

Association of High-Sensitivity C-Reactive Protein with Metabolic Syndrome and Transitions in Metabolic Status: A Combined Cross-Sectional and Cohort Study with Gender Differences in Chinese Adults

Yuyang Xiao^{1,3,*}, Xupeng Zhang^{1,2,*}, Jia Wang², Xuchen Ma², Binyu Sun², Ying Li¹, Lei Chen⁴, Yazhang Guo⁵, Xiaoyue Li⁶, Huirong Guo⁷, Shanhu Yao⁸, Yuexiang Qin^{1,9}

¹Health Management Medicine Center, The Third Xiangya Hospital of Central South University, Changsha, Hunan, 410013, People's Republic of China; ²Xiangya School of Medicine, Central South University, Changsha, Hunan, 410013, People's Republic of China; ³Department of Otolaryngology, Head and Neck Surgery, Xiangya Hospital, Central South University, Changsha, Hunan, 410008, People's Republic of China; ⁴Department of Cardiothoracic Surgery, The Second Affiliated Hospital of Soochow University, Suzhou, Jiangsu, 215005, People's Republic of China; ⁵Health Management Center, First Affiliated Hospital of Jishou University, Jishou, Hunan, 416000, People's Republic of China; ⁶Department of Health Management, Aerospace Center Hospital, Beijing, 100000, People's Republic of China; ⁷Health Management Center, Changji BRANCH of The First Affiliated Hospital, Xinjiang Medical University, Changji, Xinjiang, 831118, People's Republic of China; ⁸Department of Radiology, The Third Xiangya Hospital, Central South University, Changsha, Hunan, 410013, People's Republic of China; ⁹Hunan Clinical Medical Research Center for Chronic Disease Health Management, The Third Xiangya Hospital, Central South University, Changsha, Hunan, 410013, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yuexiang Qin, Health Management Medicine Center, Third Xiangya Hospital, Central South University, Changsha, Hunan, 410013, People's Republic of China, Email 602466@csu.edu.cn; Shanhu Yao, Department of Radiology, Third Xiangya Hospital, Central South University, Changsha, Hunan, 410013, People's Republic of China, Email yaoshanhu09@163.com

Objective: To investigate the association between high-sensitivity C-reactive protein (hs-CRP) and the risk of metabolic syndrome (MetS) as well as its outcome development, and to evaluate its potential value as an early biomarker for MetS.

Methods: From August 2017 to December 2023, a total of 23,148 participants were enrolled from the Health Management Departments of five general tertiary hospitals in northern and southern China. Their basic demographic data, clinical information, and hs-CRP levels were collected. Among them, 531 participants who were free of MetS at baseline were followed up, and the incidence of MetS was analyzed at their second physical examination six years later. Multivariate logistic regression models were employed to evaluate the association between hs-CRP and the risk of prevalent and incident MetS.

Results: The prevalence of MetS was 32.3%, significantly higher in males than females. MetS-positive individuals exhibited elevated hs-CRP levels and higher age, BMI, blood pressure, lipid, and glucose parameters. Multivariate logistic regression analysis showed that hs-CRP was independently and positively associated with the risk of prevalent MetS in the overall population and in males. In females, this association was attenuated but remained statistically significant after adjusting for confounding factors. Among the 531 participants without MetS at baseline, 16.8% (89 individuals) developed new-onset MetS during the six-year follow-up period. Elevated baseline hs-CRP levels were significantly associated with the risk of incident MetS in males, but the association did not reach statistical significance in females.

Conclusion: Higher hs-CRP levels were associated with both prevalent and incident MetS in this Chinese adult population, with a stronger and more consistent association observed in males. These findings suggest that the relationship between inflammation and MetS may differ by gender. Given the observational design, further studies are needed to confirm these associations and explore underlying mechanisms.

Keywords: metabolic syndrome, high-sensitivity C-reactive protein, inflammatory marker, multivariate logistic regression

Introduction

Metabolic Syndrome (MetS) is a major public health issue with serious implications for global health outcomes. It is a multifactorial condition characterized by a combination of cardiovascular risk factors, including central obesity, hypertension, impaired glucose tolerance, insulin resistance, and dyslipidemia. MetS is strongly associated with the development of various serious health conditions, such as type 2 diabetes mellitus (T2DM), cardiovascular diseases, cancers, renal disease, and disability, all of which significantly increase the risk of cardiovascular events and overall mortality.¹⁻⁴ Between 2000 and 2017, the prevalence of MetS among Chinese adults aged 20 and older increased from 13.7% to 31.1%.^{5,6} By 2020, approximately 3% of children and 5% of adolescents worldwide had been diagnosed with MetS.⁷ These concerning trends emphasize the need for early detection and intervention to manage MetS and prevent its associated complications.

The development of MetS is thought to result from a complex interplay of genetic and environmental factors, with chronic systemic inflammation being a key driver.⁸ Elevated immune-inflammatory markers are strongly associated with the onset of MetS, including IL-6, C-reactive protein (CRP), and TNF- α , which are found at higher levels in individuals with MetS.⁹⁻¹¹ Findings suggest that stress can contribute to a state of chronic, low-grade inflammation that leads to metabolic dysregulation.¹² It has been shown that increased release of proinflammatory factors can lead to many diseases in the MetS spectrum, such as obesity, diabetes, and hypertension.¹³ Moreover, higher inflammation scores correlate with both overall and cardiovascular mortality in these patients.¹⁴ Our previous work has demonstrated a close association between the gastritis-related biomarker gastrin-17 and MetS.¹⁵ However, the relationship between hs-CRP and MetS remains to be elucidated.

CRP is an evolutionarily conserved pentamer consisting of five identical subunits, which bind to phosphocholine in a calcium ion (Ca^{2+})-dependent manner.¹⁶ CRP plays an essential role in the body's response to bacterial infections, tissue injury, and autoimmunity.¹⁷ Studies have shown that elevated CRP levels worsen the relationship between exposure to air pollution and MetS,¹⁸ and that patients with both MetS and elevated CRP are at a significantly higher risk of developing osteoarthritis.¹⁹ Moreover, the CRP/high-density lipoprotein cholesterol (HDL-C) ratio has been identified as a reliable indicator of MetS in individuals with T2DM.²⁰ High-sensitivity C-reactive protein (hs-CRP) is a low-concentration protein synthesized by the liver and serves as a reliable marker of low-grade inflammation.^{21,22} Given that inflammation is a key mechanism underlying cardiovascular disease,²³ numerous studies have shown that hs-CRP is a significant risk indicator for such conditions.²⁴ Study have demonstrated that hs-CRP levels correlate with the risk of cardiovascular events like myocardial infarction and atherosclerotic cardiovascular disease (ASCVD).²⁵ Additionally, hs-CRP has been found to predict cardiovascular risk more effectively than low-density lipoprotein cholesterol (LDL-C).²⁶ The 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease also highlighted hs-CRP's ability to independently predict coronary events.²⁷ These findings confirm hs-CRP as a robust risk indicator for cardiovascular disease.

Despite these findings, direct studies exploring the relationship between hs-CRP and MetS remain limited. To address this gap, we analyzed data from 23,148 individuals recruited from five hospitals. Additionally, we sought to explore whether these biomarkers were associated with transitions of MetS status based on 531 MetS-negative participants from baseline to the second healthexam after 6 years. Our study aims to investigate the association between hs-CRP and MetS through a combined cross-sectional and longitudinal analysis, providing novel insights into the prevention, diagnosis, and clinical management of MetS.

Method and Materials

Study Population

This study employed a dual analytic approach combining cross-sectional and longitudinal designs to comprehensively evaluate the association between hs-CRP and MetS. From August 2017 to December 2023, we initially enrolled 24,722 participants from the health management centers of five tertiary general hospitals in northern and southern China. For the cross-sectional analysis, we applied a two-phase screening process to establish the baseline cohort. First, we excluded individuals with missing data ($n=785$), resulting in 23,937 participants. Second, we excluded those aged <18 or >80 years

(n=441), those with a history of malignancy (n=339), and those with psychiatric disorders (n=78), yielding a final cross-sectional cohort of 23,148 participants. This cross-sectional component aimed to assess the association between hs-CRP levels and prevalent MetS at baseline. For the longitudinal analysis, we identified a subcohort of participants who were free of MetS at baseline and subsequently underwent a follow-up examination approximately six years later. Of the 15,582 participants without MetS at baseline, 531 individuals (3.4%) had complete follow-up data and were included in the longitudinal analysis. The selection of these 531 participants was not based on random sampling but rather on the availability of follow-up data from routine annual health examinations. Participants were included in the longitudinal cohort if they had undergone at least one additional comprehensive health assessment at the same hospital center within the specified follow-up window. This follow-up cohort was used to examine the association between baseline hs-CRP levels and incident MetS. Demographic data, clinical indicators, and hs-CRP levels were systematically collected for all participants. Detailed procedures are illustrated in Figure 1.

This study adheres to the reporting guidelines outlined in the RECORD Statement and all the relevant items of the RECORD checklist have been addressed in the article. This retrospective study was reviewed and approved by the Ethics Committee of The Third Xiangya Hospital, Central South University (Ethics Approval No. I15323), in accordance with

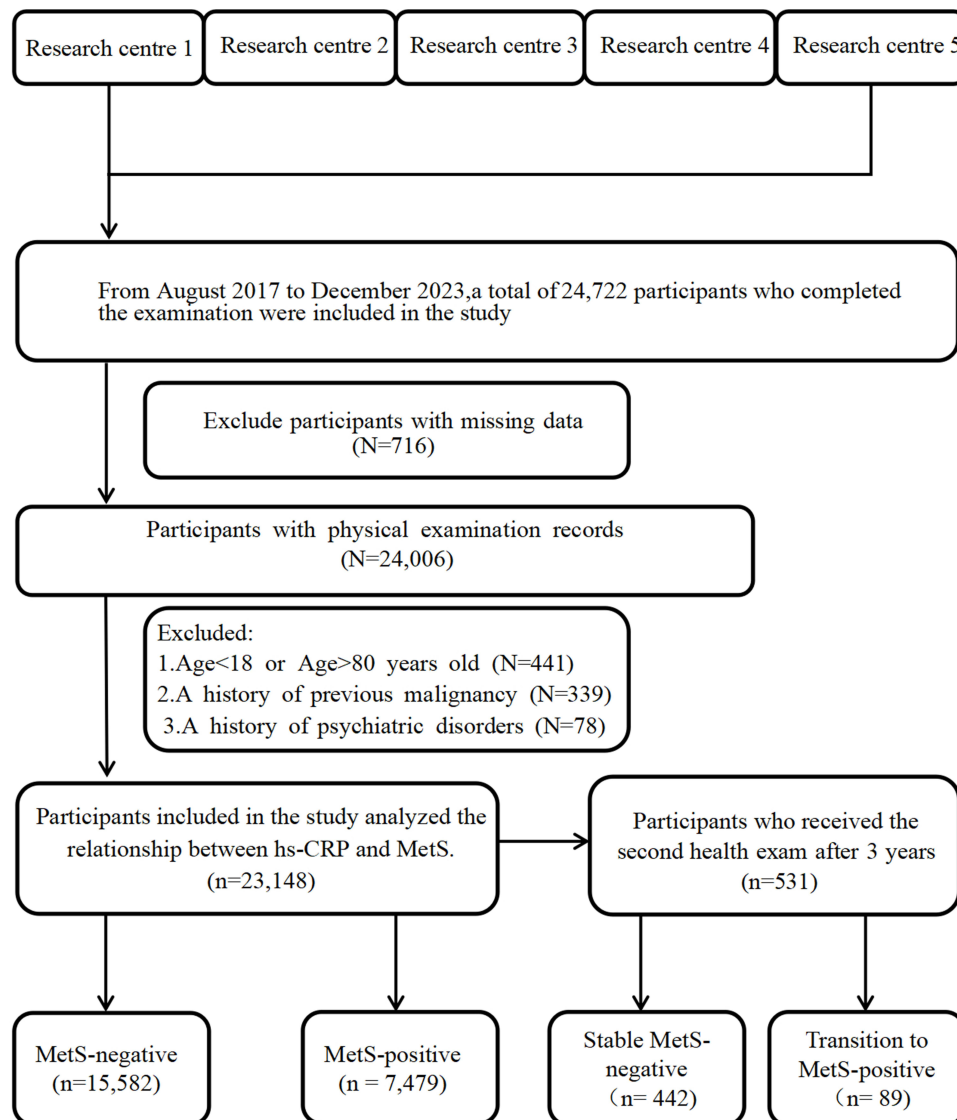


Figure 1 Flowchart of participant screening and follow-up in the multicenter cohort study on MetS.

the Declaration of Helsinki. As the research involved only de-identified clinical data meeting exemption criteria under 45 CFR §46.104(d)(4)(ii), the requirement for informed consent was waived. All personal data remained anonymized throughout analysis and reporting.

Determination of Hs-CRP Levels in Serum

Hs-CRP levels in blood were measured using the Liedmann hs-CRP Assay Kit-HCRP, with serum or plasma samples required. Calibration was performed by creating a working curve with water as the zero point and exponentially diluting the high-value calibration solution in deionized water. The endpoint method was used to monitor the antigen-antibody reaction at 600 nm. The sample volume was 5 µL, and reagents 1 (R1) and 2 (R2) were 125 µL each. Absorbance A1 was measured at 37°C for 1 minute after mixing S+R1+R2, followed by absorbance A2 after 4 minutes. The difference (A2-A1) was used to generate the working curve. The sample's absorbance difference was then measured, and the corresponding concentration was determined from the working curve. All laboratory tests were performed by certified laboratory physicians from the central laboratory department of the hospital using standard protocols. Quality control was conducted at all subcentres for operating physicians and equipment. The kappa values of the TN(s) measurements among doctors at each check-up centre were greater than 0.80.

Covariates

Baseline demographic, clinical, and laboratory data were systematically collected. Medical records were reviewed to obtain age, sex, smoking status, drinking status, dyslipidemia, diabetes mellitus, and hypertension. Physical parameters, including height, weight, waist circumference (WC), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured. BP measurements were taken bilaterally with an OMRON automatic digital BP monitor (OMRON HBP-9021, OMRON Healthcare, Scarborough, Ontario, Canada), following the Chinese Guidelines for Blood Pressure Measurement. Body mass index (BMI) was calculated by dividing weight (kg) by height (m²). Fasting blood samples were analyzed for levels of FBG, total cholesterol, TG, LDL-C, and HDL-C cholesterol using a LEADMAN monitoring kit (Beijing LEADMAN Biochemical Co, China).

The Definitions for MetS and Its Components

MetS was defined according to the criteria established by the International Diabetes Federation. A diagnosis of MetS requires the presence of at least three of the following five conditions: (1) WC ≥ 80.00 cm (female) or ≥ 90.00 cm (male); (2) TG > 1.70 mmol/L or being treated for lipid abnormalities; (3) HDL-C < 1.29 mmol/L (female) or < 1.03 mmol/L (male); (4) BP ≥ 130.00/85.00 mmHg, or being treated for hypertension, or diagnosed with hypertension; and (5) FBG > 5.60 mmol/L, or diagnosed with type 2 diabetes mellitus (T2DM).

Statistical Analysis

Data from the 23,148 participants were expressed as means with standard deviations for continuous variables and frequencies with percentages for categorical variables. The Student's *t*-test was used to compare continuous variables between groups, and the Pearson χ^2 -test was used for categorical variable comparisons. For clinical interpretation, hs-CRP levels were categorized according to widely accepted cardiovascular risk stratification thresholds: low risk (<1 mg/L), moderate risk (1–3 mg/L), and high risk (>3 mg/L), as recommended by the American Heart Association and the Centers for Disease Control and Prevention.^{28,29} Binary logistic regression analyses were performed after adjusting for age, gender, and other potential confounders, to evaluate the independent risk variables for MetS. To examine the relationship between hs-CRP and transitions in MetS status, three models were built. Model 1 adjusted for age and gender, while Model 2 included adjustments for age, gender, hypertension, hyperlipidemia, and other factors. Model 3 included a wider range of variables (age, sex, hypertension, hyperlipidemia, smoking, BMI, WC, BP, blood lipids, blood glucose, creatinine (Cr), blood uric acid (BUA), glycated hemoglobin (HbA1c), triglyceride-glucose (TyG), and sleep duration) for all participants. Multicollinearity was assessed using the variance inflation factor, and independent variables with the variance inflation factor (VIF) < 10 and *P* < 0.05 were included in the logistic regression model. The results were presented as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical analyses were performed using SPSS 27.0.

(IBM Corp., Armonk, NY, United States) and GraphPad Prism 9 (GraphPad Software, Inc., San Diego, CA, United States).

Results

Descriptive Analysis of Enrolled Participants with and without MetS

The baseline characteristics of the MetS-positive and MetS-negative groups are presented in [Table 1](#). The study population comprised 23,148 participants (15,709 males and 7370 females), of whom 7479 (32.40%) were diagnosed with MetS, including 5926 males and 1553 females, indicating a significantly higher prevalence of MetS in males (37.70%) than in females (21.10%) ($p < 0.001$). Comparative analyses revealed significant differences in most health-related parameters between the MetS-positive and MetS-negative groups ($p < 0.001$). The levels of age, BMI, WC, FBG, TyG index, TG, TC, LDL-C, SBP, DBP, HDL-C, Cr, hs-CRP, BUA, HbA1c ([Supplementary Table S1](#)), and sleep quality score in the MetS-positive group were all significantly higher than those in the MetS-negative group ($p < 0.001$).

Hs-CRP Levels in Participants with and without MetS

The median concentration of hs-CRP in subjects with MetS was 1.71 mg/L (IQR: 1.03–2.70), which was significantly higher than that in the MetS-negative group [1.10, (IQR: 0.66–1.87)]. The between-group difference was confirmed to be statistically significant by independent samples *t*-test ($p < 0.001$) ([Table 1](#)).

Baseline Characteristics and Hs-CRP Levels by Sex

The demographic and physiological characteristics of participants stratified by sex are presented in [Supplementary Table S2](#). In the MetS-positive group, males accounted for 79.2%, while females accounted for 20.8% ($p < 0.001$). In addition, the proportions of males in terms of age, smoking, alcohol consumption, and poor sleep quality are higher than those of females. Physiological parameters, including weight, BMI, WC, SBP, DBP, TG, TC, LDL-C, FBG, hs-CRP, Cr, and UA, were significantly higher in males than in females ($p < 0.001$). Notably, hs-CRP levels were also higher in males than in females.

Table 1 Baseline Characteristics of Participants Negative and Positive for MetS

Variant	Total	Metabolic State		P value
	23 148	MetS-Positive (7479)	MetS-Negative (15582)	
Age (yr)	53.00 (47.00–59.00)	54.00 (48.00–59.00)	53.00 (47.00–59.00)	<0.001
Sex (male), n (%)	15,745 (68.00)	5926 (79.20)	9783 (62.80)	<0.001
BMI (kg/m ²)	25.32 (23.34–27.39)	26.71 (25.00–28.58)	23.95 (22.12–25.91)	<0.001
WC (cm)	88.00 (82.00–88.00)	92.00 (87.00–98.00)	81.54 (53.00–134.00)	<0.001
SBP (mmHg)	130.00 (119.00–141.00)	136.00 (127.00–146.00)	123.00 (113.00–135.00)	<0.001
DBP (mmHg)	80.00 (72.00–144.00)	85.00 (77.00–91.00)	76.00 (69.00–84.00)	<0.001
TG (mmol/L)	1.65 (1.10–2.50)	2.26 (1.72–3.27)	1.24 (0.91–1.65)	<0.001
TC (mmol/L)	4.96 (4.30–5.64)	5.04 (4.36–5.79)	4.89 (4.24–5.54)	<0.001
HDL-C (mmol/L)	1.24 (1.08–1.42)	1.12 (1.02–1.28)	1.33 (1.19–1.53)	<0.001
LDL-C (mmol/L)	2.71 (2.14–3.31)	2.62 (2.03–3.23)	2.78 (2.26–3.34)	<0.001
FBG (mmol/L)	5.62 (5.18–6.50)	6.05 (5.56–7.10)	5.34 (5.02–5.75)	<0.001
Cr (μmol/L)	75.00 (63.00–85.00)	76.00 (65.00–87.00)	73.00 (62.00–84.00)	<0.001
UA (μmol/L)	354.00 (298.00–418.00)	379.00 (323.00–438.00)	336.00 (281.00–395.00)	<0.001
hs-CRP (mg/L)	1.40 (0.80–2.30)	1.71 (1.03–2.70)	1.10 (0.66–1.87)	<0.001
HbA1c (%)	5.70 (5.40–6.20)	5.90 (5.90–6.50)	5.60 (5.30–5.90)	<0.001
TyG	1.58 (1.17–2.07)	1.97 (1.62–2.39)	1.25 (0.90–1.58)	<0.001

Note: Values were given as median (interquartile range).

Characteristics and Hs-CRP of Participants with or without MetS Stratified by Sex

The demographics and clinical markers of male and female participants with and without MetS are shown in [Supplementary Table S3](#). Both male and female participants with MetS were older and more likely to have smoking history, alcohol consumption, HBP, DM, and medication history than those without MetS. They also had higher BMI, WC, SBP, DBP, TG, TC, UA, FBG, HbA1c levels, and TyG. HDL-C levels were lower in the MetS-positive group. The median levels of hs-CRP were higher in participants with MetS in both sexes.

Analysis of the Association Between Hs-CRP and MetS Using Logistic Regression Models

To explore the relationship between hs-CRP and MetS in greater depth, we divided patients into three groups based on the levels of biomarkers and conducted logistic regression analyses.

The multicollinearity analysis results shown in [Supplementary Table S4](#) indicate that the higher the value of VIF, the more significant the multicollinearity among variables. In both Model 1 and Model 2, there was a significant association between hs-CRP and the progression of MetS, not only among all participants but also in the male and female subgroups ($p<0.001$). However, in Model 3, this association remained statistically significant for all participants ($p=0.032$) and the male subgroup ($p=0.029$), yet it was no longer significant in the female subgroup ($p=0.523$) ([Table 2](#)).

The multivariate logistic regression analysis ([Table 3](#)) indicates that the association between hs-CRP and MetS is dependent on the extent of confounder adjustment and exhibits distinct patterns across clinical risk categories. In the overall population, individuals with hs-CRP levels in the moderate-risk category (1–3 mg/L) exhibited significantly higher odds of MetS in Models 1 and 2 (OR=1.603, 95% CI: 1.459–1.761; OR=1.572, 95% CI: 1.418–1.742, respectively). However, this association was attenuated and became borderline non-significant after full adjustment in Model 3 (OR=1.139, 95% CI: 0.988–1.314, $p=0.053$). A similar pattern was observed for the low-risk category (<1 mg/L), where a strong association in the minimally adjusted models was no longer significant in the fully adjusted model ($p=0.053$). No statistically significant association was detected for the high-risk category (>3 mg/L) in any of the models among all participants.

Sex-stratified analyses revealed notable heterogeneity. In males, hs-CRP levels in the 1–3 mg/L range were consistently and significantly associated with MetS across all three models, including after full adjustment (Model 3: OR=1.246, 95% CI: 1.053–1.474, $p=0.010$). In contrast, females exhibited a significant association only in the <1 mg/L category in Model 3 (OR=4.026, 95% CI: 1.489–10.883, $p=0.006$), while no significant associations were observed in the 1–3 mg/L or >3 mg/L categories after full adjustment.

These findings are largely consistent with the primary tertile-based analysis, supporting the robustness of the association between hs-CRP and MetS, particularly in males. The use of clinically meaningful cut-offs enhances the translational relevance of our results and reinforces the potential utility of hs-CRP as an adjunctive marker for metabolic risk stratification.

Table 2 Multivariate Logistic Regression Analysis of the Relationship Between Hs-CRP and MetS State Transitions

		Model 1			Model 2			Model 3		
		P value	OR	95% CI for OR	P value	OR	95% CI for OR	P value	OR	95% CI for OR
All participants	hs-CRP	<0.001	1.481	1.439–1.532	<0.001	1.529	1.479–1.581	0.032	1.062	1.005–1.122
Man	hs-CRP	<0.001	1.418	1.372–1.465	<0.001	1.499	1.441–1.559	0.029	1.077	1.008–1.152
Woman	hs-CRP	<0.001	1.585	1.497–1.677	<0.001	1.547	1.450–1.650	0.523	1.031	0.939–1.131

Notes: Adjusted Model 1: For all participants, adjusted for age and sex; for males and females, adjusted for age; Adjusted Model 2: For all participants, adjusted for age, sex, hypertension, hyperlipidemia, smoking; for males and females, adjusted for age and hypertension, hyperlipidemia, smoking. Adjusted Model 3: For all participants, adjusted for age, sex, hypertension, hyperlipidemia, smoking, BMI, WC, SBP, DBP, TC, TG, HDL-C, FBG, blood Cr, UA, HbA1c, TyG, and sleep time levels; for men and women, adjusted for age, hypertension, hyperlipidemia, smoking, BMI, WC, SBP, DBP, TC, TG, HDL-C, FBG, blood Cr, UA, HbA1c, TyG and sleep duration.

Table 3 Multivariable Logistic Regression Analysis of the Association Between Clinically Defined Hs-CRP Categories and MetS

All Participants	Model1			Model2			Model3		
	P value	OR	95% CI for OR	P value	OR	95% CI for OR	P value	OR	95% CI for OR
hs-CRP trisomy									
Third level 1 (<1)	<0.001	4.496	3.340–6.052	<0.001	4.490	3.267–6.170	0.053	1.587	0.995–2.532
Third level 2 (1–3)	<0.001	1.603	1.459–1.761	<0.001	1.572	1.418–1.742	0.042	1.139	0.988–1.314
Third round (>3)	0.231	0.944	0.859–1.037	0.258	0.931	0.859–1.037	0.181	1.098	0.957–1.260
Man									
Third level 1 (<1)	<0.001	4.026	2.867–5.653	<0.001	3.696	2.572–5.309	0.551	1.178	0.687–2.019
Third level 2 (1–3)	<0.001	1.642	1.473–1.831	<0.001	1.646	1.460–1.856	0.010	1.246	1.053–1.474
Third round (>3)	0.643	0.967	0.840–1.113	0.333	0.922	0.781–1.087	0.036	1.239	1.014–1.513
Woman									
Third level 1 (<1)	<0.001	5.482	2.945–10.207	<0.001	7.863	4.013–15.406	0.006	4.026	1.489–10.883
Third level 2 (1–3)	<0.001	1.477	1.220–1.789	0.002	1.376	1.125–1.684	0.370	0.880	0.666–1.163
Third round (>3)	0.199	0.897	0.761–1.059	0.368	0.919	0.764–1.105	0.807	0.969	0.752–1.248

Notes: The table presents the results of multifactorial Logistic regression analyses of the relationship between hs-CRP levels according to three tertiles (<0.8, 0.8–1.64, >1.64) and the three models (Model 1, Model 2, and Model 3) in the context of the different genders (All Participants, Males, Females). Among them, Model 1, Model 2, and Model 3 each have specific adjustment factor settings. Model 1: For all participants, adjusted for age and gender; for males and females, adjusted for age only. Model 2: for all participants, adjusted for a combination of age, sex, hypertension, hyperlipidemia, and smoking; for males and females, also adjusted for age, as well as hypertension, hyperlipidemia, and smoking. Model 3: For all participants, adjusted for age, sex, hypertension, hyperlipidemia, smoking, BMI, WVC, SBP, DBP, TC, TG, HDL-C, FBG, blood Cr, UA, HbA1c, TyG, and sleep time levels; adjustments were made for men and women based on many of the above indicators.

Hs-CRP and MetS Components

The associations between each MetS component and hs-CRP are shown in [Supplementary Table S5](#). The results indicated that hs-CRP levels were higher in individuals with higher WC and levels of TG, HDL-C, SBP, DBP, and FBG ($p<0.001$). As the MetS score increased, hs-CRP levels increased both in males and females ([Figure 2A](#)).

Relationship Between Hs-CRP and Clinical Parameters

The analysis of the associations between the components of MetS and hs-CRP revealed that individuals with elevated levels of WC, TG, HDL-C, SBP, DBP, and FBG exhibited significantly higher levels of hs-CRP ($p<0.001$) ([Supplementary Table S6](#)).

The associations between each MetS component and hs-CRP are shown in [Supplementary Table S7](#) and [Figure S1](#). Hs-CRP is strongly positively correlated with the MetS score, and is also significantly correlated with TG, FBG, and HbA1c ($p<0.05$). It has a negative association with HDL-C and sleepquality, while having a relatively weak correlation with WC. [Figure 2B](#) shows that hs-CRP increases with age in both male and female patients.

Association Between Hs-CRP and Transition of MetS Status

Through a 6-year prospective cohort study involving 531 individuals negative for MetS, we found that the baseline levels of hs-CRP biomarkers could predict the outcome of MetS. During the follow-up period, 16.76% ($n=89$) progressed to MetS-positive. The median level of baseline hs-CRP in these individuals was significantly higher than that in those who remained MetS-negative (1.27 [IQR 0.80–2.49] vs 0.6 [0.40–0.90] mg/L, $p<0.05$) ([Supplementary Table S5](#) and [Figure 3](#)). A cross-sectional analysis was further conducted ([Figure 3](#)). In the overall population, the hs-CRP level in the MetS-positive group was higher than that in the MetS-negative group. This difference showed an obvious gradient characteristic after gender stratification analysis: the difference in hs-CRP levels between the MetS-positive and MetS-negative groups was more significant in females, while the corresponding difference between the male groups was relatively smaller ($p<0.05$).

Sensitivity Analysis

We compared baseline characteristics between participants included in the longitudinal analysis ($n=531$) and those lost to follow-up among the baseline MetS-negative population ($n=15,051$) to assess the representativeness of the longitudinal

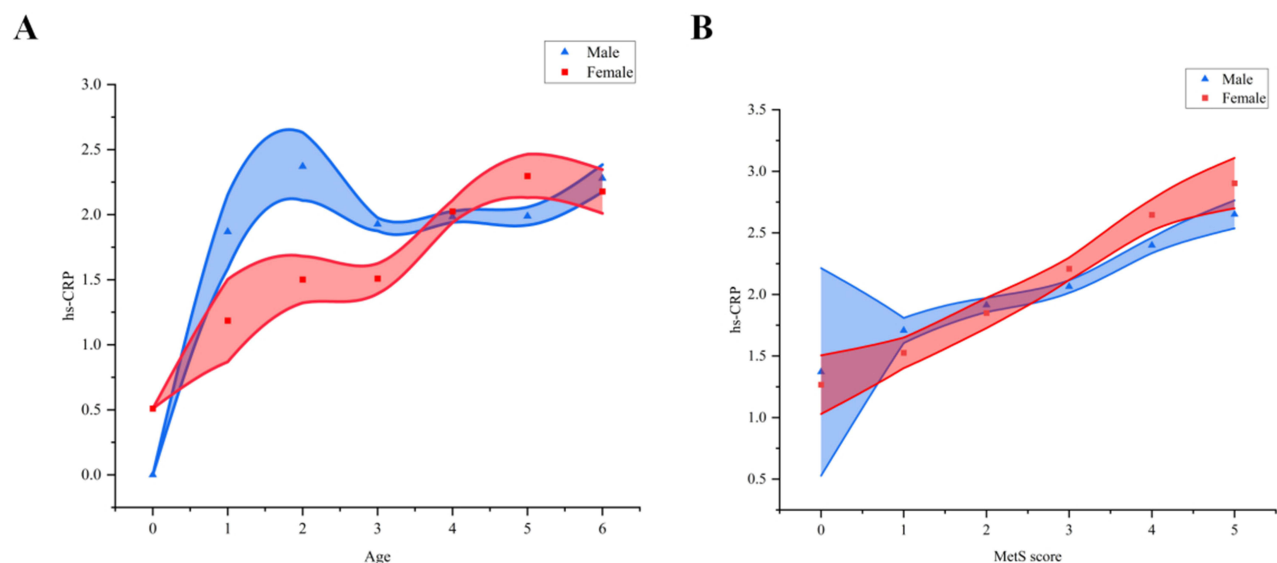


Figure 2 Dynamic variation patterns of the levels of hs-CRP with the severity of MetS and age distribution. **(A)** The subjects were divided into 7 age groups: 0: <20 years old; 1: 20–29 years old; 2: 30–39 years old; 3: 40–49 years old; 4: 50–59 years old; 5: 60–69 years old; 6: ≥70 years old. **(B)** 0–5: Subjects without and with 1, 2, 3, 4 and 5 components of metabolic syndrome. The error bars are plotted as transparent bands. Transparency has been set for all curves so that the data in the overlapping areas can be clearly seen. The dots represent the mean values ± SE.

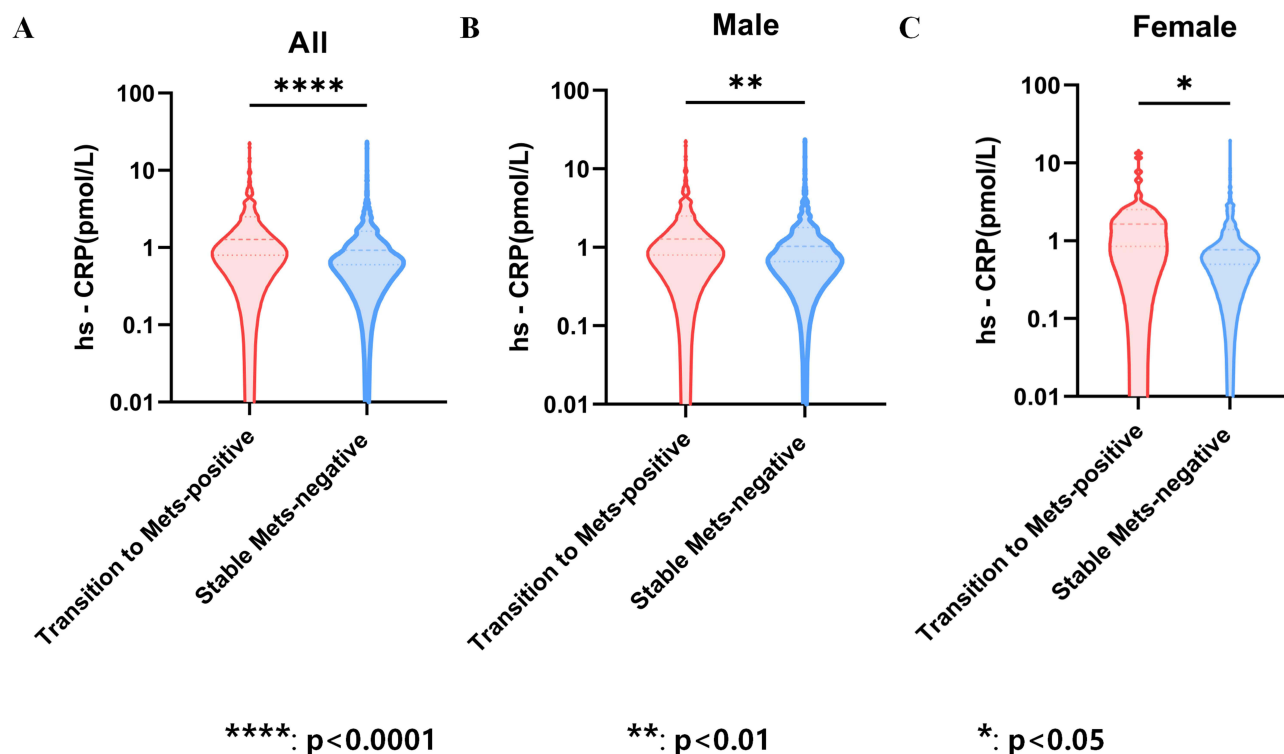


Figure 3 Gender differences in hs-CRP levels: transition from metabolically healthy to MetS. **(A)** Relationship between the transition of MetS status and hs-CRP levels in the general population. **(B)** Relationship between the transition of metabolic syndrome status and hs-CRP levels in the male population. **(C)** Relationship between the transition of MetS status and hs-CRP levels in the female population.

subcohort ([Supplementary Table S8](#)). No statistically significant differences were observed in most key metabolic parameters, including BMI, blood pressure, lipid profiles, fasting glucose, hs-CRP, HbA1c, and TyG index (all $p > 0.05$). However, participants in the longitudinal cohort were slightly older (49.08 vs 46.51 years, $p < 0.001$), more likely to be male (72.32% vs 65.00%, $p < 0.001$), and had modestly higher serum Cr and uric acid levels (both $p < 0.01$). These findings indicate that the longitudinal subcohort was broadly representative of the baseline MetS-negative population with respect to the primary metabolic variables of interest.

To assess the robustness of the core findings, this study conducted a sensitivity analysis by excluding extreme values (the 1st and 99th percentiles) of hs-CRP and related metabolic indicators and re-evaluating the association between hs-CRP and MetS using the same three-stage stepwise adjusted logistic regression model as in the primary analysis ([Supplementary Table S9](#)). The results showed that after removing extreme values, the association between hs-CRP and MetS remained statistically significant in the overall population, with a stable trend and less than 10% fluctuation in the OR across all models. Sex-stratified analyses revealed clear heterogeneity: in the male subgroup, the association remained significant in all three models with OR changes within 10%, whereas in the female subgroup, it was only significant in Model 1 and Model 2 and became non-significant after full adjustment in Model 3, though the variations in OR across models were also within 10%. These findings are consistent with the main analysis.

Discussion

In our study, the potential correlation between hs-CRP and MetS was examined from both horizontal and vertical perspectives. The results indicate that patients with MetS exhibited significantly higher hs-CRP levels compared to those without the condition. This suggests that hs-CRP may serve as a potential biomarker of MetS. Further analysis revealed that males were more susceptible to unfavorable metabolic status compared to females. Logistic regression analysis demonstrated a significant correlation between hs-CRP levels and the transition to MetS in participants, with a stronger association observed in male participants. Additional research has shown that hs-CRP, in combination with other factors such as age and gender, influences the metabolic phenotypic transition, in addition to its independent effect.

MetS is a complex, multifactorial condition with significant genetic, epigenetic, and environmental components. To better understand the complex pathophysiology of MetS and facilitate accurate diagnosis, substantial research has been conducted in recent years to identify biomarkers associated with the disease, particularly oxidative stress indicators and inflammatory markers.^{30,31} A novel hypothesis posits that adipose tissue dysfunction may contribute to MetS, with persistent low-grade systemic inflammation being one of its key features,^{32–35} closely associated with insulin resistance.^{36,37} Both hs-CRP levels and white blood cell count have been identified as reliable indicators of inflammatory components. However, a stronger correlation has been observed between insulin resistance and hs-CRP.³⁸ Therefore, understanding the interaction between hs-CRP and MetS may aid in the development of diagnostic, therapeutic, and management strategies for MetS.

Hs-CRP is an acute-phase protein synthesized and secreted by hepatocytes, promoting the release of pro-inflammatory cytokines during the inflammatory response, and interacting with Fc receptors.³⁹ Therefore, hs-CRP has been widely used as a marker to monitor inflammatory states.³⁹ Our study demonstrated that hs-CRP levels varied between individuals with MetS and those without the condition across participants. Multivariate logistic regression analysis confirmed that hs-CRP influenced the transition to MetS both independently and in combination with various other covariates, including gender. Ben-Assayag et al⁴⁰ found a relatively large intersection of hypertension and elevated hs-CRP in the metabolically impaired group over time, conjecturing that hypertension that occurs during the metabolic transition is widely accompanied by active inflammation. Further studies have shown that high hs-CRP levels are associated with the deterioration of children's metabolic health over time independent of waist circumference.⁴¹ Recently, hs-CRP has been identified as a predictor of cardiovascular events in individuals with MetS.⁴² Inflammation plays an important role in several components of MetS, including insulin resistance^{43,44} and obesity,^{43–46} which may help explain the correlation between hs-CRP and MetS. One of the hallmark features of MetS is increased abdominal circumference. CRP levels and visceral fat volume showed a positive correlation in a sample of 14 healthy females.⁴⁷ In healthy individuals with normal weight status, abdominal adiposity was similarly linked to an increase in CRP levels, regardless of BMI.⁴⁸ The accumulation of free fatty acids in adipose tissue, which promotes the release of cytokines and increases

CRP production, may link abdominal obesity with elevated CRP levels.⁴⁹ Studies have shown that high CRP levels can reduce nitric oxide production, leading to vasoconstriction and endothelial dysfunction thereby, further promoting the development of atherosclerosis.⁵⁰ Additionally, recent studies have suggested that hs-CRP/HDL-C ratio can predict the risk of all-cause mortality in patients with cardiovascular-kidney-metabolic (CKM) syndrome,⁵¹ and CRP-triglyceride-glucose index demonstrates potential as a predictive biomarker for CKM syndrome patients.⁵² These findings collectively support the association between hs-CRP and CKM syndrome.

In the early stages of new-onset hypertension, research in older individuals revealed that elevated CRP levels often precede the onset of elevated blood pressure.⁵³ Another explanation is that vascular inflammation induced by high blood pressure increases CRP levels.⁵⁴ Elevated CRP is widely recognized as being associated with cardiovascular disease, and it can serve as either a cause or an effect of hypertension. CRP was identified as a predictor of hypertension development.^{33,55} In risk factor-adjusted models, the mean CRP level in women with blood pressure <120/<75 mmHg was 1.33mg/L, controlling for other cardiovascular risk factors. In contrast, the mean CRP level in women with blood pressure $\geq 160/\geq 95$ mmHg was 1.84mg/L.⁵⁵ In this 8-year prospective follow-up study involving 14,719 women, the authors found that patients with MetS and hs-CRP >3mg/L had a higher age-adjusted risk of future cardiovascular events.⁵⁵

Data from cross-sectional studies show that the levels of hs-CRP exhibit a age-dependent characteristic, and they show a gradient upward trend with age in both genders. This phenomenon of the accumulation of age-related inflammatory markers suggests that the elderly population may have a unique metabolic susceptibility phenotype. Their metabolic homeostasis is more likely to be mediated by the pathophysiological process of chronic low-grade inflammation, thus promoting the transition to adverse metabolic states such as insulin resistance and lipid metabolism disorders.⁵⁶ Some studies have found that, compared with the group with low CRP levels and without diabetes, the group with high CRP levels and diabetes exhibits a accelerated biological aging process.⁵⁷ This accelerated aging phenotype not only increases the risk of diabetes-related death but also shows the characteristic of a gradual increase in risk among individuals with continuously rising CRP levels.⁵⁷ In addition, a cohort study conducted by Wang et al⁵⁸ indicate that participants in the highest quartile of hs-CRP levels exhibit a accelerated rate of cognitive function decline, and the risk of developing cognitive impairment is times higher compared to other groups. These reveal the role of the inflammatory response mediated by CRP or hs-CRP in aging-related metabolic disorders and neurodegenerative diseases from different dimensions, providing an important theoretical basis for understanding the interaction mechanism among age, inflammation, and metabolism.

Through the analysis of clinical data, we explored the potential associative characteristics between hs-CRP and MetS. We particularly paid attention to the potential modulating effects of age and gender and provided a perspective for understanding the relationship between hs-CRP and metabolic disorders. In addition to enhancing dietary control guidelines for patients with MetS, this study explores various factors influencing MetS, providing valuable insights into the relationship between CRP and MetS and offering a perspective on the diagnosis and treatment of diseases associated with MetS. However, our study has several limitations. Although the cross-sectional analysis included a large sample (23,148 participants), the longitudinal follow-up was limited to only 531 individuals. While baseline metabolic characteristics were generally comparable between those followed up and those lost to follow-up, individuals who voluntarily returned for follow-up may represent a more health-conscious subgroup, introducing potential selection bias; thus, the findings on metabolic transition should be interpreted with caution. In Model 3, adjustment for multiple components of MetS may have led to overadjustment, with a marked attenuation of the association observed particularly in females. Therefore, this model should be regarded as exploratory, with primary conclusions drawn from Models 1 and 2. Furthermore, the relatively short observation period for MetS status transition limits our ability to capture long-term dynamic changes in metabolic status. Although multiple confounders were adjusted for, unmeasured factors such as dietary patterns and physical activity may still contribute to residual confounding, and the observational design precludes causal inference. The study population was predominantly recruited from tertiary hospitals in selected regions of China, with a higher proportion of male participants, warranting caution in generalizing the findings. Furthermore, the unexpectedly low reported rates of medication use in this cohort may limit the generalizability of our findings regarding the natural history of the disease to other clinical populations. In view of these limitations, future studies should extend

follow-up duration to track long-term metabolic trajectories, include more diverse populations to enhance generalizability, and integrate multi-omics technologies to further elucidate the mechanisms underlying the role of hs-CRP in MetS, explore the biological basis of sex differences, and provide more comprehensive evidence for precision interventions.

Conclusion

Our study demonstrates that elevated hs-CRP is associated with an increased risk of both prevalent and incident MetS in a large Chinese adult population. This association was consistently observed across cross-sectional and longitudinal analyses, with a stronger and more robust relationship in males than in females. In fully adjusted models, hs-CRP remained independently associated with MetS in males but not in females, highlighting potential sex-based differences in the inflammation-metabolism relationship. However, given the observational design and the modest size of the longitudinal subcohort, these findings should be interpreted as hypothesis-generating rather than definitive. Further research is needed to validate the sex-specific predictive value of hs-CRP and to explore the underlying mechanisms in diverse populations.

Approval for Human Experiments

This retrospective analysis of anonymized clinical data was determined to be exempt from further IRB review by the Ethics Committee of The Third Xiangya Hospital, Central South University (Ethics Approval No. I15323). Informed consent was waived in accordance with 45 CFR §46.116(f) because the research involved no more than minimal risk and the data could not be linked to individual subjects.

Abbreviations

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; Cr, creatinine; CRP, c-reactive protein; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; ORs, odds ratios; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride; TyG, triglyceride-glucose index; WC, waist circumference.

Data Sharing Statement

All the data generated or analyzed during this study are included in this article. Further inquiries can be directed to the first author.

Ethics Approval and Consent to Participate

This study adheres to the reporting guidelines outlined in the RECORD Statement and all the relevant items of the RECORD checklist have been addressed in the article. The study protocol and consent forms were approved by the Ethics Committee of the Third Xiangya Hospital (Ethics Approval No. I15323), with all procedures followed by the World Medical Association Declaration of Helsinki. This study utilized a broad consent form, which was signed by each participant undergoing a physical examination prior to their examination. All personal information was anonymized during analysis and reporting to ensure confidentiality and privacy.

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Author Contributions

Yuyang Xiao: Data curation, Investigation, Writing-original draft, Writing-review & editing; Xupeng Zhang: Methodology, Visualization, Writing-original draft, Writing-review & editing; Jia Wang: Visualization, Writing-original draft, Writing-review & editing; Xuchen Ma: Data curation, Writing-original draft, Writing-review & editing; Binyu Sun: Data curation, Writing-review & editing; Ying Li: Data curation, Writing-review & editing; Lei Chen: Data

curation, Writing-review & editing; Yazhang Guo: Data curation, Writing-review & editing; Xiaoyue Li: Data curation, Writing-review & editing; Huirong Guo: Data curation, Writing-review & editing; Shanhu Yao: Funding acquisition, Methodology, Writing-review & editing; Yuexiang Qin: Data curation, Methodology, Funding acquisition, Project administration, Writing-review & editing. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Yuyang Xiao and Xupeng Zhang share first authorship.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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