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Association Between High-Sensitivity C-Reactive Protein Trajectories and the Incidence of Metabolic Syndrome:A Retrospective Cohort Study

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Purpose: Understanding the role of systemic inflammation in the development of Metabolic Syndrome (MetS) is crucial for identifying individuals at a higher risk of this cluster of conditions that increase the risk of heart disease, stroke, and diabetes.

Patients and Methods: A retrospective cohort study was conducted with 4,312 participants who were free from MetS at the study's onset and had high-sensitivity C-reactive protein (hsCRP) levels measured. Latent class trajectory modeling was utilized to identify distinct hsCRP trajectory patterns. Multivariable regression and proportional hazards analyses were employed to evaluate the predictive value of hsCRP trajectories for the development of MetS.

Results: During the 1.63-year follow-up period, 1,308 participants developed metabolic syndrome (MetS). Individuals with high hsCRP levels exhibited a significantly increased risk of developing MetS compared to those with low hsCRP levels (HR = 1.062, 95% CI 1.103–1.113). The hsCRP trajectory analysis identified three distinct groups: low-stable, increasing, and decreasing. The decreasing and increasing hsCRP trajectory groups demonstrated a 1.408-fold (95% CI 1.115–1.779) and a 1.618-fold (95% CI 1.288–2.033) increased risk of MetS, respectively.

Conclusion: This study suggests that participants with higher baseline hsCRP levels and increasing hsCRP trajectories are associated with a progression toward MetS. Long-term hsCRP trajectories may serve as useful tools for identifying individuals at higher risk of MetS who could benefit from targeted preventive and therapeutic interventions.

Keywords: high-sensitivity C-reactive protein, metabolic syndrome, trajectory analysis, retrospective cohort study, risk prediction

Introduction

Metabolic syndrome (MetS) is a cluster of interconnected metabolic conditions, including central obesity, dyslipidemia, hypertension, and hyperglycemia, that collectively elevate the risk of cardiovascular disease, stroke, and type 2 diabetes mellitus.[1] The prevalence of MetS has been rising globally, driven by lifestyle factors such as poor diet, physical inactivity, and increasing rates of obesity.[1,2] In China, this trend is reflected in the high and increasing prevalence rates. According to recent studies, the prevalence of MetS among Chinese adults has reached 33.9%, estimating that 450 million people in China are affected by MetS.[3] Given its significant public health implications, understanding the underlying mechanisms and identifying predictive biomarkers for MetS are of paramount importance.

High-sensitivity C-reactive protein (hsCRP), an acute-phase protein produced by the liver in response to inflammatory stimuli, has emerged as a robust biomarker for systemic inflammation.[4] This inflammatory response is intricately linked to key components of metabolic syndrome (MetS), including insulin resistance and central obesity.[5] A multitude of cohort studies have established a direct correlation between elevated CRP levels and the development of MetS, as well as the subsequent risk

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of cardiovascular diseases.[6,7] Notably, studies conducted across mainland Asia and Europe have found that higher hsCRP levels are associated with a heightened risk of developing MetS among adults from China,[8] Japan,[9] Korea.[10] Despite extensive research, there remains a need for longitudinal studies that explore how changes in hsCRP levels over time relate to the risk of developing MetS. Trajectory analysis, a statistical technique that identifies distinct patterns of change within a population, has been widely applied to various health outcomes, including depressive symptoms, peripheral artery disease, and arterial stiffness[11,12]. This method provides a powerful approach to uncovering the dynamic nature of high-sensitivity C-reactive protein (hsCRP) and its association with the risk of metabolic syndrome (MetS).

This retrospective cohort study aims to fill this gap by characterizing hsCRP trajectories in individuals without MetS at baseline and evaluating the predictive value of these trajectories for the incidence of MetS. Our study aimed to explore the associations between baseline levels and the trajectory of the hsCRP and MetS progression through a single-center, longitudinal cohort study of the Chinese population.

Methods

Study Design and Setting

The foundational clinical data for this analysis were obtained from individuals undergoing health assessments at the Health Promotion Center of Sir Run Run Shaw Hospital, Zhejiang University, located in Hangzhou, China. The main contents included the chief complaint, current disease, previous illness, personal history, and physical examination. Alcohol consumption was classified as current (>6 months on a daily basis) or non-current drinker. Smoking status was classified as current (>6 months on a daily basis) or non-current smoker. Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, or the use of antihypertensive medications.[13] Diabetes was defined according to American Diabetes Association (ADA) criteria: fasting blood glucose (FBG) ≥7.0 mmol/L, glycated hemoglobin (HbA1c) ≥6.5%, or the use of antidiabetic medications.[14] Weight, height, blood pressure (BP), and waist circumference (WC) were measured by trained nurses. An individual's body mass index (BMI) was determined by the division of their weight (kg) by their height squared (m2). Total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), fasting blood glucose (FBG). The data spans the period from January 2017 to December 2023. Initially, a cohort of 58,994 individuals was considered. However, after applying exclusion criteria, the following groups were excluded: (1) hsCRP value > 10 mg/L (n = 5,411); (2) individuals without documented history of diabetes, hypertension, hyperlipidemia, systolic blood pressure, diastolic blood pressure, triglycerides, high-density lipoprotein cholesterol, and fasting glucose (n = 1,183); (3) individuals with only one general health check (n = 25,092); and (4) individuals meeting the MetS diagnostic criteria (n = 6,191). These exclusions resulted in a final sample size of 4,312 individuals for analysis, as depicted in Figure 1

The Exposure and Outcome Variable Definition

Characteristics and Definition

Metabolic Syndrome

In this study, MetS was defined according to the International Diabetes Federation (IDF) criteria. According to the IDF definition,[15] an individual is considered to have MetS if they have central obesity (waist circumference ≥90 cm for men and ≥80 cm for women) plus two or more of the following four factors:

1. Raised triglyceride (TG) concentration: ≥150 mg/dL (1.7 mmol/L) or receiving specific treatment for this lipid abnormality.
2. Reduced high-density lipoprotein cholesterol (HDL-C) concentration: <1.03 mmol/L (40 mg/dL) in males and <1.29 mmol/L (50 mg/dL) in females or receiving specific treatment for this lipid abnormality.
3. Raised fasting blood glucose (FBG) concentration: ≥100 mg/dL (5.6 mmol/L) or previously diagnosed with type 2 diabetes mellitus (T2DM).
4. Raised blood pressure: systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure (DBP) ≥85 mmHg or receiving specific treatment for previously diagnosed hypertension (HTN).

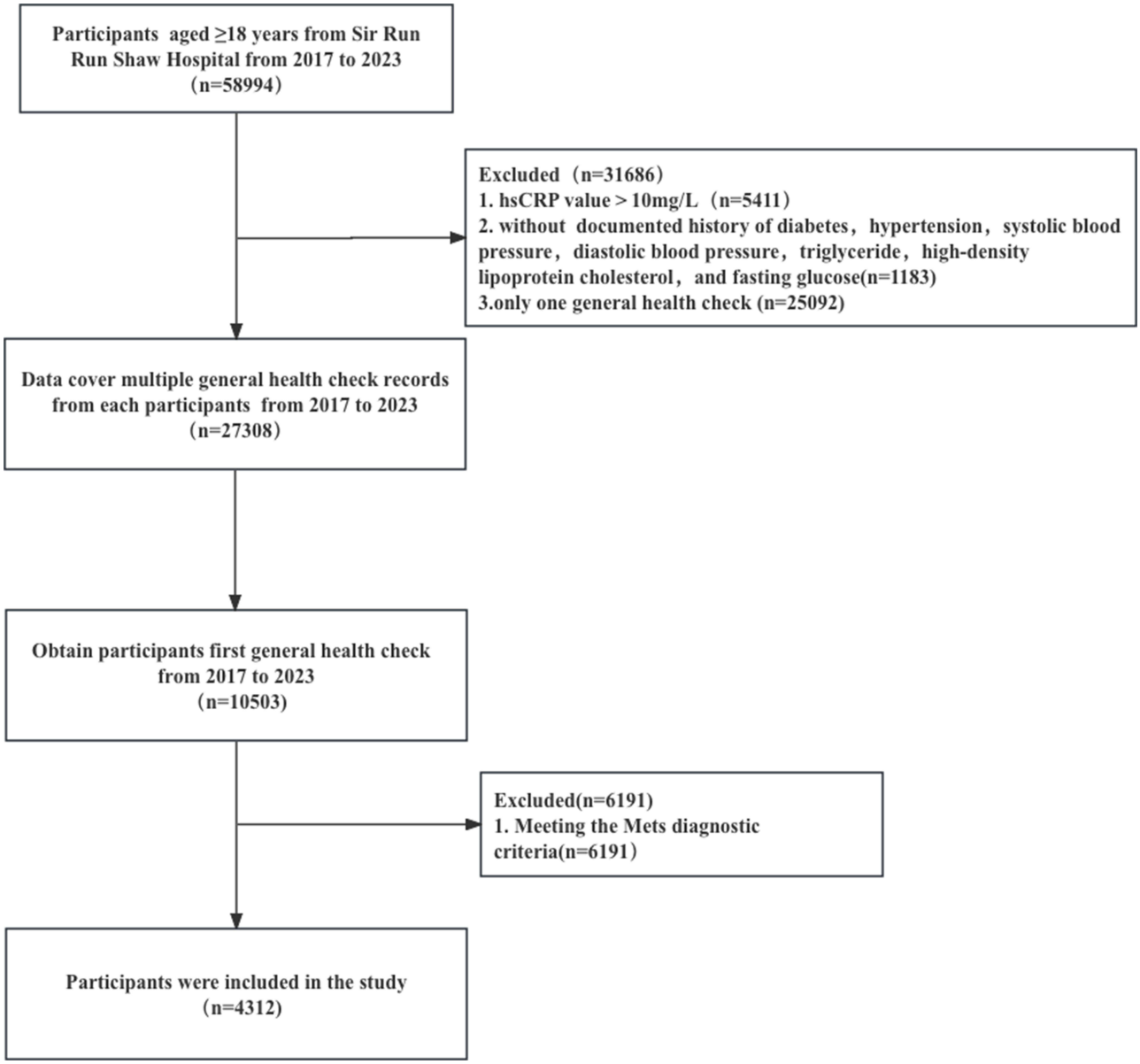

Figure 1 Flowchart of current study.

High-Sensitivity C-Reactive Protein

During the first visit, hsCRP levels were measured from fasting blood serum samples using an immunoturbidimetric method. Participants with an hsCRP value >10 mg/L were excluded as such values may indicate an active infection. Therefore, the included hsCRP values ranged from 0.1 to 10.0 mg/L. Based on these values, we categorized hsCRP levels according to the CDC and AHA guidelines as low (<1.0 mg/L), moderate (1.0–3.0 mg/L), or high (>3.0 mg/L).[16]

Statistical Analyses

A comprehensive statistical analysis was conducted to investigate the relationship between the hsCRP index and Metabolic Syndrome (MetS) progression. Descriptive statistics were utilized to summarize baseline hsCRP index quartiles. For normally distributed data, the mean ± standard deviation were presented; for skewed distributions, medians with interquartile ranges (IQRs) were used; and for categorical variables, frequencies with percentages (%) were reported. Mann–Whitney *U*-tests or Kruskal–Wallis H-tests were employed to compare continuous variables across groups, while the chi-squared test or Fisher's exact test was used for categorical variables.

The Cox proportional hazards regression model was utilized to investigate the relationship between baseline hsCRP index quartiles, hsCRP index per standard deviation change, and the progression of MetS, while considering covariates such as age, sex, BMI, and alcohol consumption.

To discern the trajectories of hsCRP over time, we employed latent class trajectory models (LCTMs), a form of finite mixture modeling that identifies distinct subgroups of individuals with similar hsCRP progressions. The optimal number of trajectories was determined using the Bayesian Information Criterion (BIC), selecting the model with the lowest BIC value. To ensure robust classification, posterior probabilities ≥0.70 were required for each group, and each group had to represent at least 2% of the population.[11] The identified trajectories were then labeled based on their graphical patterns, such as "low-stable", "increasing-stable", or "decreasing-stable", providing insights into different hsCRP evolution paths over time.

All statistical analyses were performed using IBM SPSS software (version 23.0, SPSS Inc., Chicago, IL) and RStudio (version 2022.02.3, Boston, MA) along with associated packages. Statistical significance was defined as two-tailed P values < 0.05.

Results

Baseline Characteristics of Study Participants

The study population consisted of 4,312 individuals categorized into three hsCRP index groups: low (n=3,189), moderate (n=973), and high (n=150), as detailed in Table 1. Mean hsCRP levels were 0.85±1.00 mg/L overall, with the low group having significantly lower levels (0.44 ± 0.22 mg/L) compared to the moderate (1.57±0.54 mg/L) and high (4.90 ±1.60 mg/L) groups ($p < 0.001$). Over a median follow-up duration of 1.63 years follow-up, 1308 participants (30%) developed MetS. Figure 2 demonstrates that illustrates the cumulative incidence of individual MetS components across different hsCRP categories, showing higher incidences of MetS in participants with elevated hsCRP levels. Figure 3 depicts the cumulative incidence of the total number of Metabolic Syndrome (MetS) components per individual, stratified by hsCRP levels, highlighting a clear association between elevated hsCRP levels and a higher likelihood of developing multiple MetS components.

Table 1 Baseline Characteristics of Study Participants According to hsCRP Index Group

Characteristic	Overall, N = 4,312	Low, N = 3,189	Moderate, N = 973	High, N = 150	p-value
hsCRP	0.85 ± 1.00	0.44 ± 0.22	1.57 ± 0.54	4.90 ± 1.60	<0.001
Age (years)	46.2 ± 10.6	46.1 ± 10.3	46.2 ± 10.8	49.1 ± 13.0	0.078
Sex					<0.001
F	1,433 (33%)	1,136 (36%)	257 (26%)	40 (27%)	
M	2,879 (67%)	2,053 (64%)	716 (74%)	110 (73%)	
SBP (mmHg)	117 ± 15	117 ± 15	118 ± 15	118 ± 15	0.012
DBP (mmHg)	70 ± 10	70 ± 10	71 ± 11	70 ± 10	0.003
WC(cm)	78 ± 8	78 ± 8	81 ± 7	80 ± 7	<0.001
Current smoker, %	543 (13%)	381 (12%)	136 (14%)	26 (17%)	0.051
Current alcohol use, %	1,105 (26%)	797 (25%)	279 (29%)	29 (19%)	0.014
BMI	22.43 ± 2.26	22.20 ± 2.26	23.14 ± 2.08	22.84 ± 2.31	<0.001
Diabetes, %	43 (1.0%)	28 (0.9%)	14 (1.4%)	1 (0.7%)	0.3
Hypertension, %	278 (6.4%)	202 (6.3%)	62 (6.4%)	14 (9.3%)	0.3
TG (mg/dL)	1.14 ± 0.53	1.10 ± 0.51	1.26 ± 0.58	1.21 ± 0.49	<0.001
Cholesterol (mg/dL)	4.98 ± 0.91	4.94 ± 0.90	5.11 ± 0.93	4.94 ± 0.88	<0.001
HDL-C (mg/dL)	1.40 ± 0.30	1.42 ± 0.30	1.33 ± 0.28	1.27 ± 0.24	<0.001
LDL-C (mg/dL)	2.99 ± 0.75	2.95 ± 0.74	3.14 ± 0.77	3.02 ± 0.75	<0.001
FBG (mg/dL)	5.04 ± 0.58	5.02 ± 0.51	5.09 ± 0.77	5.11 ± 0.41	0.006

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; hs-CRP, high-sensitive C-reactive protein; TG, triglyceride; WC, waist circumference.

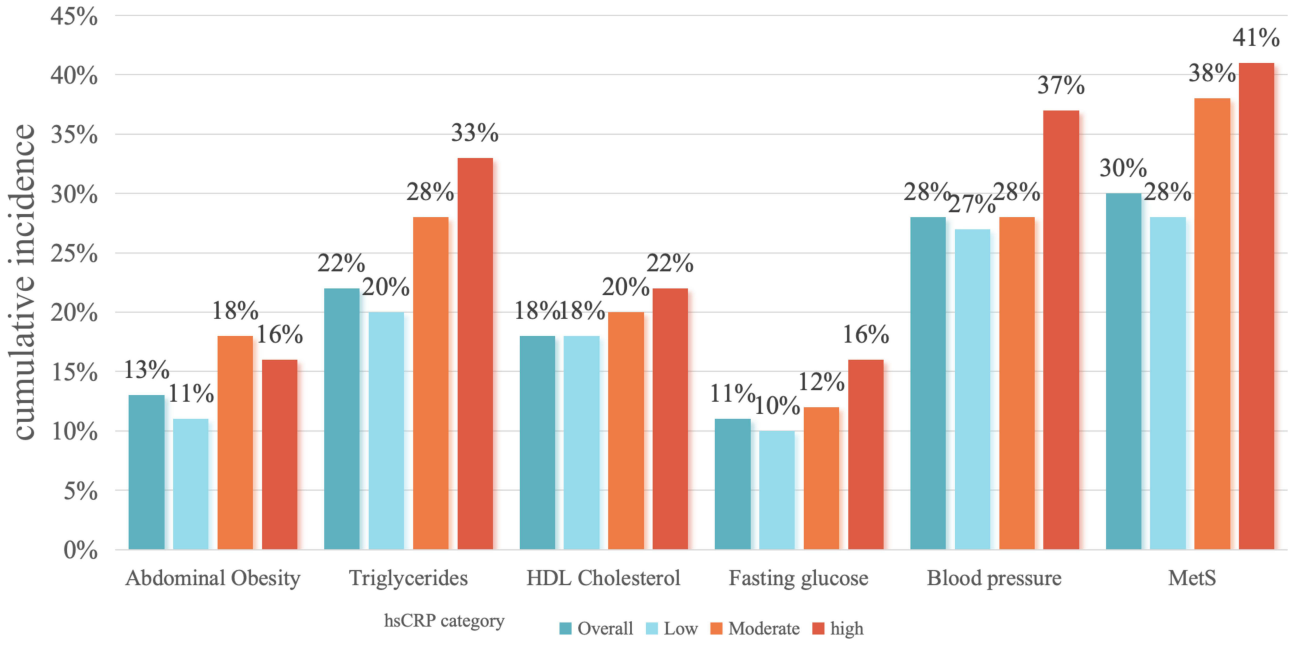

Figure 2 Cumulative incidence of individual MetS components by hsCRP category.

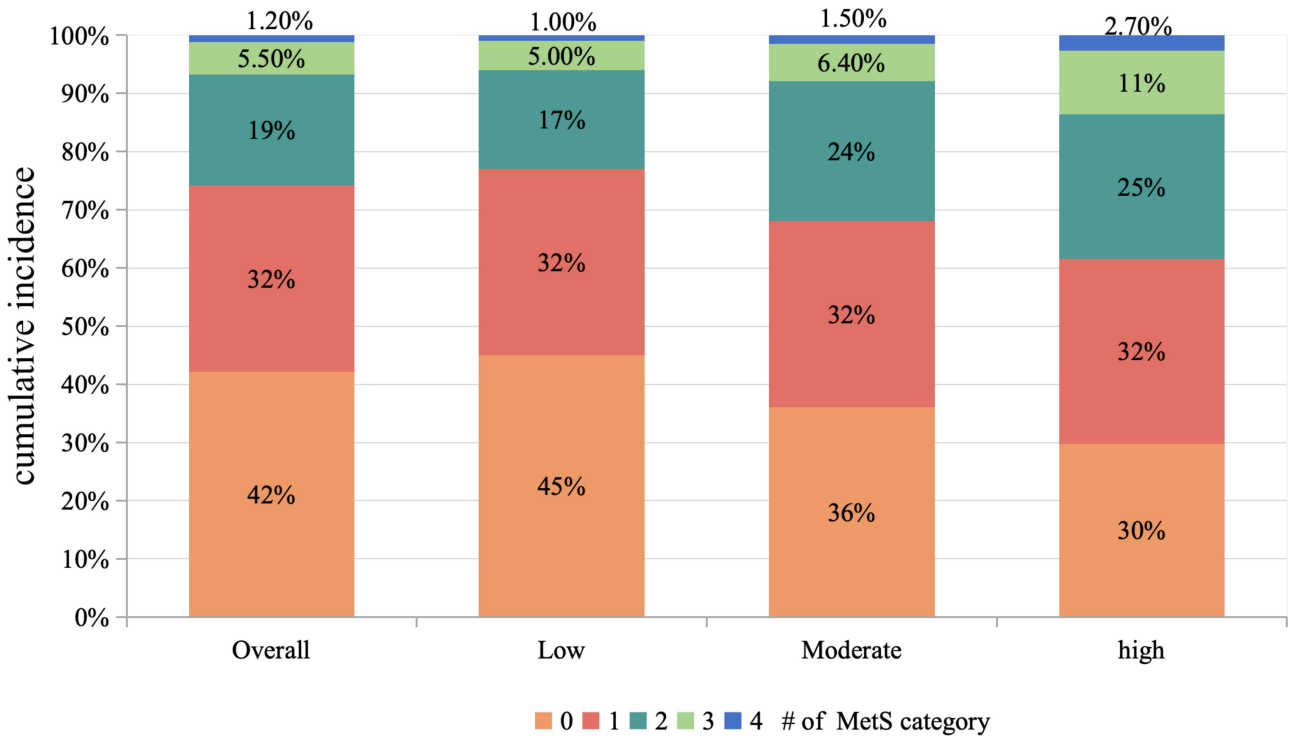

Figure 3 Cumulative incidence of the number of MetS components by hsCRP category.

Associations Between Baseline hsCRP Level and Metabolic Syndrome Progression

Metabolic Syndrome (MetS) progression showed a significant association with elevated hsCRP levels. The unadjusted hazard ratios (HRs) for the moderate and high hsCRP groups were 1.432 (95% CI 1.268, 1.618) and 1.551 (95% CI 1.197, 2.011), respectively (both $p < 0.001$). After adjusting for age, BMI, sex, current smoking, and current alcohol use, the HRs for the Moderate hsCRP groups were attenuated but remained significant, indicating a positive relationship

Table 2 Hazard Ratios (95% Confidence Intervals) of MetS Progression by Baseline hsCRP Levels

hsCRP Category	MetS (N)	Unadjusted HR (95% CI)	*p*	Model 1 HR (95% CI)	*p*	Model 2 HR (95% CI)	*p*
Low hsCRP	882/3189	Reference		Reference		Reference	
Moderate hsCRP	365/973	1.432(1.268, 1.618)	<0.001	1.142(1.009, 1.293)	0.036	1.133(1.0003, 1.282)	0.049
High hsCRP	61/150	1.551(1.197, 2.011)	<0.001	1.329 (1.024, 1.723)	0.032	1.295(0.9981, 1.681)	0.051
Per 1 SD	1,308/4,312	1.131(1.084,1.181)	<0.001	1.068 (1.019,1.119)	0.005	1.062(1.013, 1.113)	0.011

Notes: Model 1: Adjusted for age and BMI; Model 2: Adjusted for age, BMI, sex, Current smoker, and Current alcohol use.

between hsCRP levels and the risk of MetS progression, as demonstrated in Table 2. Figure 4 stratified by hsCRP levels, displays Kaplan–Meier survival curves for MetS progression (Log rank test, $P < 0.05$), highlighting that individuals with higher hsCRP levels experience a significantly shorter time to progression to MetS.

Baseline Characteristics According to hsCRP Trajectories

Following thorough evaluation utilizing model-adequacy criteria and interpretability guidelines, three clearly defined trajectories of the hsCRP were identified. Figure 5 displays the finalized models of latent class trajectory delineating the low-stable (n=3,961), decreasing(n=1,65), and increasing (n=1,86). Table 3 offers a comprehensive overview of the initial demographic and clinical traits pertaining to the hsCRP trajectories. Mean hsCRP levels varied significantly among the trajectory groups, with the low-stable group having the lowest levels (0.67 ± 0.55mg/L) and the decreasing-stable group having the highest levels (4.43 ± 1.97 mg/L) ($P < 0.001$).

The Relationship Between hsCRP Trajectories and MetS Progression

The risk of MetS progression was significantly higher for participants in the decreasing-stable and increasing-stable hsCRP trajectory groups compared to the low-stable group. Specifically, the unadjusted hazard ratios (HRs) were 1.663 (95% CI: 1.318–2.097) for the decreasing-stable group and 1.900 (95% CI: 1.514–2.384) for the increasing-stable group (both $p < 0.001$). After adjusting for potential confounders, the HRs remained statistically significant, with the increasing-stable group showing the highest risk of MetS progression (adjusted HR: 1.618, 95% CI: 1.288–2.033, $p<$

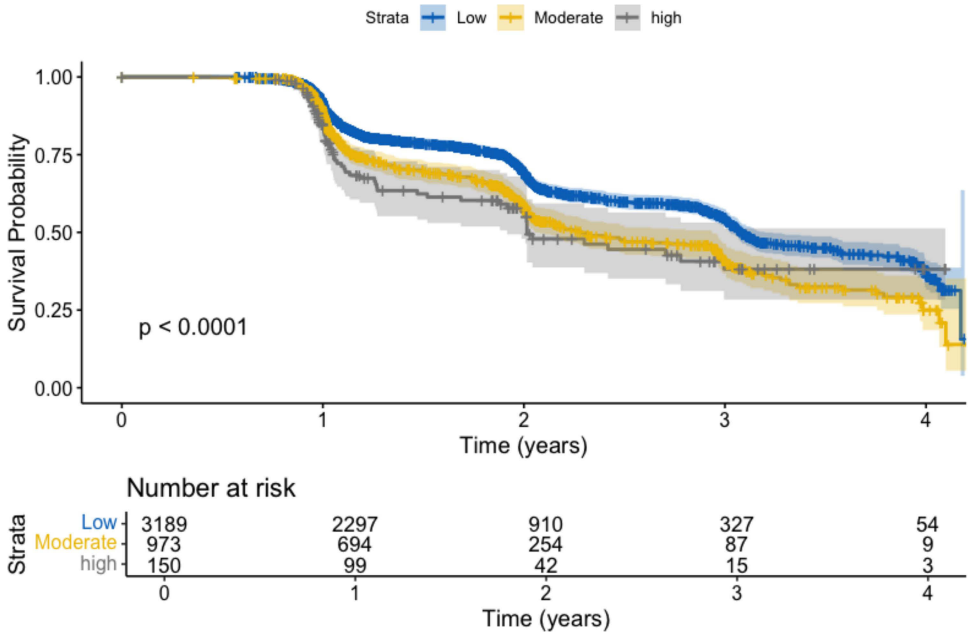

Figure 4 Kaplan-Meier survival analysis for MetS progression stratified by hsCRP category.

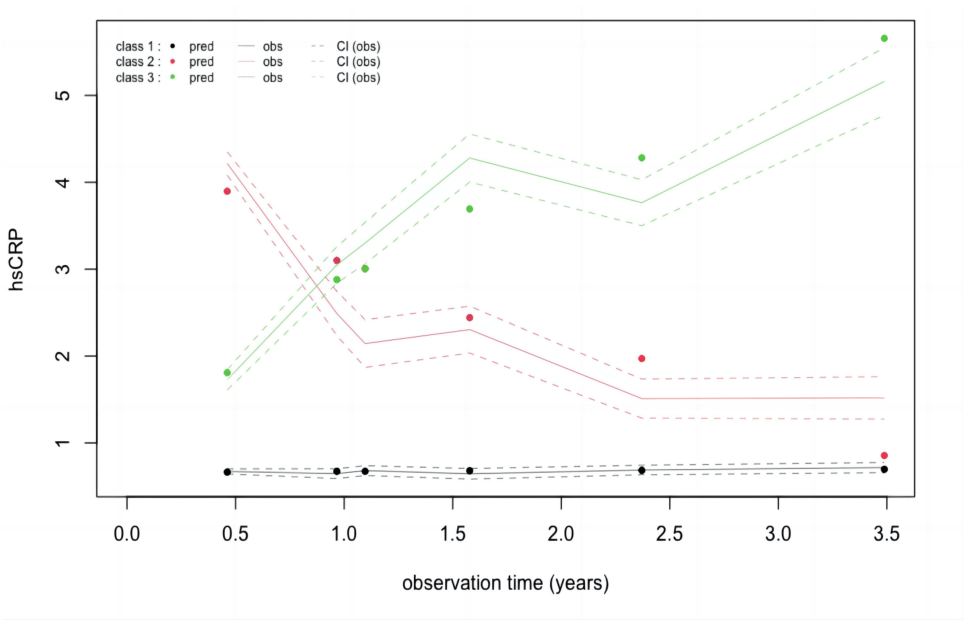

Figure 5 Trajectories of Over Time by hsCRP class (class1=low-stable, class2=decreasing, class3=increasing).

0.001). These results are summarized and presented in Table 4. Moreover, Figure 6 displays the Kaplan–Meier survival curves for MetS Progression, with statistical significance determined by the Log rank test ($P < 0.05$).

Discussion

In this longitudinal cohort study derived from general health check-ups, we first examined the relationship between baseline and longitudinal trajectories of the hsCRP index and MetS progression. A higher baseline hsCRP index was

Table 3 Baseline Characteristics of Study Participants Grouped by Trajectories of the hsCRP

Characteristic	Overall, N = 4,312	Low-stable, N = 3,961	Decreasing, N = 165	Increasing, N = 186	p-value
hsCRP	0.85 ± 1.00	0.67 ± 0.55	4.43 ± 1.97	1.47 ± 0.89	<0.001
Age (years)	46.2 ± 10.6	46.1 ± 10.3	49.6 ± 12.9	45.0 ± 11.9	0.002
Sex					<0.001
F	1,433 (33%)	1,349 (34%)	41 (25%)	43 (23%)	
M	2,879 (67%)	2,612 (66%)	124 (75%)	143 (77%)	
SBP (mmHg)	117 ± 15	117 ± 15	119 ± 15	117 ± 15	0.2
DBP (mmHg)	70 ± 10	70 ± 10	70 ± 9	70 ± 10	0.6
WC(cm)	79 ± 8	79 ± 9	81 ± 7	83 ± 7	<0.001
Current smoker, %	543 (13%)	483 (12%)	28 (17%)	32 (17%)	0.03
Current alcohol use, %	1,105 (26%)	1,006 (25%)	33 (20%)	66 (35%)	0.002
BMI	22.43 ± 2.26	22.38 ± 2.25	22.92 ± 2.32	23.18 ± 2.16	<0.001
Diabetes, %	43 (1.0%)	40 (1.0%)	2 (1.2%)	1 (0.5%)	0.8
Hypertension, %	278 (6.4%)	246 (6.2%)	17 (10%)	15 (8.1%)	0.073
TG (mg/dL)	1.14 ± 0.53	1.13 ± 0.52	1.23 ± 0.48	1.32 ± 0.69	<0.001
Cholesterol (mg/dL)	4.98 ± 0.91	4.96 ± 0.91	5.01 ± 0.93	5.26 ± 0.93	<0.001
HDL-C (mg/dL)	1.40 ± 0.30	1.40 ± 0.30	1.31 ± 0.28	1.34 ± 0.24	<0.001
LDL-C (mg/dL)	2.99 ± 0.75	2.98 ± 0.75	3.04 ± 0.80	3.29 ± 0.77	<0.001
FBG (mg/dL)	5.04 ± 0.58	5.03 ± 0.54	5.11 ± 0.43	5.18 ± 1.13	0.009

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; FBG, fasting blood glucose; hs-CRP, high-sensitive C-reactive protein; TG, triglyceride; WC, waist circumference.

Table 4 Hazard Ratios (95% Confidence Intervals) of MetS Progression by Baseline hsCRP Index

hsCRP Category	MetS (N)	Unadjusted	*P*	Model 1	*P*	Model 2	*P*
		HR (95% CI)		HR (95% CI)		HR (95% CI)	
Low-stable	1152/3961	Reference		Reference		Reference	
Decreasing	76/165	1.663(1.318, 2.097)	<0.001	1.462 (1.158, 1.845)	0.001	1.408(1.115, 1.779)	0.004
Increasing	80/186	1.900(1.514, 2.384)	<0.001	1.658(1.320, 2.081)	<0.001	1.618 (1.288, 2.033)	<0.001

Notes: Model 1: Adjusted for age and BMI; Model 2: Adjusted for age, BMI, sex, Current smoker, and Current alcohol use.

significantly associated with MetS progression. Furthermore, we identified three distinct trajectories of the hsCRP index conferring a different risk of MetS progression, including the low-stable, decreasing and increasing trajectories. The high-increasing trajectory of the hsCRP tended to be associated with MetS progression. These results suggest a pathophysiological mechanism for continuously higher levels of systemic inflammation in the pathogenesis of MetS progression.

Inflammation is a key biological mechanism in the development of MetS, involving the interaction of multiple inflammatory cytokines, which are co-regulated by genetic and environmental factors.[17] The adipose tissue inflammatory response due to abdominal obesity activates the inflammatory pathway and promotes insulin resistance,[18] endothelial dysfunction, and metabolic abnormalities, all of which are characteristic of MetS.[19,20] In this study, we observed a positive correlation between high-sensitivity C-reactive protein (hs-CRP) levels and metabolic syndrome (MetS), which is largely consistent with previous cross-sectional research.[17,21–23] While the association of hs-CRP with type 2 diabetes and cardiovascular disease has been extensively studied, there is a relative paucity of research on the relationship between hs-CRP and MetS in the Chinese population.[8] This study addresses this gap, offering novel insights into the relationship between the long-term trajectory of hs-CRP and the progression of MetS. However, discrepancies exist between our findings and those of some prospective studies. A limited number of prospective cohort studies conducted in Finland,[24] Mexico,[25] and South Korea[26] have reported varying results regarding the association between hs-CRP and MetS. Notably, two out of three prospective studies conducted exclusively in male cohorts identified a positive association between CRP and MetS, while the third did not. These differences can be attributed to a variety of factors, including study design, population characteristics, and methodologies employed for measuring hs-CRP. For instance, the

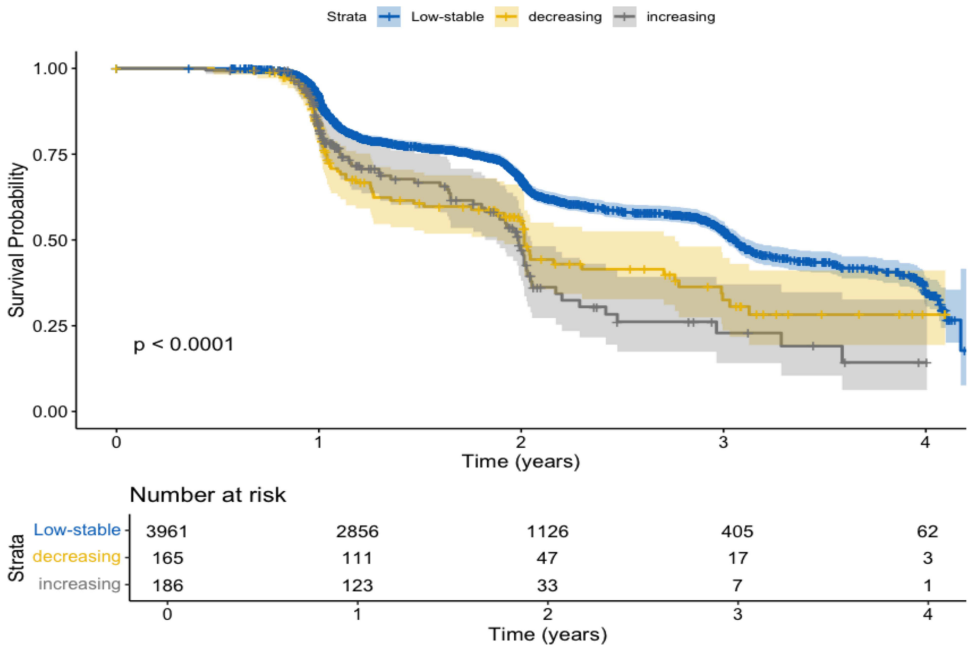

Figure 6 Kaplan–Meier survival analysis curves for MetS progression stratified by trajectories of the baseline hsCRP.

Mexican study lacked detailed information on population sources and sampling methods, and its age range (35–64 years) did not represent the general population. Additionally, the diagnostic criteria in that study did not include waist circumference (WC).[25]

In this study, we identified distinct hsCRP trajectory patterns using latent class trajectory models, revealing that individuals with high baseline hsCRP levels and increasing hsCRP trajectories are at significantly higher risk of developing metabolic syndrome (MetS). This finding underscores the potential of long-term hsCRP trajectories as valuable tools for identifying high-risk individuals who could benefit from targeted prevention and treatment strategies. A major strength of our study lies in our large, well-characterized cohort with multiple repeated hsCRP measurements, which allows us to robustly track dynamic changes in inflammation. Additionally, our inclusion of diverse participants from health assessments enhances the generalizability of our findings to real-world settings. Overall, our findings emphasize the importance of ongoing monitoring of inflammatory markers in clinical practice, which could inform future research directions and improve treatment strategies.

However, several limitations should be considered. The retrospective cohort design limits our ability to infer causality, and the generalizability of our findings may be restricted due to the relatively homogeneous study population.Moreover, while we adjusted for several potential confounders, we were unable to include detailed information on specific medication regimens for hypertension, diabetes, and dyslipidemia. This limitation is important, as medications for these conditions can significantly influence metabolic outcomes. Addressing this gap, we recommend future studies to collect more comprehensive treatment data to enhance the robustness of the analysis. Future research should replicate these findings in more diverse populations and further investigate the biological mechanisms underlying the different hsCRP trajectories. Intervention studies are also warranted to explore whether modifying hsCRP trajectories through lifestyle changes or pharmacological treatments can effectively reduce the risk of MetS progression. By addressing these gaps, we can develop more precise, personalized strategies for MetS prevention and management.

Conclusions

Our longitudinal cohort study has elucidated a significant association between high-sensitivity C-reactive protein (hs-CRP) levels and the progression of metabolic syndrome (MetS). By identifying distinct hs-CRP trajectory patterns, we have shown that individuals with higher baseline hs-CRP levels and increasing hs-CRP trajectories are at greater risk of developing MetS. These findings underscore the potential of hs-CRP trajectories as predictive markers for MetS progression and highlight the critical role of systemic inflammation in the pathogenesis of MetS.

Data Sharing Statement

The datasets produced and analyzed in the present study can be obtained from the corresponding author upon reasonable inquiry.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Helsinki Declaration (2013 revision) and received approval from the Ethics Committee of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine (Approval No: 2024-2313-01). Informed consent from individual patients was waived by the Ethics Committee (Sir Run Run Shaw Hospital, Zhejiang University School of Medicine) due to the retrospective nature of the study, involving the analysis of data derived from previous clinical diagnoses and treatments. Notably, medical records of patients who explicitly refused consent were excluded from the study. The research did not adversely affect the rights and health of the subjects, and stringent measures were implemented to protect the privacy and personal identity information of the participants.

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Author Contributions

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

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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 paper.

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