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High-sensitivity C-reactive protein: an independent predictor of coronary heart disease risk in middle-aged and elderly population with hyperuricemia

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Abstract

OBJECTIVES: Hyperuricemia patients are at relatively high risk of developing coronary heart disease (CHD). The purpose of this study was to examine the relationship between high-sensitivity C-reactive protein (hs-CRP) and CHD risk in a middle-aged and elderly population with hyperuricemia.

DESIGN: A cross-sectional study.

SETTING AND PARTICIPANTS: This study was conducted in a health examination center of China. Participants diagnosed with hyperuricemia by the uric acid ≥ 416 μmol/L in male population and ≥ 360 μmol/L in female population were included.

MAIN OUTCOME MEASURES: 10-year CHD risk for each individual was evaluated using Framingham risk score based on the Adult Treatment Panel III charts.

RESULTS: A total of 517 hyperuricemia patients (438 males and 79 females) aged from 40 to 85 years old were included in the present study. 193 (37.3%) patients were defined with relatively high 10-year CHD risk. Compared with the lowest quintile, the crude odds ratio (ORs) of relatively high 10-year CHD risks were 2.05 (95%CI 1.14-3.67, P=0.016), 2.77 (95%CI 1.54-4.98, P=0.001), 2.12 (95%CI 1.18-3.80, P=0.012) in the second, third and fifth quintiles of serum hs-CPR level, respectively (P for trend = 0.057). The multivariable-adjusted ORs of relatively high 10-year CHD risk were 2.05 (95%CI 1.13-3.72, P=0.019) in the third, 2.69 (95%CI 1.47-4.89, P=0.001) in the fourth, and 2.10 (95%CI 1.15-3.84, P=0.016) in the fifth quintile of serum hs-CRP level when compared with the lowest quintile (P for trend = 0.068).

CONCLUSION: This study showed that high serum hs-CRP level was independently correlated with high CHD risk in middle-aged and elderly population with hyperuricemia, which suggested that serum

hs-CRP, a routine index in clinical practice, may be used to predict CHD risk in hyperuricemia patients.

Key words: hyperuricemia, high-sensitivity C-reactive protein, coronary heart disease

Strengths and limitations of this study

1. This is the first study exploring the association between hs-CRP and the CHD risk in patients with hyperuricemia in a middle-aged and elderly population with hyperuricemia.

2. The relationship of hs-CRP and the CHD risk was analyzed by multivariable models.

3. As result of the nature of cross-sectional design, the causal relationship cannot be established in the present study.

Background

Serum uric acid is the catabolic end-product of purine metabolism via the catalysis of xanthine oxidase. With the rapid economic development, the dietary habits of Chinese people have changed greatly towards an increasingly heavier intake of meat, dairy products and other purine enriched foods, which has led to a higher prevalence of hyperuricemia and gout susceptibly. [1 2] A systematic review and meta-analysis involving 44 studies showed that the pooled prevalence of hyperuricemia was 13.3% in mainland China from 2000 to 2014. [3] Some previous studies reported that an increase in serum uric acid was incriminated in the pathogenesis of metabolic syndrome, [4 5] chronic kidney disease, [6 7] stroke, [8] and coronary heart disease (CHD), [9 10]

Over the past several decades, relevant studies have shown that an increased serum uric acid was significantly associated with CHD, independent of conventional CHD risk factors. [9-12] Besides, it was also demonstrated that increased uric acid was correlated with hypertension, diabetes mellitus, metabolic syndrome, hypertriglyceridemia and endothelial dysfunction. [6 13-19] All of which could lead to an increased risk of CHD. With the trend of population aging, CHD has become one of the most common causes of death. [20] Therefore, it is urgent to seek effective predictors or biomarkers to identify subjects at a high risk of CHD, especially among the hyperuricemia patients, who are deemed a high risk group of CHD. A wide array of studies indicated that inflammation was involved in the pathogenesis of CHD. [21 22] C-reactive protein (CRP), one of the acute phase respondents, is commonly used in clinical practice to reflect chronic inflammation as an inexpensive measurement. [23] Several epidemiological studies were undertaken to clarify the relationship between CRP and CHD, but no agreement has been reached. [24-26] To the best of the authors' knowledge, there has been no study yet examining the association between

hs-CRP and the CHD risk in hyperuricemia patients. Meaningful outcomes in this respect would not only have important implications in understanding the pathophysiological mechanisms of CHD in hyperuricemia patients, but also contribute to the development of a simple and inexpensive method to predict the future CHD risk of this population.

To fill this knowledge gap, the present cross-sectional study was carried out to clarify the correlation between hs-CRP and the 10-year estimated CHD risk measured by the Framingham risk score (FRS) in the middle-aged and elderly population with hyperuricemia, with adjustment of conventional cardiovascular risk factors.

Materials and Methods

Study population

The participants of the present cross-sectional study were chosen from a pool of subjects who were undergoing routine medical examinations at the Department of Health Examination Center Xiangya Hospital, Central South University in Changsha, Hunan Province of China. The detailed methodology has been described in some earlier studies. [27-32] Briefly, all the qualified participants must be 40 years old or above and undergoing measurements of serum uric acid, hs-CRP and other basic biochemical assessments during the specified period. In addition, the subjects should be diagnosed with hyperuricemia (i.e., the uric acid ≥ 416 μmol/L for male and ≥ 360 μmol/L for female), with availability of demographic and clinical data including age, gender, body mass index (BMI) (weight/height^2), smoking status, alcohol drinking status, activity level, medication status, etc. Initially, a total of 5994 subjects were included based on the age requirement and availability of blood biochemical

assessments (serum uric acid and hs-CRP measurement) during the period of October 2013 to December 2015. Then, 3420 subjects were disqualified: 30 were lack of basic health characteristics such as blood pressure and BMI; and 3390 were lack of information of health-related habits. Of the remaining 2574 subjects, only 517 were diagnosed with hyperuricemia and were finally enrolled in the present study. The study protocol had been reviewed and approved by the local Ethics and Research Committee and the written informed consent had been obtained from all participants prior to execution.

Blood biochemistry

All blood samples were drawn from the antecubital vein using vacuum tubes after an overnight fast of ≥12 hours, and were kept at 4°C until analysis. The hs-CRP was detected by the Latex turbidity method. The uric acid and other blood biochemical data were detected using a Beckman Coulter AU 5800 (Beckman Coulter Inc., Brea, CA, USA). The low concentrations (2.5 mmol/L for glucose and 118 μmol/L for uric acid) and high concentrations (6.7 mmol/L for glucose and 472 μmol/L for uric acid) of standard human samples were used respectively to evaluate the intra- and inter-assay coefficients of variation. The intra-assay coefficients of variation were 0.98% (2.5 mmol/L) and 1.72% (6.7 mmol/L) for glucose, 1.39% (118 μmol/L) and 0.41% (472 μmol/L) for uric acid. The inter-assay coefficients of variation were 2.45% (2.5 mmol/L) and 1.46% (6.7 mmol/L) for glucose, 1.40% (118 μmol/L) and 1.23% (472 μmol/L) for uric acid. A subject was diagnosed with diabetes mellitus if his/her fasting plasma glucose level ≥ 7.0 mmol/L or if he/she was currently receiving medication for blood glucose control.

Assessment of other exposures

The BMI was calculated as the weight (kg) divided by the square of the height (m). The blood pressure

was detected at the upper arm using an electronic sphygmomanometer after a rest of at least 10 min. Then, the status of physical activity, including the average frequency (never, one to two times per week, three to four times per week, five times and above per week) and the average duration of physical activity (within half an hour, half an hour to one hour, one to two hours, more than two hours) was collected from each subject. Lastly, the smoking and alcohol drinking status, as well as the medication conditions of the subjects were inquired.

Assessment of 10-year CHD risk

The risk level of developing CHD was measured by the FRS according to The Adult Treatment Panel III (ATP III) charts, [33] and the FRS was calculated based on 7 risk factors, which are age, gender, smoking, systolic blood pressure, use of antihypertensive medication, total cholesterol and HDL cholesterol, respectively. The specific risk scoring process is as follows: 1) calculate the number of points for each risk factor; 2) sum up the points of each risk factor to obtain the total risk score; 3) generate the estimated 10-year CHD risk for each patient. The subjects with the 10-year risk above 10% were classified into the high 10-year CHD risk group.

Statistical analysis

For statistical analysis, the continuous variables with a normal distribution were presented as mean ± standard deviation, and the category variables were described by frequency and percentage. The one-way ANOVA (normally distributed data) or Kruskal-Wallis H test (non-normally distributed data) was adopted to assess the continuous variables, while the χ^2 test was used to calculate the differences between categorical variables. The participants were classified into five categories based on the quintile

distribution of hs-CRP, namely ≤ 0.50, 0.51-0.90, 0.91-1.63, 1.63-3.04, and ≥ 3.05 mg/L. The association between hs-CRP and the CHD risk has been described as the odds ratio and 95% confidence intervals, which were calculated for each quintile of hs-CRP; the lowest quintile was regarded as the reference category. Then, the factors of BMI, educational background, alcohol drinking status, activity level, serum creatinine and diabetes that might affect both hs-CRP and the outcomes of interest were included in these models as adjustors. The trend for relatively high CHD risk according to quartile of hs-CRP was analyzed using the linear regression model. All data analyses were performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA), and the level for statistical significance was set as the p-value equal to 0.05. All tests were two tailed.

Results

A total of 517 hyperuricemia patients (438 males and 79 females) aged from 40 to 85 years old were included in the present study. There were 193 (37.3%) patients were defined with relatively high 10-year CHD risk. The basic characteristics of study population based on the quintiles of hs-CRP were showed in Table 1. Significant differences across all quintiles of hs-CRP were observed in terms of BMI, relatively high CHD risk, systolic blood pressure, diastolic blood pressure, activity level, and educational background.

The results of the associations between hs-CRP and relatively high 10-year CHD risk (≥10%) were shown in Table 2. According to the crude OR values, a significant higher prevalence of relatively high CHD risk was observed in the third (OR=2.05, 95%CI 1.14-3.67, P=0.016), fourth (OR=2.77, 95%CI 1.54-4.98, P=0.001) and highest quintiles (OR=2.12, 95%CI 1.18-3.80, P=0.012)

of hs-CRP when comparing with the reference category, and P for trend was 0.057. Multivariable adjusted OR value also suggested that hs-CRP was positively associated with relatively high 10-year CHD risk in the third (OR=2.05, 95%CI 1.13-3.72, P=0.019), fourth (OR=2.69, 95%CI 1.47-4.89, P=0.001) and highest quintiles (OR=2.10, 95%CI 1.15-3.84, P=0.016) of hs-CRP when comparing with the reference category, and P for trend was 0.068.

Discussion

The present cross-sectional study revealed a significant positive association between hs-CRP and the high 10-year risk of CHD in the middle-aged and elderly population with hyperuricemia. This correlation remained significant with adjustment of several potential confounding factors such as BMI, educational background, alcohol drinking status, activity level, serum creatinine and diabetes. These findings suggested that hs-CRP could serve as a marker for the risk of CHD in hyperuricemia patients.

The relationship between CRP and CHD has aroused intensive arguments. Some earlier studies demonstrated that a high level of CRP concentration was positively associated with CHD, and that CRP was predictive of CHD. [34-37] For example, in two nested case–control studies — the Nurses' Health Study and the Health Professionals Follow-up Study — Jennifer et al. found that a high level of CRP was associated with an increased risk of CHD among participants with no history of cardiovascular disease and that the level of CRP could be considered as a predictor of CHD. [38] In the Cardiovascular Health Study, elevated CRP was found to be associated with an increased 10-year risk of CHD, regardless of the presence of conventional risk factors. [39] Besides, a cross-sectional study conducted in Japan demonstrated that hs-CRP was associated with the estimated risk level of CHD in the middle-aged men.

[40] However, controversy remains with respect to the association of CRP with CHD, and the predictive value of CRP. According to the data obtained from the MONICA Optional Haemostasis Study, no significant correlation was observed between the CHD event rate and the plasma CRP in the European populations. [41] Similarly, it was shown that the CRP level was not significantly associated with CHD with adjustment of conventional risk factors in the post-menopausal women. [42] Meanwhile, the findings from the 1999–2004 NHANES suggested that hs-CRP was not associated with the CHD mortality. [43] The present study further revealed that CRP was positively associated with CHD in patients with hyperuricemia.

Previous in vivo and in vitro studies have suggested that CRP modulated many factors involved in atherosclerosis, which might explain the positive association between the CRP level and CHD. CRP could reduce the endothelial nitric oxide synthase both at the protein and mRNA levels and promote the production of inducible nitric oxide synthase and endothelin-1 in endothelial cells. [38 39] Besides, it was reported that the adhesion and internalization of white blood cells onto the arterial wall were improved by CRP by inducing the expression of vascular cell adhesion molecule-1, intercellular adhesion molecule-1, E-selectin, and monocyte chemoattractant protein-1. [44 45] Moreover, CRP could also induce the monocyte chemotaxis and differentiation, [46 47] and facilitate the uptake of oxidized low-density lipoprotein through macrophages and monocyte-platelets aggregation. [48 49] Further evidence supported CRP as a participant in later stages of atherosclerosis with the expression of matrix metalloproteinases and collagenase activity in human monocyte-macrophages. [50 51]

The present study clarified that high hs-CRP was correlated with a high CHD risk in the middle-

aged and elderly population with hyperuricemia. It is suggested that hyperuricemia interacts synergistically with high hs-CRP subjects, and may subsequently enhance the risk of CHD predictor value of hs-CRP. This has implications for clinicians to predict the CHD risk in hyperuricemia patients based on hs-CRP, a frequently used biomarker, and thereby providing preventive measures accordingly. Meanwhile, it also prompts that uric acid may interact with other risk factors during the development and progression of CHD, but such conclusion needs to be validated by further study.

Several strengths and shortcomings of this study are worth mentioning. First, this is the first study exploring the association between hs-CRP and the CHD risk in patients with hyperuricemia in the middle-aged and elderly population. Second, multivariable models were used to analyze the aforementioned relationship by adjusting a considerable number of potential confounding factors, such as BMI, serum creatinine and diabetes. As for the limitation, no causal relationship can be established in the present study due to the nature of cross-sectional design. However, the primary objective of this study was to examine the association between CRP and the CHD risk rather than to prove that CRP could increase the incidence of CHD. As CRP was deemed to be correlated with the CHD risk score, it can be used to reflect this complicated index in clinical practice. Subsequently, other more complicated indexes such as the Framingham risk score could be used to examine the CHD risk. Therefore, it can be speculated that CRP could be taken as an easily accessible screening method.

Conclusion

This study showed that high serum hs-CRP level was independently correlated with high CHD risk in middle-aged and elderly population with hyperuricemia, which suggested that serum hs-CRP, a routine

index in clinical practice, may be used to predict CHD risk in hyperuricemia patients.

Contributors MX, DX, HL and XD were responsible for the conception and design of the study. KL and BZ contributed to the statistical analyses. MX, DX, HL, XD, YY and YZ contributed to the data collection and interpretation. MX, DX, HL and XD drafted the manuscript. HL and XD contributed to the revision of the manuscript. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent Not required.

Ethics approval This study was approved by the ethics committee of Xiangya Hospital, Central South University.

Data sharing statement: No additional data available.

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Table 1 Basic characteristics of study population based on the quintiles of hs-CRP level (n=517)

Characteristics	Quintiles of hs-CRP					P#
	1 (lowest)	2	3	4	5 (highest)	
N	108	99	106	100	104	
Age (years)	50.2 (6.6)	50.2 (5.6)	51.3 (7.3)	51.4 (6.0)	51.5 (7.4)	0.314
Female (%)	13.0	13.1	13.2	19.0	18.3	0.568
BMI (kg/m^2)	25.3 (3.2)	26.0 (2.6)	26.8 (3.1)	26.8 (3.0)	27.0 (3.6)	0.001
Relatively high CHD risk (≥10%, %)	25.0	32.3	40.6	48.0	41.3	0.007
Total cholesterol (mg/dl)	202.8 (35.6)	209.1 (37.9)	207.8 (40.9)	211.1 (41.4)	206.7 (49.6)	0.683
HDL cholesterol (mg/dl)	53.2 (13.4)	51.6 (13.5)	51.8 (9.6)	50.7 (12.1)	49.5 (10.6)	0.308
Systolic blood pressure (mmHg)	129.4 (14.3)	132.7 (15.7)	133.6 (15.5)	135.6 (16.9)	136.3 (17.4)	0.023
Diastolic blood pressure (mmHg)	82.1 (11.0)	84.3 (11.5)	85.1 (11.3)	86.3 (11.6)	87.5 (12.2)	0.006
Diabetes (yes, %)	12.0	12.1	11.3	18.0	17.3	0.476
Activity level (h/week)	2.0 (2.5)	1.3 (2.3)	1.8 (2.9)	1.6 (2.7)	1.2 (2.3)	0.015
Smoking (yes, %)	24.1	29.3	34.9	36.0	35.6	0.266
Alcohol drinking (yes, %)	53.7	61.6	63.2	61.0	52.9	0.407
Educational background (High school or above, %)	66.7	53.5	75.5	66.0	62.5	0.024
Serum creatinine	100.5 (32.8)	104.4 (49.7)	98.9 (14.9)	99.5 (34.9)	99.1 (17.6)	0.663

Data are mean (standard deviation), unless otherwise indicated; hs-CRP, hypersensitive C-reactive protein; BMI, body mass index; HDL, high density lipoprotein.

P values are for test of difference across all quintiles of hs-CRP.

Table 2 Associations between hs-CRP and relatively high 10-year CHD risk (≥10%) in hyperuricemia population (n=517)

	Quintiles of hs-CRP					P for trend
	1 (lowest)	**2**	**3**	**4**	**5 (highest)**	
Participants (n)	108	99	106	100	104	
Median hs-CRP (mg/L)	0.34	0.69	1.21	2.11	6.12	
Crude OR (95%CI)	1.00 (reference)	1.43 (0.78, 2.63)	2.05 (1.14, 3.67)	2.77 (1.54, 4.98)	2.12 (1.18, 3.80)	0.057
P values	-	0.245	0.016	0.001	0.012	
Multivariable adjusted OR (95% CI)	1.00 (reference)	1.40 (0.75, 2.61)	2.05 (1.13, 3.72)	2.69 (1.47, 4.89)	2.10 (1.15, 3.84)	0.068
P values	-	0.291	0.019	0.001	0.016	

*Multivariable adjusted model was adjusted for BMI, educational background, alcohol drinking status, activity level, serum creatinine and diabetes. hs-CRP, hypersensitive C-reactive protein; CHD, coronary heart disease; OR, odds ratio; CI, confidence interval.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4,5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5, 6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5,6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7, 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7, 8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	7,8

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	5, 6
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	19
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	8,9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	19
		(*b*) Report category boundaries when continuous variables were categorized	20
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	20
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9,10,11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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High-sensitivity C-reactive protein, an independent predictor of coronary heart disease risk in middle-aged and elderly Chinese population with hyperuricemia: a cross-sectional study

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High-sensitivity C-reactive protein, an independent predictor of coronary heart disease risk in middle-aged and elderly Chinese population with hyperuricemia: a cross-sectional study

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Abstract

OBJECTIVES: Hyperuricemia patients are at relatively high risk of developing coronary heart disease (CHD). The purpose of this study was to examine the relationship between high-sensitivity C-reactive protein (hs-CRP) and CHD risk in a middle-aged and elderly population with hyperuricemia.

DESIGN: A cross-sectional study.

SETTING AND PARTICIPANTS: This study was conducted in a health examination center of China. Participants were diagnosed with hyperuricemia based on uric acid concentrations. Specifically, males with a uric acid concentration ≥ 416 μmol/L were included, as well as females with a concentration ≥ 360 μmol/L.

MAIN OUTCOME MEASURES: 10-year CHD risk for each individual was evaluated using Framingham risk score based on the Adult Treatment Panel III charts.

RESULTS: A total of 517 hyperuricemia patients (438 males and 79 females) aged from 40 to 85 years old were included in the present study. 193 (37.3%) patients were defined with relatively high 10-year CHD risk. Compared with the lowest quintile, the crude odds ratio (ORs) of relatively high 10-year CHD risks were 2.05 (95%CI 1.14-3.67, P=0.016), 2.77 (95%CI 1.54-4.98, P=0.001), 2.12 (95%CI 1.18-3.80, P=0.012) in the third, fourth and fifth quintiles of serum hs-CPR level, respectively (P for trend = 0.057). The multivariable-adjusted ORs of relatively high 10-year CHD risk were 2.05 (95%CI 1.13-3.72, P=0.019) in the third, 2.69 (95%CI 1.47-4.89, P=0.001) in the fourth, and 2.10 (95%CI 1.15-3.84, P=0.016) in the fifth quintile of serum hs-CRP level when compared with the lowest quintile (P for trend = 0.068).

CONCLUSION: This study showed that there was a borderline association between high serum hs-CRP

level and high CHD risk in middle-aged and elderly population with hyperuricemia, which suggested that serum hs-CRP, a routine index in clinical practice, may be used to predict CHD risk in hyperuricemia patients.

Key words: hyperuricemia, high-sensitivity C-reactive protein, coronary heart disease

Strengths and limitations of this study

1. This is the first study exploring the association between hs-CRP and the CHD risk in patients with hyperuricemia in a middle-aged and elderly population with hyperuricemia.
2. The relationship of hs-CRP and the CHD risk was analyzed by multivariable models.
3. As result of the nature of cross-sectional design, the causal relationship cannot be established in the present study.

Background

Serum uric acid is the catabolic end-product of purine metabolism via the catalysis of xanthine oxidase. With the rapid economic development, the dietary habits of Chinese people have changed greatly towards an increasingly heavier intake of meat, dairy products and other purine enriched foods, which has led to a higher prevalence of hyperuricemia and gout susceptibly.[1 2] A systematic review and meta-analysis involving 44 studies showed that the pooled prevalence of hyperuricemia was 13.3% in mainland China from 2000 to 2014.[3] Some previous studies reported that an increase in serum uric acid was incriminated in the pathogenesis of metabolic syndrome,[4 5] chronic kidney disease,[6 7] stroke,[8] and coronary heart disease (CHD).[9 10]

Over the past several decades, relevant studies have shown that an increased serum uric acid was significantly associated with CHD, independent of conventional CHD risk factors.[9-12] Besides, it was also demonstrated that increased uric acid was correlated with hypertension, diabetes mellitus, metabolic syndrome, hypertriglyceridemia and endothelial dysfunction.[6 13-19] All of which could lead to an increased risk of CHD. With the trend of population aging, CHD has become one of the most common causes of death.[20] Therefore, it is urgent to seek effective predictors or biomarkers to identify subjects at a high risk of CHD, especially among the hyperuricemia patients, who are deemed a high risk group of CHD. A wide array of studies indicated that inflammation was involved in the pathogenesis of CHD.[21 22] C-reactive protein (CRP), one of the acute phase respondents, is commonly used in clinical practice to reflect chronic inflammation as an inexpensive measurement.[23] Several epidemiological studies were undertaken to clarify the relationship between CRP and CHD, but no agreement has been reached.[24-26] To the best of the authors' knowledge, there has been no study yet examining the association between

hs-CRP and the CHD risk in hyperuricemia patients. Meaningful outcomes in this respect would not only have important implications in understanding the pathophysiological mechanisms of CHD in hyperuricemia patients, but also contribute to the development of a simple and inexpensive method to predict the future CHD risk of this population.

To fill this knowledge gap, the present cross-sectional study was carried out to clarify the correlation between hs-CRP and the 10-year estimated CHD risk measured by the Framingham risk score (FRS) in the middle-aged and elderly population with hyperuricemia, with adjustment of conventional cardiovascular risk factors.

Materials and Methods

Study population

The participants of the present cross-sectional study were chosen from a pool of subjects who were undergoing routine medical examinations at the Department of Health Examination Center Xiangya Hospital, Central South University in Changsha, Hunan Province of China. The detailed methodology has been described in some earlier studies.[27-32] Briefly, all the qualified participants must be 40 years old or above and undergoing measurements of serum uric acid, hs-CRP, fasting plasma glucose concentration, total cholesterol, high-density lipoprotein (HDL-cholesterol) and creatinine during the specified period. In addition, the subjects should be diagnosed with hyperuricemia (i.e., the uric acid $\geq$ 416 μmol/L for male and $\geq$ 360 μmol/L for female), with availability of demographic and clinical data including age, gender, body mass index (BMI) (weight/height^2), smoking status, alcohol drinking status, activity level, medication status, etc. Initially, a total of 5994 subjects were included based on the age

requirement and availability of blood biochemical assessments (serum uric acid and hs-CRP measurement) during the period of October 2013 to December 2015. Then, 3420 subjects were disqualified: 30 were lack of basic health characteristics such as blood pressure and BMI; and 3390 were lack of information of health-related habits. Of the remaining 2574 subjects, only 517 were diagnosed with hyperuricemia and were finally enrolled in the present study. The study protocol had been reviewed and approved by the local Ethics and Research Committee and the written informed consent had been obtained from all participants prior to execution.

Blood biochemistry

All blood samples were drawn from the antecubital vein using vacuum tubes after an overnight fast of ≥12 hours, and were kept at 4°C until analysis. The hs-CRP was detected by the Latex turbidity method. The fasting plasma glucose concentration was measured using the glucose oxidase enzyme method. The uric acid, total cholesterol, HDL-cholesterol and creatinine were all detected using a Beckman Coulter AU 5800 (Beckman Coulter Inc., Brea, CA, USA). The low concentrations (2.5 mmol/L for glucose and 118 μmol/L for uric acid) and high concentrations (6.7 mmol/L for glucose and 472 μmol/L for uric acid) of standard human samples were used respectively to evaluate the intra- and inter-assay coefficients of variation. The intra-assay coefficients of variation were 0.98% (2.5 mmol/L) and 1.72% (6.7 mmol/L) for glucose, 1.39% (118 μmol/L) and 0.41% (472 μmol/L) for uric acid. The inter-assay coefficients of variation were 2.45% (2.5 mmol/L) and 1.46% (6.7 mmol/L) for glucose, 1.40% (118 μmol/L) and 1.23% (472 μmol/L) for uric acid. A subject was diagnosed with diabetes mellitus if his/her fasting plasma glucose level ≥ 7.0 mmol/L or if he/she was currently receiving medication for blood glucose control.

Assessment of other exposures

The BMI was calculated as the weight (kg) divided by the square of the height (m). The blood pressure was detected at the upper arm using an electronic sphygmomanometer after a rest of at least 10 min. Then, the status of physical activity, including the average frequency (never, one to two times per week, three to four times per week, five times and above per week) and the average duration of physical activity (within half an hour, half an hour to one hour, one to two hours, more than two hours) was collected from each subject. Lastly, the smoking and alcohol drinking status, as well as the medication conditions of the subjects were inquired.

Assessment of 10-year CHD risk

The risk level of developing CHD was measured by the FRS according to The Adult Treatment Panel III (ATP III) charts,[33] and the FRS was calculated based on 7 risk factors, which are age, gender, smoking, systolic blood pressure, use of antihypertensive medication, total cholesterol and HDL cholesterol, respectively. The specific risk scoring process is as follows: 1) calculate the number of points for each risk factor; 2) sum up the points of each risk factor to obtain the total risk score; 3) generate the estimated 10-year CHD risk for each patient. The subjects with the 10-year risk above 10% were classified into the high 10-year CHD risk group.

Statistical analysis

For statistical analysis, the continuous variables with a normal distribution were presented as mean ± standard deviation, and the category variables were described by frequency and percentage. The participants were classified into five categories based on the quintile distribution of hs-CRP, namely ≤

0.50, 0.51-0.90, 0.91-1.63, 1.63-3.04, and ≥ 3.05 mg/L. Baseline characteristics were presented according to quintiles of hs-CRP, and their trend associations were assessed using a linear regression analysis for continuous variables or a logistic regression for category variables, with the median value of hs-CRP in each category assigned to the corresponding category. The association between hs-CRP and the CHD risk has been described as the odds ratio and 95% confidence intervals, which were calculated for each quintile of hs-CRP; the lowest quintile was regarded as the reference category. Then, the factors of BMI, educational background, alcohol drinking status, activity level, serum creatinine and diabetes that might affect both hs-CRP and the outcomes of interest were included in these models as adjustors. The trend for relatively high CHD risk according to quartile of hs-CRP was analyzed using the linear regression model. All data analyses were performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA), and the level for statistical significance was set as the p-value equal to 0.05. All tests were two tailed.

Patient and public involvement

Patients and the public were not involved in setting the research question or the outcome measures, nor were they involved in the design or implementation of the study. There were no plans to disseminate the results of the research to study participants.

Results

A total of 517 hyperuricemia patients (438 males and 79 females) aged from 40 to 85 years old were included in the present study. There were 193 (37.3%) patients were defined with relatively high 10-year CHD risk. The basic characteristics of study population based on the quintiles of hs-CRP were showed in Table 1. Hyperuricemia patients in the highest level group of hs-CRP were more likely to have a higher

BMI, higher systolic and diastolic blood pressure, and lower activity level than were those in the lowest level group (P for trend < 0.05 for all).

The results of the associations between hs-CRP and relatively high 10-year CHD risk (≥10%) were shown in Table 2. According to the crude OR values, a significant higher prevalence of relatively high CHD risk was observed in the highest quintile (OR=2.12, 95%CI 1.18-3.80, P=0.012) of hs-CRP when comparing with the lowest quintile, and P for trend was 0.057. After adjustment for BMI, educational background, alcohol drinking status, activity level, serum creatinine and diabetes, a positive association between hs-CRP level and relatively high 10-year CHD risk was also observed; the multivariable OR based on a comparison of the highest and the lowest quintile of hs-CRP was 2.10 (95% CI, 1.15-3.84; P=0.016), and P for trend was 0.068.

Discussion

The present cross-sectional study revealed a borderline positive association between hs-CRP and the high 10-year risk of CHD in the middle-aged and elderly population with hyperuricemia. This correlation didn't changed significantly with adjustment of several potential confounding factors such as BMI, educational background, alcohol drinking status, activity level, serum creatinine and diabetes. These findings suggested that hs-CRP could serve as a marker for the risk of CHD in hyperuricemia patients.

The relationship between CRP and CHD has aroused intensive arguments. Some earlier studies demonstrated that a high level of CRP concentration was positively associated with CHD, and that CRP was predictive of CHD.[34-37] For example, in two nested case–control studies — the Nurses' Health Study

and the Health Professionals Follow-up Study — Jennifer et al. found that a high level of CRP was associated with an increased risk of CHD among participants with no history of cardiovascular disease and that the level of CRP could be considered as a predictor of CHD.[38] In the Cardiovascular Health Study, elevated CRP was found to be associated with an increased 10-year risk of CHD, regardless of the presence of conventional risk factors.[39] Besides, a cross-sectional study conducted in Japan demonstrated that hs-CRP was associated with the estimated risk level of CHD in the middle-aged men.[40] However, controversy remains with respect to the association of CRP with CHD, and the predictive value of CRP. According to the data obtained from the MONICA Optional Haemostasis Study, no significant correlation was observed between the CHD event rate and the plasma CRP in the European populations.[41] Similarly, it was shown that the CRP level was not significantly associated with CHD with adjustment of conventional risk factors in the post-menopausal women.[42] Meanwhile, the findings from the 1999–2004 NHANES suggested that hs-CRP was not associated with the CHD mortality.[43] The present study further revealed that CRP was positively associated with CHD in patients with hyperuricemia.

Previous in vivo and in vitro studies have suggested that CRP modulated many factors involved in atherosclerosis, which might explain the positive association between the CRP level and CHD. CRP could reduce the endothelial nitric oxide synthase both at the protein and mRNA levels and promote the production of inducible nitric oxide synthase and endothelin-1 in endothelial cells.[38 39] Besides, it was reported that the adhesion and internalization of white blood cells onto the arterial wall were improved by CRP by inducing the expression of vascular cell adhesion molecule-1, intercellular adhesion molecule-1, E-selectin, and monocyte chemoattractant protein-1.[44 45] Moreover, CRP could also induce the monocyte chemotaxis and differentiation,[46 47] and facilitate the uptake of oxidized low-density

lipoprotein through macrophages and monocyte-platelets aggregation.[48 49] Further evidence supported CRP as a participant in later stages of atherosclerosis with the expression of matrix metalloproteinases and collagenase activity in human monocyte-macrophages.[50 51]

The present study clarified that high hs-CRP was correlated with a high CHD risk in the middle-aged and elderly population with hyperuricemia, while several previous study have shown that CRP was not significantly associated with CHD in general population or other population.[24 42] It is suggested that hyperuricemia interacts synergistically with high hs-CRP subjects, and may subsequently enhance the risk of CHD predictor value of hs-CRP. This has implications for clinicians to predict the CHD risk in hyperuricemia patients based on hs-CRP, an easily measured clinical marker, and thereby providing preventive measures accordingly. Meanwhile, it also prompts that uric acid may interact with other risk factors during the development and progression of CHD, but such conclusion needs to be validated by further study.

Several strengths and shortcomings of this study are worth mentioning. First, this is the first study exploring the association between hs-CRP and the CHD risk in patients with hyperuricemia in the middle-aged and elderly population. Second, multivariable models were used to analyze the aforementioned relationship by adjusting a considerable number of potential confounding factors, such as BMI, serum creatinine and diabetes. As for the limitation, no causal relationship can be established in the present study due to the nature of cross-sectional design. However, the primary objective of this study was to examine the association between CRP and the CHD risk rather than to prove that CRP could increase the incidence of CHD. As CRP was deemed to be correlated with the CHD risk score, it can be

used to reflect this complicated index in clinical practice. Subsequently, other more complicated indexes such as the Framingham risk score could be used to examine the CHD risk. Therefore, it can be speculated that CRP may have the potential to be an easily accessible screening method in the future after further studies' confirmation.

Conclusion

This study showed that there was a borderline association between high serum hs-CRP level and high CHD risk in middle-aged and elderly population with hyperuricemia, which suggested that serum hs-CRP, a routine index in clinical practice, may be used to predict CHD risk in hyperuricemia patients.

Contributors MX, DX, HL and XD were responsible for the conception and design of the study. KL, BZ and ZY contributed to the statistical analyses. MX, DX, HL, XD, YY and YZ contributed to the data collection and interpretation. MX, DX, HL and XD drafted the manuscript. HL, XD and ZY contributed to the revision of the manuscript. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent Not required.

Ethics approval This study was approved by the ethics committee of Xiangya Hospital, Central South University.

Data sharing statement: No additional data available.

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Table 1 Basic characteristics of study population based on the quintiles of hs-CRP level (n=517)

Characteristics	Quintiles of hs-CRP (mg/L)					P for trend
	1 (≤0.50)	2 (0.51-0.90)	3 (0.91-1.63)	4 (1.64-3.04)	5 (≥3.05)	
N	108	99	106	100	104	
Demographic characteristics						
Age (years)	50.2 (6.6)	50.2 (5.6)	51.3 (7.3)	51.4 (6.0)	51.5 (7.4)	0.165
Female (%)	13.0	13.1	13.2	19.0	18.3	0.206
Educational background (High school or above, %)	66.7	53.5	75.5	66.0	62.5	0.743
Clinical characteristics						
BMI (kg/m^2)	25.3 (3.2)	26.0 (2.6)	26.8 (3.1)	26.8 (3.0)	27.0 (3.6)	0.001
Relatively high CHD risk (≥10%, %)	25.0	32.3	40.6	48.0	41.3	0.057
Systolic blood pressure (mmHg)	129.4 (14.3)	132.7 (15.7)	133.6 (15.5)	135.6 (16.9)	136.3 (17.4)	0.873
Diastolic blood pressure (mmHg)	82.1 (11.0)	84.3 (11.5)	85.1 (11.3)	86.3 (11.6)	87.5 (12.2)	0.151
Diabetes (yes, %)	12.0	12.1	11.3	18.0	17.3	0.174
Biochemical characteristics						
Total cholesterol (mg/dl)	202.8 (35.6)	209.1 (37.9)	207.8 (40.9)	211.1 (41.4)	206.7 (49.6)	0.873
HDL cholesterol (mg/dl)	53.2 (13.4)	51.6 (13.5)	51.8 (9.6)	50.7 (12.1)	49.5 (10.6)	0.151
Serum creatinine (μmol/L)	100.5 (32.8)	104.4 (49.7)	98.9 (14.9)	99.5 (34.9)	99.1 (17.6)	0.528
Lifestyle characteristics						
Activity level (h/week)	2.0 (2.5)	1.3 (2.3)	1.8 (2.9)	1.6 (2.7)	1.2 (2.3)	0.047
Smoking (yes, %)	24.1	29.3	34.9	36.0	35.6	0.165
Alcohol drinking (yes, %)	53.7	61.6	63.2	61.0	52.9	0.328

Data are mean (standard deviation), unless otherwise indicated; hs-CRP, hypersensitive C-reactive protein; BMI, body mass index; HDL, high density lipoprotein.

Table 2 Associations between hs-CRP and relatively high 10-year CHD risk (≥10%) in hyperuricemia population (n=517)

	Quintiles of hs-CRP (mg/L)					P for trend
	1 (≤0.50)	**2 (0.51-0.90)**	**3 (0.91-1.63)**	**4 (1.64-3.04)**	**5 (≥3.05)**	
Participants (n)	108	99	106	100	104	
Median hs-CRP (mg/L)	0.34	0.69	1.21	2.11	6.12	
Crude OR (95%CI)	1.00 (reference)	1.43 (0.78, 2.63)	2.05 (1.14, 3.67)	2.77 (1.54, 4.98)	2.12 (1.18, 3.80)	0.057
P values	-	0.245	0.016	0.001	0.012	
Multivariable adjusted OR (95% CI)	1.00 (reference)	1.40 (0.75, 2.61)	2.05 (1.13, 3.72)	2.69 (1.47, 4.89)	2.10 (1.15, 3.84)	0.068
P values	-	0.291	0.019	0.001	0.016	

*Multivariable adjusted model was adjusted for BMI, educational background, alcohol drinking status, activity level, serum creatinine and diabetes. hs-CRP, hypersensitive C-reactive protein; CHD, coronary heart disease; OR, odds ratio; CI, confidence interval.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4,5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5, 6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5,6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7, 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7, 8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	7,8

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	5, 6
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	19
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	8,9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	19
		(*b*) Report category boundaries when continuous variables were categorized	20
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	20
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9,10,11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association of high-sensitivity C-reactive protein in middle-aged and elderly Chinese people with hyperuricemia and risk of coronary heart disease: a cross-sectional study

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[2] Hui Li and Xiang Ding contributed equally to this article.

Abstract

OBJECTIVES: Hyperuricemia patients are at relatively high risk of developing coronary heart disease (CHD). The purpose of this study was to examine the relationship between high-sensitivity C-reactive protein (hs-CRP) and CHD risk in a middle-aged and elderly population with hyperuricemia.

DESIGN: A cross-sectional study.

SETTING AND PARTICIPANTS: This study was conducted in a health examination center of China. Participants were diagnosed with hyperuricemia based on uric acid concentrations. Specifically, males with a uric acid concentration ≥ 416 μmol/L were included, as well as females with a concentration ≥ 360 μmol/L.

MAIN OUTCOME MEASURES: 10-year CHD risk for each individual was evaluated using Framingham risk score based on the Adult Treatment Panel III charts.

RESULTS: A total of 517 hyperuricemia patients (438 males and 79 females) aged from 40 to 85 years old were included in the present study. 193 (37.3%) patients were defined with relatively high 10-year CHD risk. Compared with the lowest quintile, the crude odds ratio (ORs) of relatively high 10-year CHD risks were 1.43 (95%CI 0.78-2.63, P=0.245), 2.05 (95%CI 1.14-3.67, P=0.016), 2.77 (95%CI 1.54-4.98, P=0.001), 2.12 (95%CI 1.18-3.80, P=0.012) in the second, third, fourth and fifth quintiles of serum hs-CRP level, respectively (P for trend = 0.057). The multivariable-adjusted ORs of relatively high 10-year CHD risk were 1.40 (95%CI 0.75-2.61, P=0.291) in the second, 2.05 (95%CI 1.13-3.72, P=0.019) in the third, 2.69 (95%CI 1.47-4.89, P=0.001) in the fourth, and 2.10 (95%CI 1.15-3.84, P=0.016) in the fifth quintile of serum hs-CRP level when compared with the lowest quintile (P for trend = 0.068).

CONCLUSION: This study showed that ORs of relatively high 10-year CHD risk were raised in

hyperuricemia patients with higher serum hs-CRP level, however, there was a not significant but borderline trend association and that more research is needed.

Key words: hyperuricemia, high-sensitivity C-reactive protein, coronary heart disease

Strengths and limitations of this study

1. This is the first study exploring the association between hs-CRP and the CHD risk in patients with hyperuricemia in a middle-aged and elderly population with hyperuricemia.
2. The relationship of hs-CRP and the CHD risk was analyzed by multivariable models.
3. As result of the nature of cross-sectional design, the causal relationship cannot be established in the present study.
4. Though FRS has been used to assess the risk of cardiovascular events in Chinese population, it is noteworthy that FRS was originally constructed for the US population using a US population data.

Background

Serum uric acid is the catabolic end-product of purine metabolism via the catalysis of xanthine oxidase. With the rapid economic development, the dietary habits of Chinese people have changed greatly towards an increasingly heavier intake of meat, dairy products and other purine enriched foods, which has led to a higher prevalence of hyperuricemia and gout susceptibly.[1 2] A systematic review and meta-analysis involving 44 studies showed that the pooled prevalence of hyperuricemia was 13.3% in mainland China from 2000 to 2014.[3] Some previous studies reported that an increase in serum uric acid was incriminated in the pathogenesis of metabolic syndrome,[4 5] chronic kidney disease,[6 7] stroke,[8] and coronary heart disease (CHD).[9 10]

Over the past several decades, relevant studies have shown that an increased serum uric acid was significantly associated with CHD, independent of conventional CHD risk factors.[9-12] Besides, it was also demonstrated that increased uric acid was correlated with hypertension, diabetes mellitus, metabolic syndrome, hypertriglyceridemia and endothelial dysfunction.[6 13-19] All of which could lead to an increased risk of CHD. With the trend of population aging, CHD has become one of the most common causes of death.[20] Therefore, it is urgent to seek effective predictors or biomarkers to identify subjects at a high risk of CHD, especially among the hyperuricemia patients, who are deemed a high risk group of CHD. A wide array of studies indicated that inflammation was involved in the pathogenesis of CHD.[21 22] C-reactive protein (CRP), one of the acute phase respondents, is commonly used in clinical practice to reflect chronic inflammation as an inexpensive measurement.[23] Several epidemiological studies were undertaken to clarify the relationship between CRP and CHD, but no agreement has been reached.[24-26] To the best of the authors' knowledge, there has been no study yet examining the association between

hs-CRP and the CHD risk in hyperuricemia patients. Meaningful outcomes in this respect would not only have important implications in understanding the pathophysiological mechanisms of CHD in hyperuricemia patients, but also contribute to the development of a simple and inexpensive method to predict the future CHD risk of this population.

To fill this knowledge gap, the present cross-sectional study was carried out to clarify the correlation between hs-CRP and the 10-year estimated CHD risk measured by the Framingham risk score (FRS) in the middle-aged and elderly population with hyperuricemia, with adjustment of conventional cardiovascular risk factors.

Materials and Methods

Study population

The participants of the present cross-sectional study were chosen from a pool of subjects who were undergoing routine medical examinations at the Department of Health Examination Center Xiangya Hospital, Central South University in Changsha, Hunan Province of China. The detailed methodology has been described in some earlier studies.[27-32] Briefly, all the qualified participants must be 40 years old or above and undergoing measurements of serum uric acid, hs-CRP, fasting plasma glucose concentration, total cholesterol, high-density lipoprotein (HDL-cholesterol) and creatinine during the specified period. In addition, the subjects should be diagnosed with hyperuricemia (i.e., the uric acid $\geq$ 416 μmol/L for male and $\geq$ 360 μmol/L for female), with availability of demographic and clinical data including age, gender, body mass index (BMI) (weight/height^2), smoking status, alcohol drinking status, activity level, medication status, etc. Initially, a total of 5994 subjects were included based on the age

requirement and availability of blood biochemical assessments (serum uric acid and hs-CRP measurement) during the period of October 2013 to December 2015. Then, 3420 subjects were disqualified: 30 were lack of basic health characteristics such as blood pressure and BMI; and 3390 were lack of information of health-related habits. Of the remaining 2574 subjects, only 517 were diagnosed with hyperuricemia and were finally enrolled in the present study. The study protocol had been reviewed and approved by the local Ethics and Research Committee and the written informed consent had been obtained from all participants prior to execution.

Blood biochemistry

All blood samples were drawn from the antecubital vein using vacuum tubes after an overnight fast of ≥12 hours, and were kept at 4°C until analysis. The hs-CRP was detected by the Latex turbidity method. The fasting plasma glucose concentration was measured using the glucose oxidase enzyme method. The uric acid, total cholesterol, HDL-cholesterol and creatinine were all detected using a Beckman Coulter AU 5800 (Beckman Coulter Inc., Brea, CA, USA). The low concentrations (2.5 mmol/L for glucose and 118 μmol/L for uric acid) and high concentrations (6.7 mmol/L for glucose and 472 μmol/L for uric acid) of standard human samples were used respectively to evaluate the intra- and inter-assay coefficients of variation. The intra-assay coefficients of variation were 0.98% (2.5 mmol/L) and 1.72% (6.7 mmol/L) for glucose, 1.39% (118 μmol/L) and 0.41% (472 μmol/L) for uric acid. The inter-assay coefficients of variation were 2.45% (2.5 mmol/L) and 1.46% (6.7 mmol/L) for glucose, 1.40% (118 μmol/L) and 1.23% (472 μmol/L) for uric acid. A subject was diagnosed with diabetes mellitus if his/her fasting plasma glucose level ≥ 7.0 mmol/L or if he/she was currently receiving medication for blood glucose control.

Assessment of other exposures

The BMI was calculated as the weight (kg) divided by the square of the height (m). The blood pressure was detected at the upper arm using an electronic sphygmomanometer after a rest of at least 10 min. Then, the status of physical activity, including the average frequency (never, one to two times per week, three to four times per week, five times and above per week) and the average duration of physical activity (within half an hour, half an hour to one hour, one to two hours, more than two hours) was collected from each subject. Lastly, the smoking and alcohol drinking status, as well as the medication conditions of the subjects were inquired.

Assessment of 10-year CHD risk

The risk level of developing CHD was measured by the FRS according to The Adult Treatment Panel III (ATP III) charts,[33] and the FRS was calculated based on 7 risk factors, which are age, gender, smoking, systolic blood pressure, use of antihypertensive medication, total cholesterol and HDL cholesterol, respectively. The specific risk scoring process is as follows: 1) calculate the number of points for each risk factor; 2) sum up the points of each risk factor to obtain the total risk score; 3) generate the estimated 10-year CHD risk for each patient. The subjects with the 10-year risk above 10% were classified into the high 10-year CHD risk group.

Statistical analysis

For statistical analysis, the continuous variables with a normal distribution were presented as mean ± standard deviation, and the category variables were described by frequency and percentage. The participants were classified into five categories based on the quintile distribution of hs-CRP, namely ≤

0.50, 0.51-0.90, 0.91-1.63, 1.63-3.04, and ≥ 3.05 mg/L. Baseline characteristics were presented according to quintiles of hs-CRP, and their trend associations were assessed using a linear regression analysis for continuous variables or a logistic regression for category variables, with the median value of hs-CRP in each category assigned to the corresponding category. The association between hs-CRP and the CHD risk has been described as the odds ratio and 95% confidence intervals, which were calculated for each quintile of hs-CRP; the lowest quintile was regarded as the reference category. Then, the factors of BMI, educational background, alcohol drinking status, activity level, serum creatinine and diabetes that might affect both hs-CRP and the outcomes of interest were included in these models as adjustors. The trend for relatively high CHD risk according to quartile of hs-CRP was analyzed using the linear regression model. All data analyses were performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA), and the level for statistical significance was set as the p-value equal to 0.05. All tests were two tailed.

Patient and public involvement

Patients and the public were not involved in setting the research question or the outcome measures, nor were they involved in the design or implementation of the study. There were no plans to disseminate the results of the research to study participants.

Results

A total of 517 hyperuricemia patients (438 males and 79 females) aged from 40 to 85 years old were included in the present study. There were 193 (37.3%) patients were defined with relatively high 10-year CHD risk. The basic characteristics of study population based on the quintiles of hs-CRP were showed in Table 1. Hyperuricemia patients in the highest level group of hs-CRP were more likely to have a higher

BMI and lower activity level than were those in the lowest level group (P for trend < 0.05 for all).

The results of the associations between hs-CRP and relatively high 10-year CHD risk (≥10%) were shown in Table 2. According to the crude OR values, a higher prevalence of relatively high CHD risk was observed in the highest quintile (OR=2.12, 95%CI 1.18-3.80, P=0.012) of hs-CRP when comparing with the lowest quintile, and P for trend was 0.057. After adjustment for BMI, educational background, alcohol drinking status, activity level, serum creatinine and diabetes, the results did not change materially. Though ORs of relatively high CHD risk were raised in subjects with higher serum hs-CRP level, only a not significant but borderline trend association was observed; the multivariable OR based on a comparison of the highest and the lowest quintile of hs-CRP was 2.10 (95% CI, 1.15-3.84; P=0.016), and P for trend was 0.068.

Discussion

The present cross-sectional study revealed a borderline positive association between hs-CRP and the high 10-year risk of CHD in the middle-aged and elderly population with hyperuricemia. This correlation didn't changed significantly with adjustment of several potential confounding factors such as BMI, educational background, alcohol drinking status, activity level, serum creatinine and diabetes. These findings suggested that hs-CRP could serve as a marker for the risk of CHD in hyperuricemia patients.

The relationship between CRP and CHD has aroused intensive arguments. Some earlier studies demonstrated that a high level of CRP concentration was positively associated with CHD, and that CRP was predictive of CHD.[34-37] For example, in two nested case–control studies — the Nurses' Health Study

and the Health Professionals Follow-up Study — Jennifer et al. found that a high level of CRP was associated with an increased risk of CHD among participants with no history of cardiovascular disease and that the level of CRP could be considered as a predictor of CHD.[38] In the Cardiovascular Health Study, elevated CRP was found to be associated with an increased 10-year risk of CHD, regardless of the presence of conventional risk factors.[39] Besides, a cross-sectional study conducted in Japan demonstrated that hs-CRP was associated with the estimated risk level of CHD in the middle-aged men.[40] However, controversy remains with respect to the association of CRP with CHD, and the predictive value of CRP. According to the data obtained from the MONICA Optional Haemostasis Study, no significant correlation was observed between the CHD event rate and the plasma CRP in the European populations.[41] Similarly, it was shown that the CRP level was not significantly associated with CHD with adjustment of conventional risk factors in the post-menopausal women.[42] Meanwhile, the findings from the 1999–2004 NHANES suggested that hs-CRP was not associated with the CHD mortality.[43] The present study further revealed that CRP was borderline positively associated with CHD in patients with hyperuricemia.

It is interesting that, in the present study, the OR for CHD risk was lower in the highest quintile than the fourth quintile of hs-CRP. This phenomenon was also observed in several previous studies. Folsom et al. showed that the multivariate-adjusted relative risk of CHD in the fifth quintile of CRP was lower than in the fourth quintile.[44] Similar result was observed in another study which demonstrated that multivariate-adjusted relative risk of cardiovascular events was lower in the fourth quartile than in the third quartile of CRP.[45] However, our study and these previous studies are all epidemiologic studies which cannot establish mechanisms, and additional basic research on this interesting phenomenon is needed.

Previous in vivo and in vitro studies have suggested that CRP modulated many factors involved in atherosclerosis, which might explain the positive association between the CRP level and CHD. CRP could reduce the endothelial nitric oxide synthase both at the protein and mRNA levels and promote the production of inducible nitric oxide synthase and endothelin-1 in endothelial cells.[38 39] Besides, it was reported that the adhesion and internalization of white blood cells onto the arterial wall were improved by CRP by inducing the expression of vascular cell adhesion molecule-1, intercellular adhesion molecule-1, E-selectin, and monocyte chemoattractant protein-1.[46 47] Moreover, CRP could also induce the monocyte chemotaxis and differentiation,[48 49] and facilitate the uptake of oxidized low-density lipoprotein through macrophages and monocyte-platelets aggregation.[50 51] Further evidence supported CRP as a participant in later stages of atherosclerosis with the expression of matrix metalloproteinases and collagenase activity in human monocyte-macrophages.[52 53]

The present study clarified that high hs-CRP was correlated with a high CHD risk in the middle-aged and elderly population with hyperuricemia, while several previous study have shown that CRP was not significantly associated with CHD in general population or other population.[24 42] It is suggested that hyperuricemia interacts synergistically with high hs-CRP subjects, and may subsequently enhance the risk of CHD predictor value of hs-CRP. This has implications for clinicians to predict the CHD risk in hyperuricemia patients based on hs-CRP, an easily measured clinical marker, and thereby providing preventive measures accordingly. Meanwhile, it also prompts that uric acid may interact with other risk factors during the development and progression of CHD, but such conclusion needs to be validated by further study.

Several strengths and shortcomings of this study are worth being mentioned. First, this is the first study exploring the association between hs-CRP and the CHD risk in patients with hyperuricemia in the middle-aged and elderly population. Second, multivariable models were used to analyze the aforementioned relationship by adjusting a considerable number of potential confounding factors, such as BMI, serum creatinine and diabetes. As for the limitations, first, no causal relationship can be established in the present study due to the nature of cross-sectional design. However, the primary objective of this study was to examine the association between CRP and the CHD risk rather than to prove that CRP could increase the incidence of CHD. As CRP was deemed to be correlated with the CHD risk score, it can be used to reflect this complicated index in clinical practice. Subsequently, other more complicated indexes such as the Framingham risk score could be used to examine the CHD risk. Therefore, it can be speculated that CRP may have the potential to be an easily accessible screening method in the future after further studies' confirmation. Second, though FRS has been used to assess the risk of cardiovascular events in Chinese population,[54 55] it is noteworthy that FRS was originally constructed for the US population using a US population data. Third, age, sex, blood pressure, cholesterol and smoking should be included in adjusting covariates in multivariate analyses regarding CHD risk. However, FRS was calculated based on seven risk factors: age, gender, smoking, systolic blood pressure, use of antihypertensive medication, total cholesterol and HDL cholesterol. Therefore, we excluded these impotent confounders from adjusting risk factors as previous studies did.[56 57]

Conclusion

This study showed that ORs of relatively high 10-year CHD risk were raised in hyperuricemia patients

with higher serum hs-CRP level, however, there was a not significant but borderline trend association and that more research is needed.

Contributors MX, DX, HL and XD were responsible for the conception and design of the study. KL, BZ and ZY contributed to the statistical analyses. MX, DX, HL, XD, YY and YZ contributed to the data collection and interpretation. MX, DX, HL and XD drafted the manuscript. HL, XD and ZY contributed to the revision of the manuscript. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent Not required.

Ethics approval This study was approved by the ethics committee of Xiangya Hospital, Central South University.

Data sharing statement: No additional data available.

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Table 1 Basic characteristics of study population based on the quintiles of hs-CRP level (n=517)

Characteristics	Quintiles of hs-CRP (mg/L)					P for trend
	1 (≤0.50)	2 (0.51-0.90)	3 (0.91-1.63)	4 (1.64-3.04)	5 (≥3.05)	
N	108	99	106	100	104	
Demographic characteristics						
Age (years)	50.2 (6.6)	50.2 (5.6)	51.3 (7.3)	51.4 (6.0)	51.5 (7.4)	0.165
Female (%)	13.0	13.1	13.2	19.0	18.3	0.206
Educational background (High school or above, %)	66.7	53.5	75.5	66.0	62.5	0.743
Clinical characteristics						
BMI (kg/m^2)	25.3 (3.2)	26.0 (2.6)	26.8 (3.1)	26.8 (3.0)	27.0 (3.6)	0.001
Relatively high CHD risk (≥10%, %)	25.0	32.3	40.6	48.0	41.3	0.057
Systolic blood pressure (mmHg)	129.4 (14.3)	132.7 (15.7)	133.6 (15.5)	135.6 (16.9)	136.3 (17.4)	0.873
Diastolic blood pressure (mmHg)	82.1 (11.0)	84.3 (11.5)	85.1 (11.3)	86.3 (11.6)	87.5 (12.2)	0.151
Diabetes (yes, %)	12.0	12.1	11.3	18.0	17.3	0.174
Biochemical characteristics						
Total cholesterol (mg/dl)	202.8 (35.6)	209.1 (37.9)	207.8 (40.9)	211.1 (41.4)	206.7 (49.6)	0.873
HDL cholesterol (mg/dl)	53.2 (13.4)	51.6 (13.5)	51.8 (9.6)	50.7 (12.1)	49.5 (10.6)	0.151
Serum creatinine (μmol/L)	100.5 (32.8)	104.4 (49.7)	98.9 (14.9)	99.5 (34.9)	99.1 (17.6)	0.528
Lifestyle characteristics						
Activity level (h/week)	2.0 (2.5)	1.3 (2.3)	1.8 (2.9)	1.6 (2.7)	1.2 (2.3)	0.047
Smoking (yes, %)	24.1	29.3	34.9	36.0	35.6	0.165
Alcohol drinking (yes, %)	53.7	61.6	63.2	61.0	52.9	0.328

Data are mean (standard deviation), unless otherwise indicated; hs-CRP, hypersensitive C-reactive

protein; BMI, body mass index; HDL, high density lipoprotein.

Table 2 Associations between hs-CRP and relatively high 10-year CHD risk (≥10%) in hyperuricemia population (n=517)

	Quintiles of hs-CRP (mg/L)					P for trend
	1 (≤0.50)	**2 (0.51-0.90)**	**3 (0.91-1.63)**	**4 (1.64-3.04)**	**5 (≥3.05)**	
Participants (n)	108	99	106	100	104	
Median hs-CRP (mg/L)	0.34	0.69	1.21	2.11	6.12	
Crude OR (95%CI)	1.00 (reference)	1.43 (0.78, 2.63)	2.05 (1.14, 3.67)	2.77 (1.54, 4.98)	2.12 (1.18, 3.80)	0.057
P values	-	0.245	0.016	0.001	0.012	
Multivariable adjusted OR (95% CI)	1.00 (reference)	1.40 (0.75, 2.61)	2.05 (1.13, 3.72)	2.69 (1.47, 4.89)	2.10 (1.15, 3.84)	0.068
P values	-	0.291	0.019	0.001	0.016	

*Multivariable adjusted model was adjusted for BMI, educational background, alcohol drinking status, activity level, serum creatinine and diabetes. hs-CRP, hypersensitive C-reactive protein; CHD, coronary heart disease; OR, odds ratio; CI, confidence interval.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4,5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5, 6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5,6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7, 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7, 8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	7,8

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	5, 6
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	19
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	8,9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	19
		(*b*) Report category boundaries when continuous variables were categorized	20
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	20
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9,10,11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.