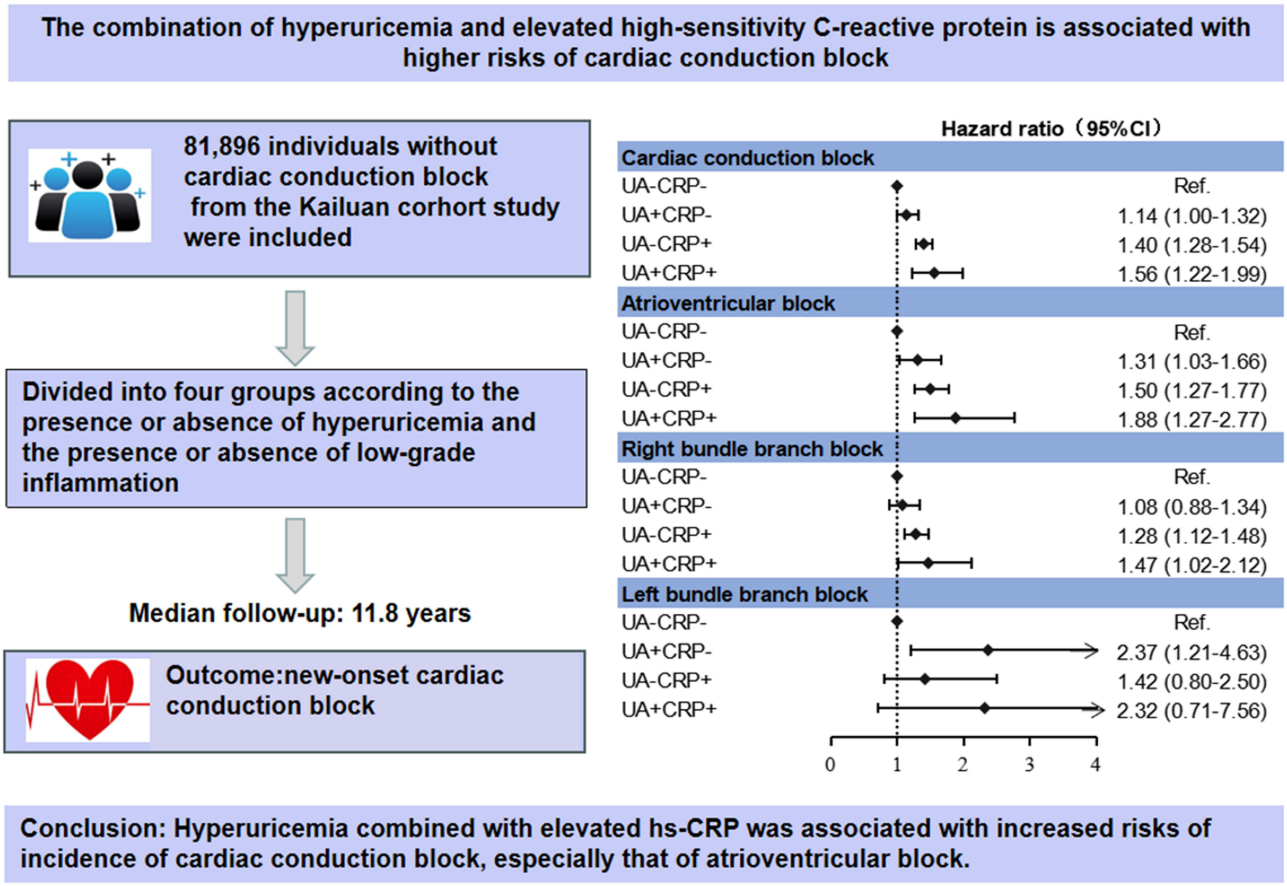
**Graphical Abstract**




branch block (BBB) was linked to worse cardiovascular outcomes and increased mortality.[4] Given the potential impact of CCB on patients' outcomes, it is of special interest to investigate underlying risk factors. In fact, prior studies have demonstrated that CCB can also be caused by hypertension, diabetes, hereditary diseases, and ischemic heart disease.[5–7] Recently, a few studies have demonstrated that elevated levels of uric acid (UA) and high-sensitivity C-reactive protein (hs-CRP) may contribute to CCB.[8,9]

UA, which is produced as a result of purine metabolism with the help of xanthine oxidase, has been extensively studied for its association with cardiovascular diseases (CVD).[10,11] Epidemiological evidence consistently suggests that hyperuricemia (HUA), characterized by elevated UA levels, is a risk factor for various cardiovascular conditions.[11,12] UA levels are positively correlated with hs-CRP levels, which are proteins produced following inflammation, infection, or tissue damage and are associated with chronic diseases.[13,14] Mantovani et al discovered that type 2 diabetes patients manifested a much twofold greater likelihood of cardiac conduction abnormalities when their levels of UA were in the upper third range, as opposed to those in the lower third range.[8] In the same line, Frimodt-Moller et al manifested an increased risk of cardiac conduction disorders when hs-CRP levels were higher at baseline.[9] Therefore it could be speculated that the simultaneous elevation of UA and hs-CRP may be linked to increased CCB risk originating from common pathophysiological pathways such as inflammation and fibrosis.[15–18] However, there are currently no prospective studies investigating the prognostic significance of HUA and elevated hs-CRP in CCB.

To address this gap, we examined the association of combined HUA and elevated hs-CRP with CCB in the general population by analyzing data from the Kailuan study. To further explore the potential mechanisms underlying the UA-CCB relationship, we used mediation analysis to investigate whether UA's effect on CCB was mediated by hs-CRP and enhanced by it.

# Materials and Methods

## Study Population

The Kailuan study, identified as ChiCTR-TNC-11001489, is a continuing cohort investigation conducted in Tangshan City, China. The research design has previously been described.[19] Typically, 101,510 individuals, encompassing 81,110 men and 20,400 women between the ages of 18 and 98, agreed to take part and satisfactorily finished the first survey executed from June 2006 to October 2007. Biochemical indicators, such as UA and hs-CRP, are part of the panel of laboratory tests, along with twelve-lead electrocardiograms (ECGs). Subsequent evaluations were carried out biennially. Consent was sought from all participants in writing, and the investigation was authorized through the Ethics Committee of Kailuan Hospital. The paper followed the principles specified in the Helsinki Declaration.

The current study focused exclusively on individuals who took part in the examinations conducted between 2006 and 2007. Participants were disqualified if they fulfilled any of the below conditions: 1) missing data on UA, hs-CRP, or ECG data in 2006 (n=3385); (2) hs-CRP >10 mg/L, implying acute inflammation or infectious disease (n=4049); (3) receiving treatment with non-dihydropyridine calcium-channel blockers or beta-blockers (n=360); (4) having a CCB history, atrial fibrillation, heart failure, or myocardial infarction at baseline (n=5116); (5) missing data on ECG during 2008–2018 (n=6704). Therefore, the final analysis included a total of 81,896 individuals (Figure 1).

## Data Collection and Definitions

EDTA tubes were employed to gather blood specimens from the antecubital vein of each participant subsequent to a fasting interval of a minimum of 8 h. The blood samples from all participants were examined employing an automated analyzer (Hitachi 747, Tokyo, Japan). Measurements were taken for serum UA, hs-CRP, triglycerides (TG), fasting blood glucose (FBG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and blood creatinine. UA was identified using the oxidase technique, with both intra- and inter-assay coefficients of variance equal to or less than 6%.[20] Hs-CRP levels were assessed through a particle-enhanced immunonephelometric assay, known for its high sensitivity.

HUA is defined as having UA values in men exceeding 420 μmol/L and in women surpassing 360 μmol/L.[21] Low-grade inflammation was identified as hs-CRP levels above 3 mg/L.[22] The participants were categorized into four groups depending on whether they had HUA and low-grade inflammation or not: (i) low UA/low hs-CRP group (UA-CRP-): those who have no HUA and with hs-CRP≤3mg/L; (ii) high UA/low hs-CRP group (UA+CRP-): those with HUA and hs-CRP≤3mg/L; (iii) low UA/high hs-CRP group (UA-CRP+): those lacking HUA and with hs-CRP>3mg/L; and (iv) high UA/high hs-CRP group (UA+CRP+): those with HUA and hs-CRP>3mg/L.

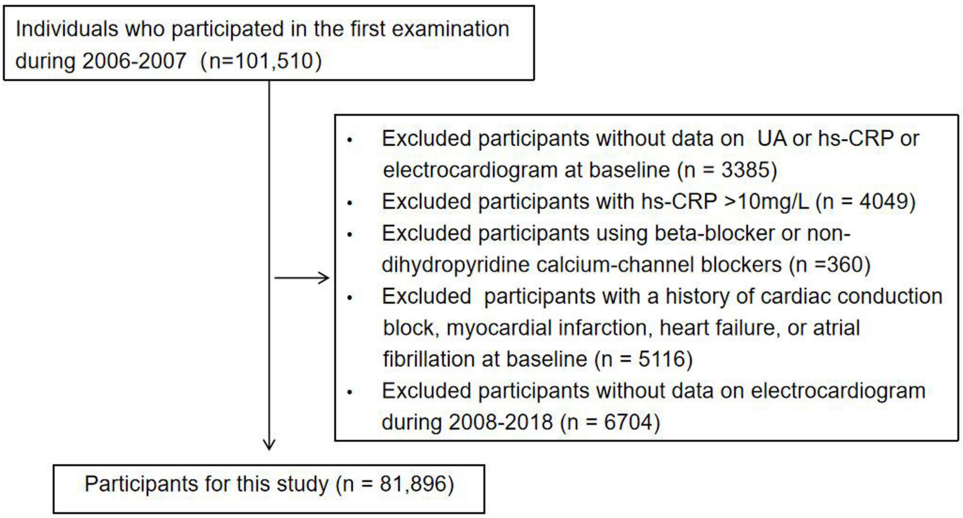



**Figure 1** Study design and flowchart.
**Abbreviations**: hs-CRP, high-sensitivity C-reactive protein; UA, uric acid.

## Measuring ECG and defining endpoint Events

ECG readings were consistently conducted during the health examination in 2006, as well as at two-year follow-up appointments thereafter. Participants were placed in a lying posture in a calm room for 5 minutes after participants underwent a twelve-lead ECG recording lasting 10s. The diagnosis of CCB was made by analyzing the ECG and verified by expert cardiologists. Furthermore, various anomalies in the ECG were categorized using the Minnesota-coded (MC) criteria as outlined in Table S1.[23,24] CCB encompasses various conditions such as AVB, incomplete right BBB (iRBBB), complete right BBB (CRBBB), incomplete left BBB (iLBBB), complete left BBB (CLBBB), left posterior fascicular block (LPFB), left anterior fascicular block (LAFB), and nonspecific intraventricular conduction block. AVB was classified as first-degree AVB (FAVB), second-, and third-degree AVB. Third-degree AVB and second-degree type 2 AVB as well as the pacemaker status resulting from AVB are stated as HAVB. The pacemaker's current condition and the rationale for its implantation were acquired via querying an electronic medical information system. Right BBB (RBBB) encompasses both CRBBB and iRBBB, whereas left BBB (LBBB) includes both CLBBB and iLBBB.

## Ascertainment of Incident Events

Following the 2006–2007 examinations, participants were followed until death or CCB occurred, or until the completion of the follow-up (December 31, 2019). The primary outcome was the occurrence of CCB. The secondary analysis separately considered the endpoints of AVB, FAVB, HAVB, RBBB, LBBB, and LAFB.

## Potential Confounders

A validated face-to-face questionnaire was employed to gather data on sex, age, smoking and drinking habits, physical activity, and self-reported medical history, including hypertension, diabetes, and CVD. Proficient staff performed assessments of individuals' stature, mass, and blood pressure throughout the investigation. To calculate an individual's body mass index (BMI), we divided their body weight (Kg) by the square of their height ($m^2$). Hypertension was stated as either self-reported hypertension, current administration of medicine to treat hypertension, or a quantified systolic blood pressure (SBP) ≥140 mmHg and/or a diastolic blood pressure (DBP) ≥90 mmHg. Self-reported diabetes, hypoglycemic medication use, or FBG levels exceeding 7.0 mmol/L were the diagnostic criteria for diabetes. The criterion for physical activity was the completion of exercise a minimum of three times per week, with each session lasting a minimum of 30 minutes. Current drinker was defined as someone who consumed alcohol every day in the last year, whereas current smoker was classed as one who smoked at minimum one cigarette per day in the past year. The eGFR was computed employing the methodology given by the Chronic Kidney Disease Epidemiology Collaboration.[25]

## Statistical Analysis

Baseline characteristics were compared using relevant statistical tests such as ANOVA, the Kruskal–Wallis test, or the Chi-square test. The study employed Cox proportional hazards regression models to ascertain the connection between different groups and the likelihood of developing CCB. Hazard ratios (HRs) and 95% confidence intervals (CIs) were computed. By examining the Schoenfeld residuals, the proportional hazard assumptions were ascertained, which indicated no violations. Model 1 was adjusted for age and sex. Model 2 was further adjusted for smoking, drinking, physical activity, BMI, eGFR, LDL-C, HDL-C, TG, hypertension, and diabetes. Model 3 was further adjusted for antihypertensive drugs, hypoglycemic drugs, and lipid-lowering drugs. To evaluate the short-term impact of alterations in UA and hs-CRP levels overtime on the endpoint events risk, we also conducted time-dependent Cox regression models, updating UA, hs-CRP, and covariates at each follow-up, and using recent measurement results to estimate the risk throughout the follow-up period.

Mediation analysis were performed to investigate if hs-CRP acts as a mediator in the connection between UA and CCB. Following VanderWeele's recommendation, the mediation study was assessed utilizing a two-stage regression method employed on survival data.[26] VanderWeele's approach breaks down the overall impact of UA on CCB, as assessed by the HR vs the non-HUA group, into two separate components: the natural indirect consequence size, which signifies the UA implication on CCB caused by hs-CRP, and the natural immediate consequence size, which signifies the

influence of UA on CCB that is not dependent on hs-CRP.[27] Given that these estimates rely on observational data, we classify them as total, indirect, and direct links.

To examine possible variations in the likelihood of CCB across various subgroups, multiplicative models were utilized to investigate interactions among various groups, as well as age and sex. Following stratification, the Cox model was subsequently replicated. To guarantee the strength and reliability of the model, many sensitivity studies were performed. In the sensitivity analyses, individuals with an eGFR of less than 45 mL/(min·1.73m²) or a gout history were removed to consider the possible impact of impaired renal function and gout on UA concentration. To address concerns regarding reverse causation, all occurrences that took place throughout the initial 2 years of follow-up were eliminated. Additionally, to assess the influence of cancer on UA concentration, a sensitivity analysis was conducted by removing individuals who had a previous history of cancer at baseline. Furthermore, in Model 3, additional adjustments were made for white blood cell count, serum sodium, and serum potassium. To account for the potential confounding effect of competing risks, we conducted Fine-Gray competing risk regression, where deaths were considered as competing events.

All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). Statistical significance was determined by $p < 0.05$ (two-sided test).

## Results

Out of the 81,896 individuals who took part, the average age was 50.29 ± 11.84 years, and 64,226 (78.42%) were men. In Table 1, participants' characteristics are presented. The age of individuals in the UA+CRP-, UA-CRP+, and UA+CRP + groups exhibited a significant and gradual rise contrasted with the UA-CRP- group (P<0.001). The UA+CRP+ group comprised individuals with elevated levels of TG, BMI, SBP, DBP, and UA while displaying mitigated HDL-C and eGFR levels in comparison to those in the UA-CRP- group. Moreover, the prevalence of hypertension, as well as the usage of antihypertensive and lipid-lowering medications, was significantly higher (P<0.001).

**Table 1** Baseline Characteristics of the Study Population

| Characteristics | Total (n=81,896) | UA-CRP- (n=64,715) | UA+CRP- (n=4494) | UA-CRP+ (n=11,558) | UA+CRP+ (n=1129) | *P-value* |
|---|---|---|---|---|---|---|
| Age, years | 50.29 ± 11.84 | 49.44 ± 11.59 | 52.13 ± 12.98 | 53.81 ± 11.80 | 55.44 ± 12.65 | <0.001 |
| Men, n (%) | 64,226 (78.42) | 50,880 (78.62) | 3756 (83.58) | 8731 (75.54) | 859 (76.09) | <0.001 |
| Current drinker, n (%) | 33,721 (41.18) | 26,663 (41.20) | 2598 (57.81) | 3928 (33.99) | 532 (47.12) | <0.001 |
| Current smoker, n (%) | 32,657 (39.88) | 25,807 (39.88) | 2339 (52.05) | 3996 (34.57) | 515 (45.62) | <0.001 |
| Physical activity, n (%) | 12,489 (15.25) | 9698 (14.99) | 998 (22.21) | 1564 (13.53) | 229 (20.28) | <0.001 |
| BMI, kg/m$^2$ | 25.02 ± 3.39 | 24.82 ± 3.31 | 26.26 ± 3.36 | 25.49 ± 3.58 | 27.19 ± 3.65 | <0.001 |
| SBP, mmHg | 129.97 ± 20.31 | 129.09 ± 19.99 | 134.26 ± 20.58 | 132.50 ± 21.19 | 137.68 ± 22.05 | <0.001 |
| DBP, mmHg | 83.32 ± 11.51 | 82.98 ± 11.41 | 85.56 ± 11.64 | 84.08 ± 11.74 | 86.31 ± 12.23 | <0.001 |
| FBG, mmol/L | 5.44 ± 1.53 | 5.42 ± 1.48 | 5.35 ± 1.37 | 5.55 ± 1.86 | 5.48 ± 1.61 | 0.40 |
| LDL-C, mmol/L | 2.37 ± 0.86 | 2.42 ± 0.77 | 2.39 ± 0.87 | 2.10 ± 1.22 | 2.33 ± 0.95 | <0.001 |
| HDL-C, mmol/L | 1.54 ± 0.39 | 1.54 ± 0.38 | 1.53 ± 0.41 | 1.55 ± 0.41 | 1.50 ± 0.39 | <0.001 |
| TG, mmol/L | 1.27 (0.90, 1.94) | 1.23 (0.87, 1.85) | 1.79 (1.18, 2.76) | 1.32 (0.93, 2.03) | 1.83 (1.26, 2.84) | <0.001 |
| hs-CRP, mg/L | 0.73 (0.30, 1.84) | 0.54 (0.22, 1.12) | 0.90 (0.40, 1.54) | 5.30 (3.86, 7.30) | 4.90 (3.80, 6.70) | <0.001 |
| UA, umol/L | 286.79 ± 82.12 | 274.47 ± 65.96 | 464.19 ± 61.25 | 269.06 ± 70.05 | 468.02 ± 67.24 | <0.001 |
| eGFR, mL/min/1.73m$^2$ | 82.56 ± 20.85 | 82.78 ± 20.66 | 77.59 ± 20.96 | 83.95 ± 21.54 | 75.58 ± 19.78 | <0.001 |
| Hypertension, n (%) | 34,580 (42.22) | 25,917 (40.05) | 2356 (52.43) | 5631 (48.72) | 676 (59.88) | <0.001 |
| Diabetes, n (%) | 7046 (8.60) | 5207 (8.05) | 350 (7.79) | 1372 (11.87) | 117 (10.36) | <0.001 |
| Use of antihypertensive drugs, n (%) | 8077 (9.86) | 5540 (8.56) | 956 (21.27) | 1264 (10.94) | 317 (28.08) | <0.001 |
| Use of hypoglycemic drugs, n (%) | 1717 (2.10) | 1288 (1.99) | 110 (2.45) | 283 (2.45) | 36 (3.19) | <0.001 |
| Use of lipid-lowering drugs, n (%) | 644 (0.79) | 440 (0.68) | 58 (1.29) | 118 (1.02) | 28 (2.48) | <0.001 |

**Notes**: Data are presented as mean ± SD, median (interquartile range), or n (%).
**Abbreviations**: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triacylglycerol; UA, uric acid.

## Risks associated with different groups

Over an average follow-up of 11.8 (8.9–12.8) years, we identified 3160 cases of CCB. Among subtypes, there were 996 incidents of AVB, 1504 incidents of RBBB, and 84 incidents of LBBB. In the UA-CRP-, UA+CRP-, UA-CRP+, and UA +CRP+, new-onset CCB incidence rates were 33.70, 44.85, 49.41, and 58.98 per 10,000 person-years, respectively. The Log rank test manifested significant variations in the cumulative incidence rates of CCB, AVB, RBBB, and LBBB between the groups (P<0.05, Figure 2).

The HUA group had a 1.14 (1.01–1.30) adjusted HR for CCB compared to the non-HUA group. Compared with those with hs-CRP ≤3mg/L, HR (95% CI) of CCB in hs-CRP >3mg/L were 1.40 (1.29–1.53). Regarding the risk of CCB, a significant interaction between UA and hs-CRP was observed (p for interaction = 0.007) (Table 2). Table 3 presents the associations of a combination of HUA and low-grade inflammation with the risk of CCB. The adjusted HRs with 95% CIs for CCB were 1.14 (1.00–1.32) for UA+CRP-, 1.40 (1.28–1.54) for UA-CRP+, and 1.56 (1.22–1.99) for UA+CRP+ when compared to UA-CRP-. In addition, as compared with those who are UA-CRP-, those who are UA+CRP+ had adjusted HRs of 1.88 (95% CI: 1.27–2.77), 1.47 (95% CI: 1.02–2.12), and 2.32 (95% CI: 0.71–7.56) for the risk of AVB, RBBB, and LBBB, respectively. Additionally, compared with UA-CRP-, the adjusted HRs (95% CI) for the connection of UA+CRP+ with the risk of FAVB, HAVB, and LAFB were 1.88 (1.24–2.83), 1.74 (0.54–5.64), and 0.89 (0.42–1.89), respectively (Table S2).

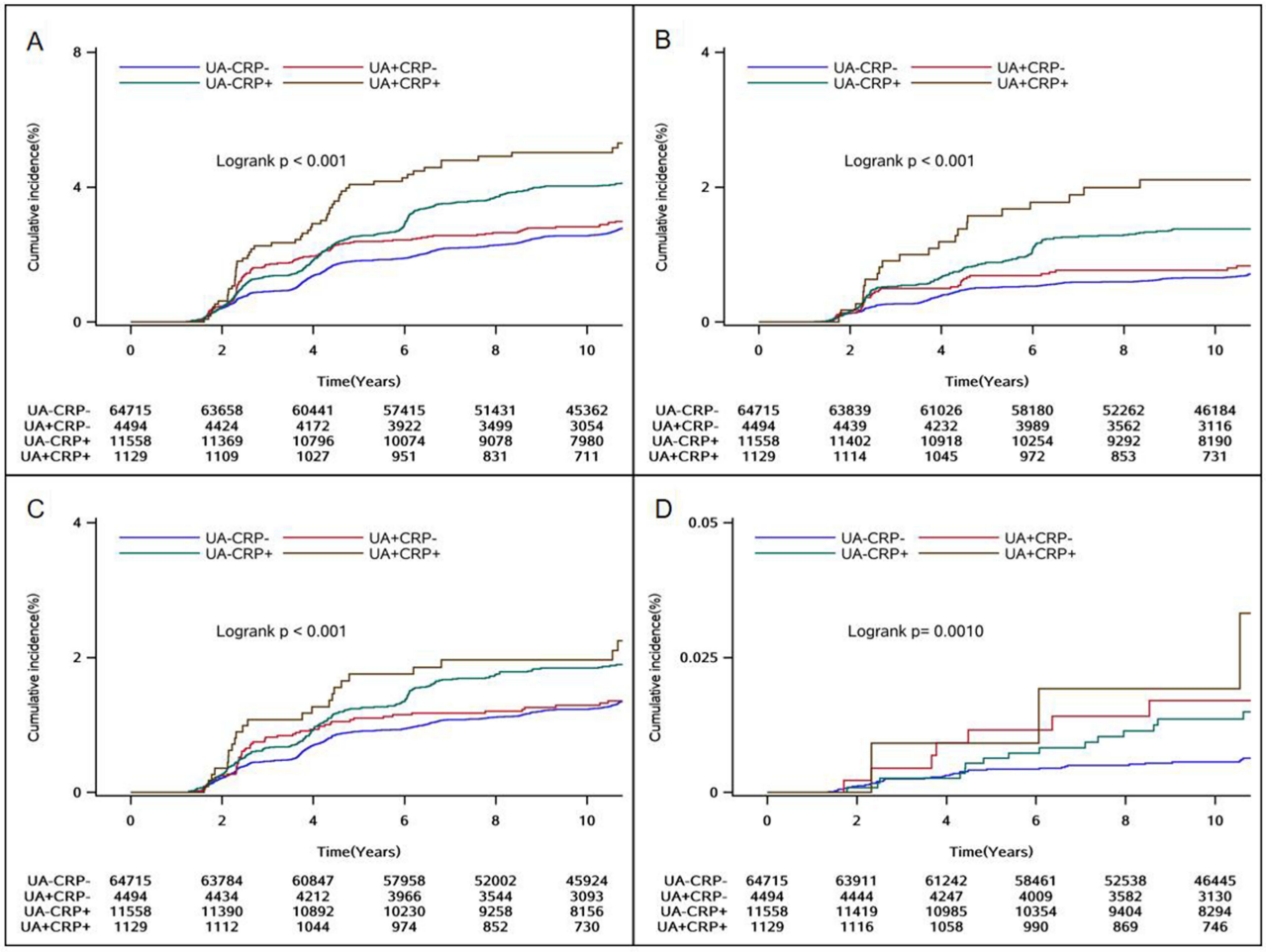



**Figure 2** Cumulative incidence of clinical outcomes in total participants stratified by UA and hs-CRP. (**A**) Cardiac conduction block; (**B**) Atrioventricular block; (**C**) Right bundle branch block; (**D**) Left bundle branch block.

**Abbreviations**: hs-CRP, high-sensitivity C-reactive protein; UA, uric acid.

**Table 2** Adjusted HRs and 95% CIs for Risks of Cardiac Conduction Block According to UA or Hs-CRP

| Group | Cases/Total | Incidence Rate[a] | Model 1 | Model 2 | Model 3 |
|---|---|---|---|---|---|
| | | | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| Hyperuricemia | | | | | |
| No | 2883/76,273 | 36.08 | Ref. | Ref. | Ref. |
| Yes | 277/5623 | 47.60 | 1.20 (1.06–1.35) | 1.16 (1.02–1.31) | 1.14 (1.01–1.30) |
| hs-CRP | | | | | |
| ≤3mg/L | 2497/69,209 | 34.42 | Ref. | Ref. | Ref. |
| >3mg/L | 663/12,687 | 50.23 | 1.41 (1.29–1.54) | 1.40 (1.28–1.53) | 1.40 (1.29–1.53) |
| *p* for interaction[b] | | | | | 0.007 |

**Notes**: Model 1: Adjusted for age and sex; Model 2: Adjusted for variables in Model 1 plus smoking, drinking, physical activity, BMI, eGFR, LDL-C, HDL-C, TG, hypertension (yes or no) and diabetes (yes or no); Model 3: Adjusted for variables in Model 2 plus antihypertensive drug use (yes or no), hypoglycemic drug use (yes or no), and lipid-lowering drug use (yes or no). [a]Case per 10,000 person-years. [b]Interaction between UA and hs-CRP for the risk of cardiac conduction block.

**Abbreviations**: BMI, body mass index; CIs, confidence intervals; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; UA, uric acid.

**Table 3** Adjusted HRs and 95% CIs for Risks of Different Events According to UA and Hs-CRP

| Group | Cases/Total | Incidence Rate[a] | Model 1 | Model 2 | Model 3 |
|---|---|---|---|---|---|
| | | | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| **Cardiac conduction block** | 3160/81,896 | 36.85 | | | |
| UA-CRP- | 2287/64,715 | 33.70 | Ref. | Ref. | Ref. |
| UA+CRP- | 210/4494 | 44.85 | 1.19 (1.04–1.37) | 1.15 (1.00–1.33) | 1.14 (1.00–1.32) |
| UA-CRP+ | 596/11,558 | 49.41 | 1.41 (1.29–1.55) | 1.40 (1.28–1.54) | 1.40 (1.28–1.54) |
| UA+CRP+ | 67/1129 | 58.98 | 1.63 (1.28–2.08) | 1.58 (1.24–2.02) | 1.56 (1.22–1.99) |
| **Atrioventricular block** | 996/81,896 | 11.48 | | | |
| UA-CRP- | 695/64,715 | 10.13 | Ref. | Ref. | Ref. |
| UA+CRP- | 80/4494 | 16.85 | 1.49 (1.18–1.88) | 1.37 (1.08–1.74) | 1.31 (1.03–1.66) |
| UA-CRP+ | 194/11,558 | 15.84 | 1.52 (1.29–1.78) | 1.50 (1.27–1.76) | 1.50 (1.27–1.77) |
| UA+CRP+ | 27/1129 | 23.32 | 2.14 (1.46–3.15) | 1.99 (1.35–2.94) | 1.88 (1.27–2.77) |
| **Right bundle branch block** | 1504/81,896 | 17.39 | | | |
| UA-CRP- | 1113/64,715 | 16.27 | Ref. | Ref. | Ref. |
| UA+CRP- | 95/4494 | 20.10 | 1.10 (0.89–1.36) | 1.08 (0.88–1.34) | 1.08 (0.88–1.34) |
| UA-CRP+ | 266/11,558 | 21.77 | 1.28 (1.12–1.47) | 1.29 (1.12–1.48) | 1.28 (1.12–1.48) |
| UA+CRP+ | 30/1129 | 25.95 | 1.48 (1.03–2.12) | 1.48 (1.03–2.13) | 1.47 (1.02–2.12) |
| **Left bundle branch block** | 84/81,896 | 0.96 | | | |
| UA-CRP- | 53/64,715 | 0.77 | Ref. | Ref. | Ref. |
| UA+CRP- | 11/4494 | 2.30 | 2.60 (1.36–4.98) | 2.51 (1.29–4.90) | 2.37 (1.21–4.63) |
| UA-CRP+ | 17/11,558 | 1.38 | 1.53 (0.88–2.66) | 1.39 (0.79–2.46) | 1.42 (0.80–2.50) |
| UA+CRP+ | 3/1129 | 2.56 | 2.77 (0.86–8.87) | 2.50 (0.77–8.13) | 2.32 (0.71–7.56) |

**Notes**: Model 1: Adjusted for age and sex; Model 2: Adjusted for variables in Model 1 plus smoking, drinking, physical activity, BMI, eGFR, LDL-C, HDL-C, TG, hypertension (yes or no) and diabetes (yes or no); Model 3: Adjusted for variables in Model 2 plus antihypertensive drug use (yes or no), hypoglycemic drug use (yes or no), and lipid-lowering drug use (yes or no). [a]Case per 10,000 person-years.

**Abbreviations**: BMI, body mass index; CIs, confidence intervals; eGFR, estimated glomerular filtration rate; HRs, hazard ratio; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; UA, uric acid.

In time-dependent Cox regression models introducing UA, hs-CRP, and confounders as time-varying covariates, the whole follow-up interval was divided into 6 segments at a 2-year interval. The time-dependent Cox analyses were conducted to investigate the short-term exposure effects of a combination of HUA and low-grade inflammation on the risk of CCB. Compared with UA-CRP-, the adjusted HRs (95% CIs) linked to UA+CRP+ and the likelihood of

developing CCB, AVB, RBBB, and LBBB were as follows: 1.26 (1.14–1.38), 1.42 (1.21–1.66), 1.30 (1.12–1.49), and 2.37 (1.50–3.76) (Table S3).

## Mediation Analysis

The mediation analysis manifested that the CCB risk was 14.0% higher (HR [total connection]: 1.14; 95% CI: 1.08–1.22) in the HUA group vs the non-HUA group. Furthermore, 10.3% of this elevated risk was shown to be mediated by hs-CRP. The HR for the indirect link between HUA and the outcome was 1.02 (95% CI, 1.01–1.03) (Figure 3).

## Stratified and Sensitivity analyses Results

In subgroup analyses, the associations between various groups and CCB remained the same after stratifying by age (<65 vs ≥65 years) and sex (Figure S1, *p* for interaction >0.05). Notably, the results obtained from the sensitivity analyses corroborated the conclusions drawn in the primary analyses (Table S4).

# Discussion

The primary findings of this investigation indicated that the combination of HUA and low-grade inflammation (hs-CRP>3 mg/L) increased the incidence of CCB, especially that of AVB. The mediation analysis revealed that the connection between UA and CCB was partly influenced by hs-CRP, suggesting a pivotal role of hs-CRP in the development of CCB.

Our research revealed that when HUA and elevated hs-CRP coexist, they elevated the risk of CCB by 56%, with this risk being more pronounced than that associated with either factor alone. This investigation is the first of its kind to ascertain the connection between the combination of HUA and elevated hs-CRP with CCB in a prospective population. Although there were no relative previous studies, recent data indicated that among patients with type 2 diabetes, the odds ratio for cardiac conduction abnormalities in the third tertile group of UA was 1.84 (95% CI: 1.20–2.90) compared with the first tertile group.[8] Another recent study that followed 4314 healthy people for a median period of 7 years showed that with every 10 mg/L rise in hs-CRP, the risk of conduction disease increased by 7%.[9] In another study of 478,524 healthy individuals of the UK Biobank cohort, a notable positive connection was found between hs-CRP levels and the bradyarrhythmias risk.[28] Specifically, compared to participants with lower hs-CRP levels (<0.5 mg/L), the HR was

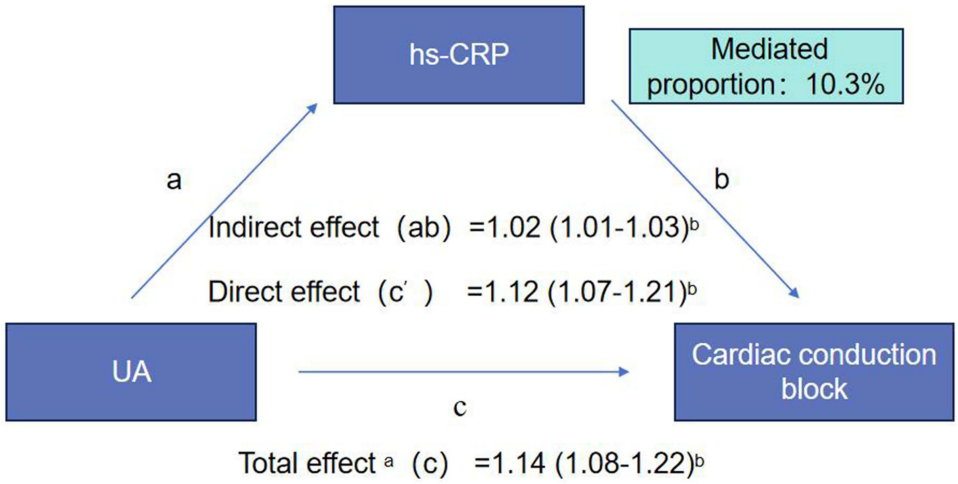



**Figure 3** Decomposition of the total association of UA and the risk of cardiac conduction block into direct and indirect associations mediated by hs-CRP. HR was adjusted for age, sex, smoking, drinking, physical activity, BMI, eGFR, LDL-C, HDL-C, TG, hypertension (yes or no), diabetes (yes or no), antihypertensive drug use (yes or no), hypoglycemic drug use (yes or no), and lipid-lowering drug use (yes or no). [a]Decomposition of total associations into natural indirect and natural direct associations was done according to the 2-stage regression method proposed by VanderWeele and performed with the SAS macro provided by ValerWeele.[27] Confidence intervals were calculated according to the delta method procedure. [b]Compared with the non-hyperuricemia group, the adjusted HRs (95% CIs) of cardiac conduction block in the hyperuricemia group.

**Abbreviations**: BMI, body mass index; CIs, confidence intervals; eGFR, estimated glomerular filtration rate; HRs, hazard ratio; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; UA, uric acid.

1.15 (95% CI: 1.05–1.27) for those with hs-CRP levels between 3.0 and 4.0 mg/L, 1.18 (95% CI: 1.08–1.29) for levels between 4.0 and 10.0 mg/L, and 1.30 (95% CI: 1.16–1.45) for levels ≥10.0 mg/L.[28] Our study expands upon previous research by demonstrating that the combination of HUA and elevated hs-CRP is connected with an elevated CCB risk. These findings manifest novel insights into the relationship between UA, hs-CRP, and cardiovascular diseases.

Our study not only found HUA to be a significant risk factor for CCB but also explored the probable mechanisms linking UA to CCB. During the mediation analysis, we discovered that hs-CRP acted as a mediator in the connection between UA and CCB. Specifically, hs-CRP accounted for 10.3% of the overall effects. Therefore, hs-CRP may have significant intermediary functions in the relationship between UA and CCB. Prior research has also shown that HUA might facilitate the elevation of hs-CRP.[13,14] Kang et al discovered a connection between the inflammatory reaction and the restructuring of blood vessels caused by UA and hs-CRP. UA induces dysfunction in the endothelium and promotes vascular smooth muscle cell proliferation by elevating levels of hs-CRP and inhibiting the NO generation.[29] The biological mechanisms linking UA to CCB are primarily considered to be oxidative stress and the promotion of inflammation. Our findings further confirmed the findings of previous studies. Our investigation discovered that the connection between UA and CCB was partly influenced by hs-CRP, indicating that hs-CRP could have a notable impact on the biological mechanisms of CCB. This finding provides important clues for further research and potential therapeutic interventions.

Notably, in our study, distinct associations were found between the concomitant presence of HUA and low-grade inflammation and certain CCB subtypes. Individuals who have elevated levels of both UA and hs-CRP have a significantly greater risk of developing AVB and RBBB. The developing AVB risk is particularly higher compared to the risk of developing RBBB. Specifically, the risks were heightened by 88% for AVB and 47% for RBBB, respectively. For other CCB subtypes, the HRs were not significant. These nonsignificant outcomes for other groups, such as LBBB and HAVB, might be attributed to the smaller number of cases of these subtypes. Only a limited number of investigations have concentrated on the distinct associations of UA with various types of conduction block. Among those with type 2 diabetes, a significant and separate connection was found between UA level and the likelihood of AVB, but no such association was seen with BBB.[8] Wu et al discovered that individuals with hs-CRP levels more than 3 mg/L had a heightened AVB risk in comparison to those with lower hs-CRP levels, and this risk was higher than for RBBB.[30] Our investigation manifested that elevated levels of both UA and hs-CRP had a more pronounced risk impact on AVB compared to RBBB. This is consistent with previous research findings. We hypothesize that variations in underlying risk factors for distinct conduction block sites may account for the observed differences across sites. The primary risk factors associated with AVB may involve inflammation and dysfunction of glycolipid metabolism. Conversely, for BBB, the main risk factors might be linked to elevated ventricular pressure load and ventricular remodeling. Therefore, different markers reflecting different pathophysiologic pathways may have a different impact on the aforementioned associations. We discovered a correlation between HUA and low-grade inflammation and a higher likelihood of CCB, namely AVB. However, it is essential to manifest that this risk factor may be modified and reversed. Therefore, if UA and inflammation levels are effectively controlled, the risk of CCB may be likely to be mitigated and the financial burden associated with pacemaker implantation avoided.

UA and hs-CRP levels are implicated by factors encompassing diet, environment, and subclinical inflammatory states and infections. We used UA, hs-CRP, and confounding factors as time-dependent variables and performed time-varying Cox regression to examine the immediate impact of elevated UA and hs-CRP on the CCB risk over a span of 2 years. We demonstrated that a mixed presence of high UA and hs-CRP levels was linked to an elevated CCB risk by 26%, which was lower than the long-term risks. Hence, the long-term association of HUA and low-grade inflammation with CCB was stronger than the short-term association.

The specific underlying pathophysiological processes that cause a raised CCB risk in individuals with raised levels of both UA and hs-CRP are not yet fully understood, although various theories have been suggested.[15,17,18,29,31–37] As mentioned earlier, HUA can induce an increase in hs-CRP.[13,14] Conversely, hs-CRP may raise UA production by improving the effectiveness of xanthine oxidase.[38,39] Simultaneous presence of elevated UA and hs-CRP levels can create a harmful cycle of UA-inflammatory-UA. This cycle can contribute to the development of CCB by activating a series of pathological and physiological processes such as oxidative stress, inflammation, and fibrosis, synergistically accelerating the progression of the disease.[32–37]

This research had many notable features, encompassing a substantial sample size, a lengthy duration of follow-up, and a well-defined technique for collecting comprehensive data on biological variables. We also considered the impact of independent and covariate changes over time on outcome events, which enhances the reliability of the findings. Furthermore, this research is subject to many constraints. Firstly, We lack information regarding the utilization of UA-lowering medications, which have previously shown efficacy in diminishing the likelihood of significant cardiovascular complications and perhaps reducing the occurrence of CCB. However, we conducted a sensitivity analysis by excluding people with a gout history to enhance the finding's reliability. Secondly, the majority of participants in this research were men, resulting in an uneven distribution of sexes among participants. Nevertheless, the investigation included subgroup analyses that were stratified by sex. Thirdly, due to the restricted scope of our research sample to the Chinese occupational population, it is not possible to directly extrapolate the findings to other groups. Fourthly, the lack of data on diet and thyroid hormones in this study limited our ability to assess their potential influence on the research findings. Fifthly, the absence of data on the menopausal status of participants in this study limited our ability to analyze the potential effects of differences in UA concentration between pre-and post-menopausal women on the research outcomes. Lastly, due to the nature of this research being observational, it is not possible to create a causal connection between the combination of HUA and hs-CRP and the CCB risk.

## Conclusion

In summary, our study found that the combination of HUA and elevated hs-CRP was linked to a higher incidence of CCB, particularly AVB. Furthermore, the connection of UA with the CCB risk was partially mediated through hs-CRP, providing crucial insights for subsequent research and potential therapeutic strategies.

## Data Sharing Statement

The datasets used and/or examined in the present investigation may be obtained from the corresponding author upon a reasonable request.

## Ethical Approval Statement

The ethics committee of Kailuan General Hospital (approval number: 2006-05). Written informed consent was obtained from all participants.

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## Disclosure

These authors declare that they have no conflicts of interest.

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