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Association of High-Sensitivity C-Reactive Protein with Metabolic Syndrome and Transitions in Metabolic Status: A Cohort Study Revealing Gender Disparities in Chinese Adults

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ABSTRACT

Objective: To explore the relationship between high-sensitivity C-Reactive Protein (hs-CRP) and metabolic syndrome (MetS)/MetS transition, aiming to provide new insights into the prevention, diagnosis, and management of MetS.

Methods: From August 2017 to December 2023, 23,148 individuals were retrospectively recruited from five health management departments of general tertiary hospitals in northern and southern China. Basic demographic, clinical data, and hs-CRP levels were collected. Among them, the study focused on 531 participants who were MetS-negative at baseline and examined the transition of MetS status during the second health check six years later. Logistic regression models were used to analyze the association between MetS/MetS transition and hs-CRP.

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 revealed a significant association between hs-CRP and MetS progression in all participants and males, while this association weakened in females after full adjustment. Among 531 MetS-negative participants at baseline, 16.8% (89 individuals) developed MetS during the 6-year follow-up. Higher baseline hs-CRP levels were linked to MetS transition in males, but not in females.

Conclusion: High-sensitivity hs-CRP emerges as a highly promising biomarker for MetS, demonstrating value not only in monitoring disease progression but also in revealing sex-specific pathophysiological divergence, with particularly superior predictive capacity for male MetS risk compared to females.

KEYWORDS: Metabolic Syndrome; High-Sensitivity C-Reactive Protein; Inflammatory Marker; Multivariate Logistic Regression

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; WC: Waist Circumference

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]. Due to the ongoing global trend of aging populations and changing lifestyles, the prevalence of MetS has steadily risen, particularly in developing countries like China. Between 2000 and 2017, the prevalence of MetS among Chinese adults aged 20 and older increased from 13.7% to 31.1% [5,6]. Furthermore, 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 such as TNF-α, IL-6, and IL-1 can lead to many diseases in the metabolic syndrome spectrum, such as obesity, diabetes, and hypertension [13]. Moreover, higher inflammation scores correlate with both overall and cardiovascular mortality in these patients [14].

CRP is an evolutionarily conserved pentamer consisting of five identical subunits, which bind to phosphocholine in a calcium ion (Ca^{2+})-dependent manner [15]. CRP is a widely recognized biomarker of inflammation, with elevated levels in plasma or serum linked to numerous diseases. As a key component of the immune defense, CRP plays an essential role in the body's response to bacterial infections, tissue injury, and autoimmunity [16]. In the context of MetS, CRP serves as a critical marker of severity. Studies have shown that elevated CRP levels worsen the relationship between exposure to air pollution and MetS [17], and that patients with both MetS and elevated CRP are at a significantly higher risk of developing osteoarthritis [18]. Moreover, the CRP/High-Density Lipoprotein Cholesterol (HDL-C) ratio has been identified as a reliable indicator of MetS in individuals with T2DM [19]. 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 [20,21]. Given that inflammation is a key mechanism underlying cardiovascular disease [22], numerous studies have shown that hs-CRP is a significant risk indicator for such conditions [23]. For example, the Copenhagen study demonstrated that hs-CRP levels correlate with the risk of cardiovascular events like myocardial infarction and Atherosclerotic Cardiovascular Disease (ASCVD) [24]. Additionally, hs-CRP has been found to predict cardiovascular risk more effectively than Low-Density Lipoprotein Cholesterol (LDL-C), even in patients on statin therapy [25]. The 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease also highlighted hs-CRP's ability to independently predict coronary events [26]. Overall, 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, and the underlying mechanisms are not yet fully understood. To address this gap, our study examines the relationship between hs-CRP and MetS in a large-scale cohort, aiming to provide novel insights into the prevention, diagnosis, and clinical management of MetS. We analyzed data from 23,148 individuals recruited from five departments of the health management of general tertiary hospitals located in northern and southern China will be analyzed. 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.

METHODS

Study Population

This study was conducted from 2017 to 2023 across health management centers of five tertiary hospitals in northern and southern China, initially enrolling 24,722 participants. A two-phase screening process was applied: first, excluding individuals with missing data (n = 785), resulting in 23,937 participants; second, excluding those aged < 18 or > 80 years (n = 441), with a history of malignancy (n = 339) or psychiatric disorders (n = 78), yielding a final cohort of 23,148 participants for analysis. Among them, 531 individuals underwent a 6-year follow-up examination. Demographic data, clinical indicators, and hs-CRP levels in blood were systematically collected. Detailed procedures are illustrated in (Figure 1).

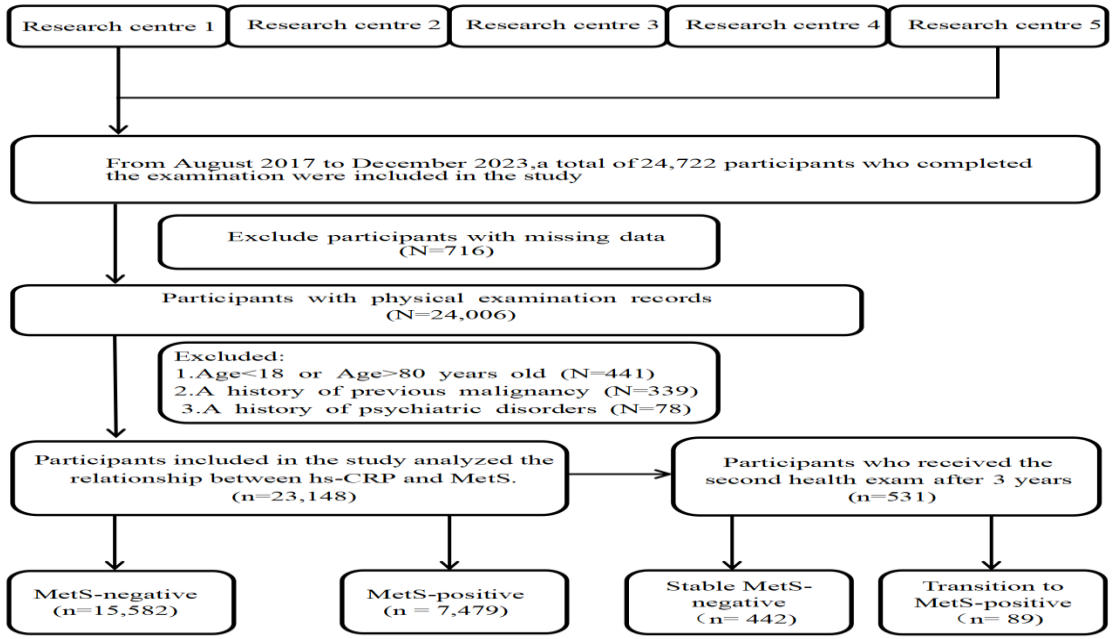

Figure 1: Flowchart of Participant Screening and Follow-up in the Multicenter Cohort Study on metabolic syndrome.

The study was approved by the Institutional Review Board of The Third Xiangya Hospital of Central South University (Ethics Approval No. I15323) and adhered to the principles of the Declaration of Helsinki. All necessary approvals were obtained from the government and the Health and Wellness Committee. 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.

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 equipmalet. The kappa values of the TN(s) measuremalets 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 (m^2). Fasting blood samples were analyzed for levels of FBG, total cholesterol, TG, LDL cholesterol, and HDL 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 cm (female) or ≥ 90 cm (male); (2) TG > 1.7 mmol/L or being treated for lipid abnormalities; (3) HDL-C < 1.29 mmol/L (female) or < 1.03 mmol/L (male); (4) BP ≥ 130/85 mmHg, or being treated for hypertension, or diagnosed with hypertension; and (5) FBG > 5.6 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, participants were categorized based on relevant markers such as hs-CRP. For example, hs-CRP levels were grouped into three tertiles (< 0.8, 0.8 - 1.64, > 1.64). 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, blood

pressure, blood lipids, blood glucose, creatinine, blood uric acid, HbA1c, 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 7,370 females), of whom 7,479 (32.4%) were diagnosed with MetS, including 5,926 males and 1,553 females, indicating a significantly higher prevalence of MetS in males (37.7%) than in females (21.1%) ($p < 0.001$). 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, Body Mass Index (BMI), Waist Circumference (WC), fasting blood glucose (FBG), Triglyceride-Glucose Index (TyG), triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), High-Density Lipoprotein Cholesterol (HDL-C), creatinine (Cr), High-Sensitivity C-Reactive Protein (hs-CRP), Blood Uric Acid (UA), Glycated Hemoglobin (HbA1c), and sleep quality score in the Metabolic Syndrome (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).

Table 1: Baseline Characteristics of Participants Negative and Positive for Metabolic Syndrome.

Variant	Total	Metabolic State		*P* value
	23148	**MetS-positive (n = 7479)**	**MetS-negative (n = 15582)**	
Age (Yr)	53(47-59)	54 (48-59)	53 (47-59)	< 0.001

Sex (Male），*N* (%)	15745 (68.0)	5926 (79.2)	9783 (62.8)	< 0.001
Smoking, *N* (%)	7620 (32.9)	2996 (40.1)	4624 (29.7)	< 0.001
Drinking, *N* (%)	8409 (36.3)	3192 (42.7)	5217 (33.5)	< 0.001
BMI (Kg/M^2)	25.32 (23.34-27.39)	26.71 (25-28.58)	23.95 (22.12-25.91)	< 0.001
WC (Cm)	88 (82-88)	92 (87-98)	81.54 (53-134)	< 0.001
SBP (Mmhg)	130 (119-141)	136 (127-146)	123 (113-135)	< 0.001
DBP (Mmhg)	80 (72-144)	85 (77-91)	76 (69-84)	< 0.001
TG (Mmol/L)	1.65 (1.1-2.5)	2.26 (1.72-3.27)	1.24 (0.91-1.65)	< 0.001
TC (Mmol/L)	4.96 (4.3-5.64)	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 (5.18-6.5)	6.05 (5.56-7.1)	5.34 (5.02-5.75)	< 0.001
Cr (μmol/L)	75 (63-85)	76 (65-87)	73 (62-84）	< 0.001
UA (μmol/L)	354 (298-418)	379 (323-438)	336 (281-395）	< 0.001
Hs-CRP(Mg/L)	1.4 (0.8-2.3)	1.71 (1.03-2.7)	1.1 (0.66-1.87）	< 0.001
Hba1c (%)	5.7 (5.4-6.2)	5.9 (5.9-6.5)	5.6 (5.3-5.9)	< 0.001
TyG Index	1.58 (1.17-2.07)	1.97 (1.62-2.39)	1.25 (0.9-1.58)	< 0.001
Sleep Quality, *n* (%)	12478 (53.9)	3834 (51.3)	8644 (55.5)	< 0.001
Medication History				
Antihypertensive Drug	1825 (7.90）	1041（13.9）	784 (5.03）	
Hypoglycemic Drug	656（2.83）	385（5.14）	271 (1.74)	
Lipid-Lowering Drug	320 (1.38)	173 (2.31)	147 (0.943)	
Personal History of Diseases				

High Blood Pressure	1015 (4.38)	882 (11.8)	133 (0.854)	
Diabetes Mellitus	214 (0.924)	199 (2.66)	15 (0.0963)	
Fatty Liver	152 (0.657)	98 (1.31)	53 (0.340)	

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

MetS: Metabolic Syndrome; HBP: Hypertension; DM: Diabetes Mellitus; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; TC: Total Cholesterol; TG: Triglycerides; HDLC: High - Density Lipoprotein Cholesterol; LDLC: Low - Density Lipoprotein Cholesterol; FBG: Fasting Blood Glucose; Hba1c: Glycosylated Hemoglobin; Cr: Creatinine; UA: Blood Uric Acid; TyG: Triglyceride - Glucose Index; Hs - CRP: High - Sensitivity C - reactive protein

Baseline Characteristics and hs-CRP Levels by Sex

The demographic and physiological characteristics of participants stratified by sex are presented in Table S1. 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.

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 Table S2. 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. HDLC 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 Table S3 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 (see Table 3) indicates that hs-CRP levels are significantly associated with the transition of MetS, especially in the low (< 0.8 mg/L) and intermediate (0.8–1.64 mg/L) ranges. Among all participants, the odds ratios (ORs) for Level III1 and Level III2 in Model 1 were 3.972 and 1.481 respectively. After adjustment in Model 2, the ORs increased to 4.249 and 1.529. In the sex-stratified analysis, the association was stronger in males, with an OR of 1.077 for Level III2 in Model 3. In contrast, the association in females was weakened and did not reach statistical significance ($p = 0.532$). As more metabolic and lifestyle factors were taken into account, the independent role of hs-CRP diminished. In both Model 1 and Model 2, hs-CRP levels were significantly associated with the transition of MetS among all participants and both genders. Nevertheless, in Model 3, this association weakened, particularly in females.

Table 2: Multivariate Logistic Regression Analysis of the Relationship between High-sensitivity C-reactive protein and Metabolic Syndrome State Transitions.

		Model1			Model2			Model3		
		***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, body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, high-density lipoprotein cholesterol, fasting blood glucose, blood creatinine, blood uric acid, glycated hemoglobin, triglyceride-glucose, and sleep time levels; for men and women, adjusted for age, hypertension, hyperlipidemia, smoking, body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, high-density lipoprotein cholesterol, fasting blood glucose, blood creatinine, blood uric acid, glycated hemoglobin, TyG and sleep duration.

hs - CRP and MetS Components

The associations between each MetS component and hs - CRP are shown in Table S4. The results indicated that hs - CRP levels were higher in individuals with higher WC and levels of TG, HDLC, 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, HDLC, SBP, DBP, and FBG exhibited significantly higher levels of hs-CRP ($P < 0.001$) (Table S5). The associations between each MetS component and hs-CRP are shown in (Table S6 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 HDLC and sleep quality, 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 0.8 - 2.49] vs 0.6 [0.4 - 0.9] mg/L, $p < 0.05$) (Table S4, 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 ($p < 0.05$).

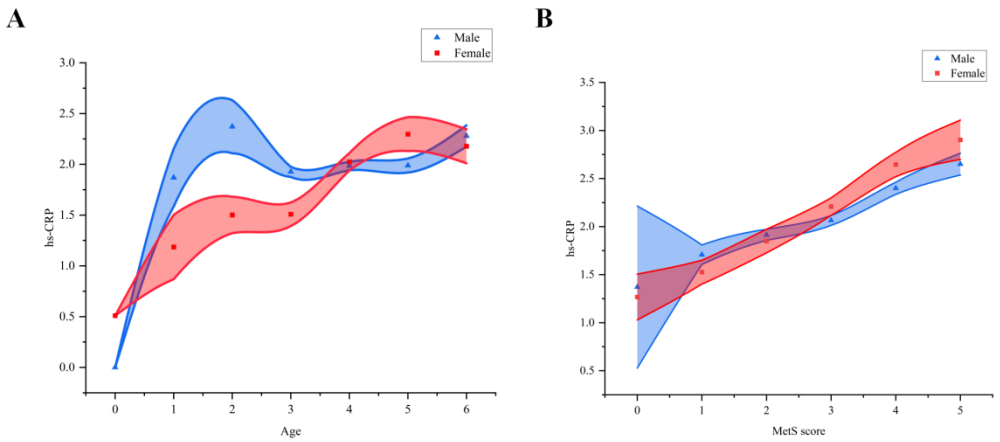

Figure 2: Dynamic variation patterns of the levels of high-sensitivity C-reactive protein with the severity of metabolic syndrome and age distribution.

(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. MetS: Metabolic syndrome, hs-CRP: High-sensitivity C-reactive protein.

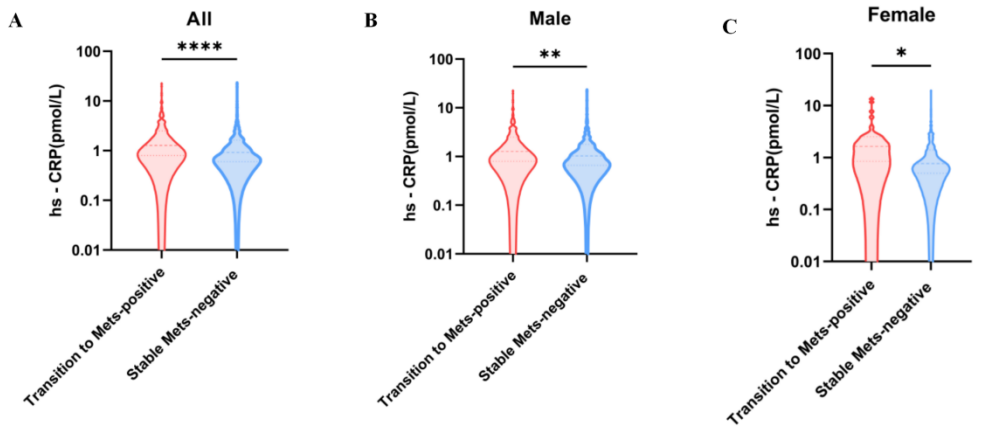

Figure 3: Gender differences in high-sensitivity C-reactive protein levels: Transition from metabolically healthy to metabolic syndrome.

(A) Relationship between the transition of metabolic syndrome status and high-sensitivity C-reactive protein levels in the general population. (B) Relationship between the transition of metabolic syndrome status and high-sensitivity C-reactive protein levels in the male population. (C) Relationship between the transition of metabolic syndrome status and high-sensitivity C-reactive protein levels in the female.

Table 3: Multifactorial Logistic Regression Analysis of the Association between High-sensitivity C-reactive protein and Metabolic Syndrome According to Tertiles.

	Model 1			**Model 2**			**Model 3**		
All participants	***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 （< 0.8)	< 0.001	3.972	2.628-6.005	< 0.001	4.249	2.657-6.796	0.338	1.496	0.657-3.410

Third Level 2（0.8-1.64)	< 0.001	1.481	1.439-1.532	< 0.001	1.529	1.479-1.581	0.032	1.062	1.005-1.122
Third Round （> 1.64）	0.332	1.013	0.987-1.041	0.002	1.076	1.027-1.128	0.258	1.056	0.960-1.162
Man									
Third Level 1 （< 0.8)	< 0.001	3.989	2.504-6.356	< 0.001	3.946	2.320-6.712	0.497	1.395	0.534-3.644
Third Level 2（0.8-1.64)	< 0.001	1.418	1.372-1.465	< 0.001	1.499	1.441-1.559	0.029	1.077	1.008-1.152
Third Round （> 1.64）	0.851	1.002	0.979-1.026	0.014	1.083	1.016-1.154	0.279	1.07	0.947-1.210
Woman									
Third Level 1 （< 0.8)	0.014	3.099	1.257-7.641	0.002	4.761	1.735-13.066	0.667	1.465	0.257-8.335
Third Level 2（0.8-1.64)	< 0.001	1.585	1.497-1.677	< 0.001	1.547	1.450-1.650	0.532	1.031	0.939-1.131
Third Round （> 1.64）	0.053	1.074	0.999-1.153	0.149	1.055	0.981-1.134	0.719	1.028	0.886-1.192

Notes: The Figure 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, body mass index, waist

circumference, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, high-density lipoprotein cholesterol, fasting blood glucose, blood creatinine, blood uric acid, glycated hemoglobin, triglyceride-glucose, and sleep time levels; adjustments were made for men and women based on many of the above indicators.

Metabolic Syndrome - Associated Characteristics and Biomarker Correlations: Supplementary Data and Analysis

Table S1: Baseline characteristics of males and females.

Variables	Sex		*P* value
	Males (15745)	**(Females) 7403**	
Age (yr)	47.00 (40.00-54.00)	46.00 (39.00-52.00)	< 0.001
Smoking, n (%)	7280 (46.2)	353 (4.77)	< 0.001
Drinking, n (%)	7727 (49.1)	699 (9.44)	< 0.001
HBP, n (%)	1466 (9.31)	454 (6.13)	< 0.001
DM, n (%)	676 (4.29)	121 (1.63)	< 0.001
Medication history, n (%)			
Antihypertensive	1380 (8.76)	445 (6.01)	< 0.001
Antidiabetic	541 (3.44)	115 (1.55)	< 0.001
lipid-lowering drugs	257 (1.63)	63 (0.851)	< 0.001
Metabolic index			
BMI (kg/m2)	25.31 (23.44-27.32)	23.02 (13-45)	< 0.001
WC（cm）	89.00 (84.00-94.00)	77.00 (72.00-82.00)	

SBP (mmHg)	125.00(115.00-135.00)	119.1 (78-206)	< 0.001
DBP (mmHg)	78.00(71.00-86.00)	71.47 (39-129)	< 0.001
TG (mmol/L)	1.76 (1.19-2.72)	1.13 (0.81-1.65)	< 0.001
TC (mmol/L)	5.06 (4.46-5.68)	5.00 (4.39-5.67)	< 0.001
HDLC (mmol/L)	1.19 (1.06-1.35)	1.44 (1.27-1.64)	< 0.001
LDLC (mmol/L)	2.83 (2.29-3.36)	2.84 (2.35-3.40)	< 0.001
Cr (μmol/L)	81.00 (74.00-89.00)	58.00 (53.00-64.00)	< 0.001
UA (μmol/L)	383.50 (335.00-436.00)	279.00 (244.00-320.00)	< 0.001
FBG (mmol/L)	5.40 (5.03-5.91)	5.20 (4.88-5.57)	< 0.001
HbA1c (%)	5.50 (5.30-5.80)	5.50 (5.30-5.70)	< 0.001
TyG	1.59 (1.17-2.06)	1.09 (0.72-1.51)	< 0.001
Biomarkers			
hs - CRP	1.27 (0.76-2.10)	1.00 (0.60-1.80)	< 0.001

Notes: MetS: Metabolic syndrome; HBP: Hypertension; DM: Diabetes mellitus; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TC: Total cholesterol; TG: Triglycerides; HDLC: High - density lipoprotein cholesterol; LDLC: Low - density lipoprotein cholesterol; FBG: Fasting blood glucose; HbA1c: Glycosylated hemoglobin; Cr: Creatinine; UA: Blood uric acid; TyG: Triglyceride - Glucose Index; hs - CRP: high - sensitivity C - reactive protein.

Table S2: Baseline characteristics of participants with or without metabolic syndrome in males and females.

Variables	Males (15745)		*P* value	Females (15745)		*P* value
	MetS-negative (n = 5962)	MetS-positive (n = 9783)		MetS-negative (n = 1517)	MetS-positive (n = 5799)	
Age (yr)	47.00 (40.00-54.00)	49.00 (42.00-54.00)	< 0.001	46.00 （39.00-52.00）	54.00 (48.00-61.00)	< 0.001
Smoking, n (%)	2936 (49.25)	4332 (44.28)	< 0.001	60 (3.96)	292 (5.04)	< 0.001
Drinking, n (%)	3091 (51.85)	4383 (44.80)	< 0.001	101 (6.66)	595 (10.26)	< 0.001
HBP, n (%)	851 (14.27)	609 (6.23)	< 0.001	252 (16.61)	201 (3.47)	< 0.001
DM, n (%)	396 (6.64)	274 (2.80)	< 0.001	78 (5.14)	41 (0.71)	< 0.001
Medication History, n (%)						
Antihypertensive	786 (13.18)	594 (6.07)	< 0.001	287 (18.92)	158 (2.72)	< 0.001
Antidiabetic	307 (5.15)	234 (2.39)	< 0.001	78 (5.14)	37 (0.64)	< 0.001
lipid-lowering drugs	139 (2.33)	118 (1.21)	< 0.001	37 (2.44)	26 (0.45)	< 0.001
Metabolic index						
BMI (kg/m2)	24.29 (22.68-25.96)	24.32 (15-46)	< 0.001	25.67 (18-35)	25.23 (23.54-27.17)	< 0.001
WC（cm）	86.00	94.00 (90.00-98.00)	< 0.001	75.00 (71.00-79.00)	85.00 (81.00-89.00)	< 0.001

	(81.00-89.00)					
SBP (mmHg)	120.00 (112.00-128.00)	132.00 (122.00-141.00)	< 0.001	112.00 (104.00-123.00)	134.00 (121.00-146.00)	< 0.001
DBP (mmHg)	75.00 (68.00-81.00)	84.00 (76.00-90.00)	< 0.001	68.00 (62.00-75.00)	79.00 (71.00-87.00)	< 0.001
TG (mmol/L)	1.40 (1.03-1.98)	2.60 (1.92-3.83)	< 0.001	1.02 (0.76-1.39)	2.00 (1.49-2.66)	< 0.001
TC (mmol/L)	4.99 (4.42-5.60)	5.15 (4.56-5.84)	< 0.001	4.94 (4.35-5.60)	5.22 (4.57-6.01)	< 0.001
HDLC (mmol/L)	1.25 (1.13-1.41)	1.07 (0.97-1.22)	< 0.001	1.49 (1.33-1.69)	1.39 (1.12-1.39)	< 0.001
LDLC (mmol/L)	2.91 (2.40-3.41)	2.67 (2.06-3.23)	< 0.001	2.83 (2.35-3.37)	2.88 (2.34-3.50)	0.181
Cr (μmol/L)	81.00 (74.00-89.00)	81.00 (73.00-89.00)	0.076	58.00 (53.00-64.00)	58.00 (53.00-65.00)	0.003
UA (μmol/L)	372.00 (326.00-422.00)	405.00 (355.00-459.00)	< 0.001	271.00 (239.00-309.00)	317.00 (274.00-359.00)	< 0.001
FBG (mmol/L)	5.23 (4.93-5.56)	5.84 (5.39-6.51)	< 0.001	5.11 (4.83-5.40)	5.80 (5.37-6.30)	< 0.001
HbA1c (%)	5.50 (5.30-5.70)	5.70 (5.50-6.10)	< 0.001	5.40 (5.20-5.60)	5.80 (5.37-6.30)	< 0.001
TyG	1.32 (0.99-1.67)	2.05 (1.71-2.47)	< 0.001	0.95 (0.64-1.29)	1.75 (1.48-2.09)	< 0.001
Biomarkers						
hs - CRP	1.10 (0.66-1.80)	1.61 (1.00-2.53)	< 0.001	0.88 (0.50-1.53)	1.70 (1.05-2.70)	< 0.001

Notes: MetS: Metabolic syndrome; HBP: Hypertension; DM: Diabetes mellitus; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TC: Total cholesterol; TG: Triglycerides; HDLC: High - density lipoprotein cholesterol; LDLC: Low - density lipoprotein cholesterol; FBG: Fasting blood glucose; HbA1c: Glycosylated hemoglobin; Cr: Creatinine; UA: Blood uric acid; TyG: Triglyceride - Glucose Index; hs - CRP: high - sensitivity C - reactive protein.

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Table S3. Results of multicollinearity analysis.

Covariates	All participants		Males		Females	
	Tolerance	VIF	Tolerance	VIF	Tolerance	VIF
Age (yr)	0.767	1.304	0.832	1.202	0.543	1.841
Smoking, n (%)	0.723	1.383	0.894	1.118	0.953	1.049
Drinking, n (%)	0.731	1.368	0.874	1.145	0.944	1.06
HBP, n (%)	0.982	1.018	0.987	1.014	0.964	1.037
DM, n (%)	0.391	2.559	0.395	2.531	0.376	2.66
BMI (kg/m2)	0.215	4.644	0.236	4.232	0.267	3.751
WC（cm）	0.169	5.934	0.234	4.278	0.24	4.174
SBP (mmHg)	0.25	4.002	0.268	3.731	0.217	4.607
DBP (mmHg)	0.292	3.422	0.302	3.311	0.333	3.001
TG (mmol/L)	0.126	7.95	0.12	8.329	0.178	5.618
TC (mmol/L)	0.068	14.74	0.077	13.052	0.05	20.076
HDLC (mmol/L)	0.299	3.342	0.39	2.566	0.289	3.455
LDLC (mmol/L)	0.092	10.908	0.1	10.018	0.072	13.96

Cr (μmol/L)	0.731	1.367	0.945	1.058	0.84	1.19
UA (μmol/L)	0.565	1.77	0.812	1.232	0.73	1.37
FBG (mmol/L)	0.225	4.436	0.203	4.926	0.328	3.049
HbA1c (%)	0.249	4.018	0.228	4.38	0.343	2.916
TyG	0.158	6.309	0.159	6.283	0.189	5.287

Notes: VIF: Variance Inflation Factor; BMI: Body Mass Index; WC: Waist Circumference; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HBP: Hypertension; TC: Total Cholesterol; TG: Triglycerides; HDLC: High - density Lipoprotein Cholesterol; LDLC: Low - density Lipoprotein Cholesterol; FBG: Fasting Blood Glucose; HbA1c: Glycosylated Hemoglobin; Cr: Creatinine; UA: Blood Uric Acid; HbA1c: Glycosylated Hemoglobin; TyG: Triglyceride - Glucose Index

Table S4: High - sensitivity C - reactive protein and the components of Metabolic Syndrome.

	WC		**SBP/DBP**		**FBG**		**HDLC**		**TG**	
	No	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
	n = 13396	**n =9752**	**n = 14488**	**n = 8660**	**n = 15691**	**n = 7477**	**n = 16105**	**n = 7043**	**n = 13257**	**n = 9891**
hs - CRP	0.93 (0.57-1.60)	*1.54 (0.92-2.43)	1.05 (0.60-1.80)	*1.40 (0.80-2.28)	1.07 (0.61-1.81)	*1.39 (0.80-2.30)	1.06 (0.60-1.80)	*1.43 (0.85-2.34)	0.98 (0.59-1.70)	*1.45 (0.90-2.33)

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

Abbreviations: MetS: metabolic syndrome; HBP: hypertension; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglycerides; HDLC: high-density lipoprotein cholesterol; FBG: fasting blood glucose; hs - CRP:High - sensitivity C - reactive protein

* Indicate statistically significant differences from the "No" group. (*$p < 0.05$).

Table S5: Correlation analysis between high - sensitivity C - reactive protein biomarkers and clinical parameters.

	Age	BMI	WC	SBP	DBP	TG	TC	HDLC	LDLC	FBG	METS score	Cr	UA	HbA1c	TyG	sleepquality	hs - CRP
Age	1	-0.054	0.046	0.31	0.0019	-0.11	-0.006	0.099	0.064	0.11	0.099	0.037	-0.027	0.16	-0.045	-0.07	0.041
BMI		1	0.85	0.21	0.31	0.22	0.016	-0.35	-0.089	0.093	0.54	0.065	0.33	0.091	0.33	-0.08	0.13
WC			1	0.2	0.29	0.24	-0.0069	-0.4	-0.11	0.15	0.56	0.11	0.4	0.15	0.37	-0.098	0.16
SBP				1	0.73	0.084	0.1	-0.017	0.046	0.12	0.41	0.091	0.1	0.11	0.15	-0.061	0.058
DBP					1	0.16	0.11	-0.12	0.014	0.07	0.083	0.017	0.19	0.051	0.22	-0.049	0.04
TG						1	0.36	-0.32	0.14	0.2	0.043	-0.038	0.23	0.13	0.81	-0.012	0.11
TC							1	0.28	0.072	0.044	-0.043	-0.03	0.019	0.045	0.34	0.032	0.094
HDLC								1	-0.3	-0.13	-0.043	-0.1	-0.31	-0.11	-0.41	0.069	-0.11
LDLC									1	0.2	0.3	-0.03	-	0.045	-0.2	0.029	0.045

													0.097				
FBG										1	-0.07	-0.038	-0.052	0.18	0.5	-0.053	0.072
METS score											1	0.027	0.26	0.87	0.6	-0.033	0.18
Cr												1	0.29	-0.067	0.19	-0.092	-0.0027
UA													1	-0.097	0.25	-0.038	0.093
HbA1c														1	0.42	-0.014	0.13
TyG															1	-0.026	0.16
sleepquality																1	-0.023
hs - CRP																	1

Abbreviations: MetS: metabolic syndrome; HBP: hypertension; WC: waist; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglycerides; HDLC: high - density lipoprotein cholesterol; FBG: fasting blood glucose; hs - CRP: High - sensitivity C - reactive protein

Table S6: Baseline characteristics of participants who have consistently been negative for metabolic syndrome and those who have transitioned from being negative for metabolic syndrome to being positive for metabolic syndrome.

	All participants		**P value**	**Males**		**P value**	**Females**		***P* value**
	Stable MetS-negative（n = 442)	**Transition to MetS-positive (89)**		**Stable MetS-negative (325)**	**Transition to MetS-positive (76)**		**Stable MetS-negative (117)**	**Transition to MetS-positive (13)**	
Age (yr)	44 (40,50)	49 (45,54)	0.239	52 (45,56)	50 (45,55)	0.061	47 (43,52)	45 (43,50.25)	0.887
Smoking, n (%)	325 (73.7)	76 (85.4)	< 0.001						
Drinking, n (%)	95 (21.54)	30 (33.7)	< 0.001	91 (28)	30 (39.47)	< 0.001	4 (4.45)	0 (0)	0.206
HBP, n (%)	149 (33.79)	34 (38.2)	0.091	139 (39.7)	33 (43.4)	0.536	10 (8.62)	1 (7.69)	0.766
DM, n (%)	26 (5.90)	9 (10.1)	0.003	24 (7.38)	7 (9.21)	0.137	2 (1.72)	2 (15.4)	< 0.001
Age (yr)	13 (2.95)	5 (5.62)	0.03	11 (3.38)	4 (5.26)	0.178	2 (1.72)	1 (7.69)	0.025
Medication History, n (%)									
Antihypertensive	29 (6.56)	10 (11.24)	0.195	9 (2.77)	8 (10.53)	0.01	20 (17.09)	2 (15.38)	0.481
Antidiabeti	9 (2.04)	5 (5.62)	0.026	8 (2.46)	4 (5.26)	0.041	1 (0.85)	1 (7.69)	1

c									
lipid-lowering drugs	9 (2.04)	2 (2.25)	0.727	9 (2.77)	2 (2.63)	0.75	0 (0)	7 (53.85)	< 0.001
Metabolic Index									
BMI (kg/m2)	21.(20.09,23.52)	24.94 (23.58,26.94)	< 0.001	24.13 (22.61,25.67)	25.06 (23.90,27.20)	< 0.001	21.78 (20.16,23.22)	23.78 (21.50,23.77)	< 0.001
WC （cm）	77 (71,83)	89 (84,92)	< 0.001	85 (81,89)	90 (86,94)	< 0.001	74 (70,78)	77 (75,81)	< 0.001
SBP (mmHg)	108 (101,116)	125 (117,134.5)	< 0.001	118 (110,126.5)	124 (116,133)	< 0.001	111 (103,120.75)	132.5 (117.75,139.5)	< 0.001
DBP (mmHg)	65 (65,72)	80(71,87)	< 0.001	73 (67,81)	80 (71,87)	< 0.001	67 (62,73)	84 (75,90.25)	< 0.001
TG (mmol/L)	0.88 (0.69,1.18)	1.72 (1.19,2.22)	< 0.001	1.28 (0.92,1.75)	1.73 (1.25,2.25)	< 0.001	1 (0.77,1.37)	1.47 (0.96,1.99)	< 0.001
TC (mmol/L)	4.42 (3.88,4.96)	5.03 (4.47，5.55)	0.4	4.95 (4.41,5.49)	4.98 (4.4 5.46)	0.979	4.98 (4.43,5.69)	5.41 (4.92,6.01)	0.006
HDLC (mmol/L)	1.19 (1.07,1.33)	1.19 (1.07,1.35)	< 0.001	1.28 (1.15,1.42)	1.17 (1.06,1.31)	< 0.001	1.54 (1.36,1.73)	1.37 (1.19,1.48)	< 0.001

LDLC (mmol/L)	2.41 (2.00,2.95)	2.93 (2.41,3.41)	0.917	2.97 (2.43,3.43)	2.89 (2.33,3.37)	0.179	2.91 (2.36,3.51)	3.27 (2.83,3.83)	0.001
Cr (μmol/L)	66 (57,77)	80 (68.5,89)	0.107	82 (75,90)	82 (74,91)	0.448	60 (55,65)	56.5 (51,64.25)	0.033
UA (μmol/L)	295 (250,353)	387 (339.5,445.5)	< 0.001	377 (333,422)	406 (358,452)	< 0.001	274 (240.25,317)	271.5 (235.75,325)	0.822
FBG (mmol/L)	4.93 (4.65,5.22)	5.52 (5.11,6.12)	< 0.001	5.27 (4.98,5.62)	5.54 (5.12,6.15)	< 0.001	5.08 (4.82,5.33)	5.29 (4.87,5.94)	0.147
HbA1c (%)	5.3 (5.1,5.5)	5.6 (5.4,6)	< 0.001	5.5 (5.3,5.7)	5.6 (5.4,6)	< 0.001	5.4 (5.2,5.6)	5.6 (5.48,5.9)	< 0.001
TyG	0.82 (0.57,1.14)	1.54 (1.24,1.80)	< 0.001	1.23 (0.91,1.91)	1.58 (1.28,1.82)	< 0.001	0.92 (0.65,1.28)	1.39 (1.02,1.66)	< 0.001
Biomarkers									
hs - CRP	0.6 (0.4,0.9)	1.27 (0.8,2.49)	< 0.001	0.97 (0.6,1.57)	1.25 (0.8,2.47)	< 0.001	0.77 (0.5,1.38)	1.46 (0.8,2.57)	< 0.001

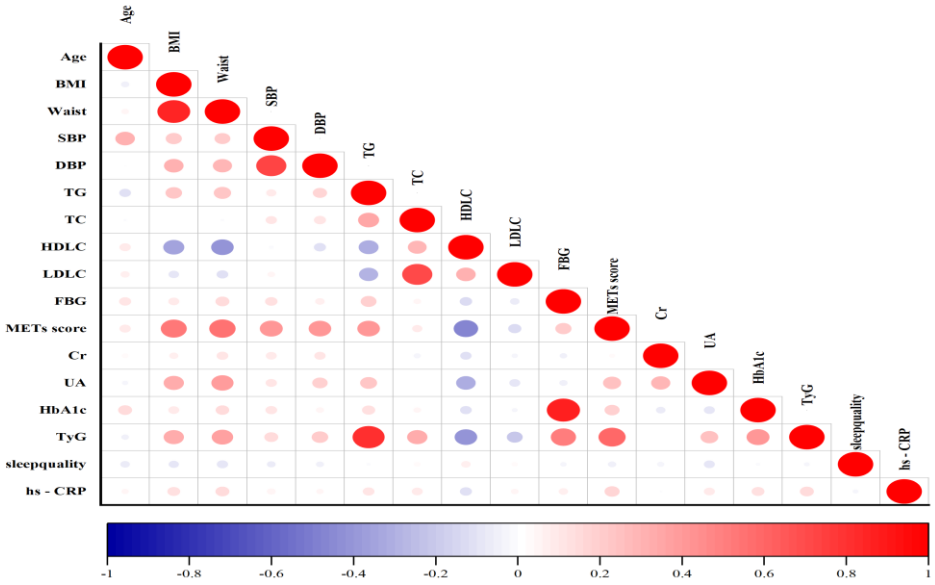

Figure S1: Spearman correlation matrix of hs-CRP biomarker and clinical variables.

Abbreviations: MetS: metabolic syndrome; HBP: hypertension; WC: waist; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglycerides; HDLC: high - density lipoprotein cholesterol; FBG: fasting blood glucose; hs - CRP:High - sensitivity C - reactive protein

DISCUSSION

The direct relationship between hs-CRP and MetS has not been extensively investigated, and the underlying mechanisms remain poorly understood. At present, there are few cohort studies on metabolic phenotypic transformation. In this study, the potential correlation between hs-CRP and MetS was thoroughly examined for the first time 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 to help elucidate the pathophysiological mechanisms of MetS. Further analysis revealed that, compared to females, males were more susceptible to unfavorable metabolic status. Logistic regression analysis demonstrated a significant correlation between hs-CRP levels and the transition to MetS in all 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. It encompasses a set of cardiometabolic risk factors that increase the likelihood of developing ASCVD and T2DM. 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 [27,28].

A novel hypothesis posits that adipose tissue dysfunction may contribute to MetS, with persistent low-grade systemic inflammation being one of its key features [29-32], closely associated with insulin resistance [33,34]. 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 [35]. Therefore, understanding the interaction between hs-CRP and MetS may aid in the development of novel diagnostic, therapeutic, and management strategies for MetS.

This study demonstrated that hs-CRP levels varied significantly between individuals with MetS and those without the condition across all 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. H et al. [36] found a relatively large intersection of hypertension and elevated hs-CRP in the metabolically impaired group over time, conjecting 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 [37]. Hs-CRP is an acute-phase protein synthesized and secreted by hepatocytes, promoting the release of pro-inflammatory cytokines during the inflammatory response [38], and interacting with Fc receptors. When an infection or injury occurs, hs-CRP levels in the serum can rise rapidly, often preceding changes in peripheral blood leukocyte count and neutrophil percentage. As a result, CRP has been widely used as a marker to monitor inflammatory states [38].

Recently, hs-CRP has been identified as an independent predictor of future cardiovascular events in individuals with MetS and has become increasingly associated with the syndrome [39]. Inflammation is thought to play a major role in several components of MetS, including insulin resistance [40,41] and obesity [40-43], 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, as determined by MRI, showed a positive correlation ($r = -0.63$, $p = 0.028$) in a sample of 14 healthy females [44]. In healthy individuals with normal weight status, abdominal adiposity was similarly linked to a significant increase in CRP levels, regardless of BMI ($p < 0.001$) [45]. Adipose tissue also produces CRP, particularly in individuals with visceral fat accumulation, where levels are markedly higher, increasing the risk of insulin resistance, T2DM, and ASCVD. The accumulation of free fatty acids in adipose tissue, which promotes the release of cytokines and increases CRP production, may strongly link abdominal obesity with elevated CRP levels [46]. Studies have shown that high CRP levels can reduce Nitric Oxide (NO) production, leading to vasoconstriction and endothelial dysfunction. Furthermore, CRP may promote the development of atherosclerosis [47].

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 [48]. Another explanation is that vascular inflammation induced by high blood pressure increases CRP levels [49]. Elevated CRP is widely recognized as being associated with cardiovascular disease, and it can serve as either a cause or an effect of hypertension. In the Women's Health Study (WHS), CRP was identified as a significant independent predictor of hypertension development [30,50]. In risk factor-adjusted models, the mean CRP level in women with blood pressure < 120/< 75 mmHg was 1.33 mg/L, controlling for other cardiovascular risk factors. In contrast, the mean CRP level in women with blood pressure ≥ 160/≥ 95 mmHg was 1.84 mg/L.

In a large population-based cohort from the Women's Health Study (WHS), Ridker et al. [50] evaluated the potential association between CRP, MetS, and cardiovascular events. In this 8-year prospective follow-up study involving 14,719 women, the authors found that patients with MetS and hs-CRP > 3 mg/L had a significantly higher age-adjusted risk of future cardiovascular events. Additionally, the investigators reported that CRP provided additional prognostic information regarding the risk of subsequent cardiovascular events at all severity levels of MetS and was incorporated into the Framingham risk score. As a result, hs-CRP has been proposed as an additional clinical criterion for MetS [30].

Data from cross-sectional studies show that the levels of hs-CRP exhibit a significant 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[51]. Some studies have found that, compared with the group with low CRP levels and without diabetes (CRPlow/non-DM), the group with high CRP levels and diabetes (CRPhigh/DM) exhibits a significantly accelerated biological aging process. This accelerated aging phenotype not only significantly 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 [52]. In addition, the findings from the cohort study conducted by Wang et al.[53] indicate that participants in the highest quartile of hs-CRP

levels exhibit a significantly accelerated rate of cognitive function decline, and the risk of developing cognitive impairment is times higher compared to other groups. The above-mentioned studies have revealed the crucial role of the inflammatory response mediated by 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. During the exploration, particular attention was paid to the potential modulating effects of age and gender, providing a new perspective for understanding the complex relationship between this biomarker 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 mechanisms underlying the relationship between CRP and MetS. It also offers a new perspective on the diagnosis and treatment of diseases associated with MetS.
This study has limitations in multiple aspects, which may affect the generalizability of the results and the reliability of the conclusions. The research participants mainly came from the health management centers of tertiary hospitals in some regions of China and did not cover a broader general population.

The insufficient representativeness of the sample limits the generalizability of the results. The observation duration of the state transition of MetS is relatively short, making it difficult to capture the long-term dynamic changes in the metabolic state. In terms of the control of confounding factors, although multiple metabolic and lifestyle variables have been adjusted, factors such as dietary structure and physical activity that have not been recorded in detail may still produce residual confounding effects. In view of the above limitations, future studies should extend the follow-up time, include a diverse population, and combine multi-omics technologies such as genomics and metabolomics to deeply reveal the specific mechanism of action of hs-CRP in MetS, explore the biological basis of gender differences, and provide more comprehensive evidence for precise interventions.

CONCLUSION

This study identifies hs-CRP as a male-specific predictor of 6-year MetS onset, exhibiting significantly greater sex-based predictive disparity compared to females. Sex-stratified mechanistic analysis further uncovers the dominant role of male inflammatory pathways in MetS pathogenesis, offering critical evidence to advance sex-tailored metabolic prevention and the clinical translation of inflammation-driven mechanisms.

DECLARATION

Ethics Approval and Consent to Participate

The study protocol and consent forms were approved by the Ethics Committee of the Third Xiangya Hospital (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.

Consent for Publication

All authors agree to publish this review in your esteemed journal.

Availability of Data and Materials

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

Competing Interests

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 review.

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Authors' Contributions

YX, XZ and YQ designed this study. YX, XZ, XM, JW, BS, SY, YL, LC, YG, XL, HG and YQ reviewed and revised the manuscript. YX, XZ and JW drafted the original manuscript. YX, XZ, XM and YQ designed and completed the Figures and tables. All authors approved the final manuscript submission and agreed to be responsible for all aspects of the work.

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