Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy Dovepress
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ORIGINAL RESEARCH

High-Sensitivity C-Reactive Protein Leads to Increased Incident Metabolic Syndrome in Women but Not in Men: A Five-Year Follow-Up Study in a Chinese Population

This article was published in the following Dove Press journal:
Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

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Purpose: Metabolic syndrome (MetS), characterized by a constellation of insulin resistance, central obesity, hypertension, and hyperlipidemia, is a global health threat. High-sensitivity C-reactive protein (hs-CRP) has been shown to be associated with type 2 diabetes and cardiovascular disease; however, its association with incident MetS is less known. Therefore, the aim of this study was to examine the prospective association between hs-CRP and MetS among a Chinese population in a 5-year follow-up study.

Patients and Methods: The levels of hs-CRP were measured using serum samples collected at baseline recruitment in 2012 from 886 participants without MetS. Follow-up interviews were conducted in 2018, and MetS was diagnosed by 2017 criteria from the Chinese Diabetes Society. Multivariate logistic regression models were used to assess the overall and sex-specific associations between hs-CRP and incident MetS. The odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were computed with adjustment for demographic, socioeconomic, clinical, and lifestyle factors.

Results: After a mean follow-up duration of 5.40 ± 0.56 years, 116 (13.3%) participants developed MetS. In the total study population, increased hs-CRP levels were associated with a higher risk of MetS (OR comparing extreme quartiles of hs-CRP: 4.06 [95% CI: 1.91–8.65]) in the fully-adjusted model. When stratified by sex, the positive association was only observed in women (OR: 4.82 [1.89–12.3]) but not in men (OR: 3.15 [0.82–12.1]; *P*-interaction = 0.039).

Conclusion: In this study of a Chinese population, a positive association between hs-CRP and incident MetS was found only in women and not in men. Sex-specific prediction and intervention of MetS using hs-CRP as a target should be further evaluated.

Keywords: inflammation, high-sensitivity C-reactive protein, metabolic syndrome, cohort study, follow up

Introduction

According to the World Health Organization,[1] metabolic syndrome (MetS) is a global health epidemic;[2] it is characterized by a constellation of interrelated cardiac risk factors consisting of insulin resistance, central obesity, hypertension, and hyperlipidemia. In 2010, one in three adults suffered from MetS in the USA,[1] and a similar prevalence was observed in China (33.9%).[3] Moreover, the prevalence of MetS has skyrocketed in the past few decades due to the sharp increase in obesity worldwide, and it is predicted to continue to increase at an alarming rate.[1]

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DovePress
http://doi.org/10.2147/DMSO.S241774

In addition, MetS has been shown to be associated with increased risks of subsequent development of diabetes mellitus, cardiovascular disease, and mortality.[4] Faced with the immense health burden, prediction and prevention of MetS is of utmost importance at the global level.

Chronic low-grade inflammation has been suggested as a major factor for both MetS and subsequent clinical outcomes.[5] Furthermore, high-sensitivity C-reactive protein (hs-CRP), a known biomarker for acute and chronic inflammation,[6] has been shown to be correlated with MetS in various cross-sectional studies.[7–15] However, the temporal association between hs-CRP and MetS cannot be inferred from cross-sectional studies, and prospective cohort studies are warranted. Although numerous prospective studies and meta-analyses have been conducted to evaluate the associations between hs-CRP and type 2 diabetes[16–19] and cardiovascular disease,[14,15,20,21] only a few studies have assessed the association between hs-CRP and incident MetS in Finland,[22,23] Mexico,[24] and Korea;[25] to date, no prospective study has evaluated the association among a Chinese population. Moreover, the results from prior studies have not been consistent:[20,22,24,25] some prospective studies have found a positive association between hs-CRP and MetS in both women and men,[22,23,25] while one study reported no such association in men.[24] Furthermore, the potential sex difference also has been reported in cross-sectional studies between hs-CRP and MetS, with a stronger correlation in women than in men.[26–29] According to a national representative survey among 31 provincial-level administrative units in China, the prevalence of MetS was also higher in women compared to men (36.8% vs 31.0%). Therefore, it is of scientific interest to examine whether the sex difference between hs-CRP and MetS is also observed in China. This information would be vital for the sex-specific prevention and prediction of MetS. However, no prospective studies have been conducted in China to examine the potential sex heterogeneity.

Therefore, the aim of this study was to examine the association between hs-CRP and incident MetS and the potential sex dissimilarity in a 5.4-year prospective follow-up study among a representative population of Chinese adults.

Materials and Methods

Study Population

The detailed design of the current cohort study has been described previously.[30–35] Briefly, in 2012, 2142 southern Chinese adults aged ≥18 years old from Wanzai Town (Zhuhai City, China) were recruited by the stratified random sampling method. At recruitment, trained research coordinators used structured questionnaires to collect information on sociodemographic, clinical, and lifestyle factors; in addition, they measured the waist circumference (WC) and blood pressure of the participants. In 2018, follow-up interviews were conducted. This study was approved by the Ethics Committee of the Third Affiliated Hospital of Southern Medical University (IRB approval number: 201708011). All subjects provided their written informed consent at recruitment.

Ascertainment of Outcome: MetS

At both baseline and follow-up, we used the diagnostic criteria from the most updated Chinese Diabetes Society version (2017) to diagnose MetS.[36] Specifically, MetS was defined as having at least three of the following five components: (1) abdominal obesity: WC ≥ 90 cm in men or ≥ 80 cm in women; (2) hyperglycemia: fasting plasma glucose ≥ 6.1 mM and/or 2-h postprandial blood glucose ≥ 7.8 mM, or previously diagnosed as having type 2 diabetes and treated; (3) high blood pressure: systolic blood pressure (SBP)/diastolic blood pressure (DBP) ≥ 130/85 mmHg, or previously diagnosed as having hypertension and treated; (4) hypertriglyceridemia: triglyceride (TG) ≥ 1.7 mM, and (5) low high-density lipoprotein cholesterol (HDL-C) levels: HDL-C < 1.04 mM.[36] A total of 239 participants had MetS at baseline, and 79 had missing data regarding the MetS status (for one or more MetS components); thus, they were excluded from the current study.

Data Collection

Data on sociodemographic status, family, healthy lifestyle habits, and drug use were collected by structured questionnaires. The WC was measured according to the protocols recommended by the World Health Organization.[37] SBP and DBP were measured on the right arm using a calibrated mercury sphygmomanometer in a seated position. All subjects rested for at least 15 min, their SBP and DBP were measured three times in succession, and the average of three readings was taken.

Laboratory Measurement of hs-CRP and Other Biochemical Indicators

All blood specimens were collected after an overnight fasting for at least 10 h. First morning urine samples and fasting blood samples were collected, stored at 2–8 °C immediately

after collection, and then transported to the Central Laboratory of the Third Affiliated Hospital of Southern Medical University within 3 h of collection.[38] Hs-CRP was tested using an enzymatic immunoassay turbidimetric method (reagent: Orion Corporation, Espoo, Finland; apparatus: Roche Cobas 6000, Penzberg, Germany). A total of 37 participants had extremely high hs-CRP levels (>10 mg/L), and 7 had missing hs-CRP values. After further excluding these participants, 1780 subjects were eligible for the current study at baseline. After the 5-year follow-up, 894 dropped out of the study, leaving a total of 886 for the current analysis. A total of 17 subjects had missing values for all components of MetS and thus were further excluded. Therefore, 869 subjects were selected for the current analysis. The detailed flowchart is shown in Figure 1. Serum creatinine, urinary creatinine, serum uric acid (UA), fasting glucose, serum TG, low-density lipoprotein cholesterol, and HDL-C were measured by a colorimetric method. Urinary albumin was measured by an immune nephelometric method.[39]

Statistical Analysis

Continuous variables with normal distributions were reported as the mean and standard deviation, while those with skewed distributions were reported as the median and interquartile range. Categorical data were presented as percentages. The baseline characteristics of the participants included in the current study and those excluded due to prevalent MetS were compared using the independent-samples Student's *t*-test or analysis of variance for continuous variables, and the chi-squared test or Fisher's exact test for categorical variables.

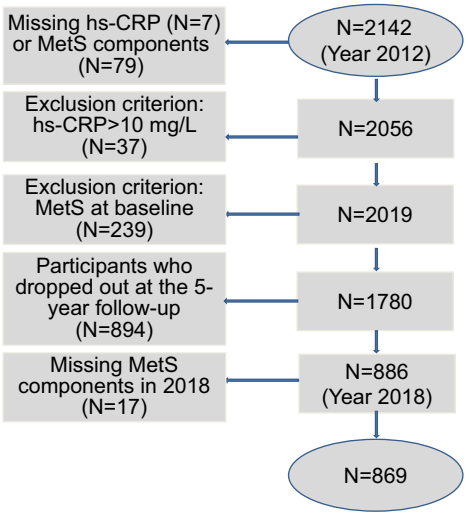

Figure 1 Flow diagram for the selection of study subjects.

According to the quartile distribution of serum hs-CRP in the baseline population, four groups were created, with the first group serving as a reference. The ranges of hs-CRP for the four groups were as follows: ≤0.39 mg/L, 0.39 mg/L to ≤0.79 mg/L, 0.79 mg/L to ≤1.73 mg/L, and 1.73 mg/L to ≤10 mg/L. The association between hs-CRP and incident MetS was analyzed using multivariate logistic regression models to compute the odds ratio (OR) and the corresponding 95% confidence interval (CI). Potential confounding factors were chosen based on both the biological

Table 1 Baseline Characteristics of Participants Included in This Study and Those Excluded Participants with Prevalent Metabolic Syndrome (MetS) at Baseline

Characteristics	All Included Participants n = 886	Excluded Participants Due to Prevalent MetS n = 239	P value
Sex, male (%)	31.3	45.2	<0.001
Age	52.0 ± 12.7	57.5 ± 10.6	<0.001
History of hypertension (%)	13.7	48.1	<0.001
History of diabetes (%)	2.50	18.60	<0.001
History of coronary heart disease (%)	1.9	3.8	0.09
History of stroke (%)	3.0	1.0	0.85
Education of high school or above (%)	37.9	29.2	0.08
Physical inactivity (%)	36.8	34.2	0.32
Smoking status (%)			
Nonsmoker	86.4	82.2	0.34
Current smoker	9.7	12.3	0.34
Current alcohol use (%)	22.2	25.2	0.08
SBP (mmHg)	124.7 ± 18.5	141.1 ± 14.7	<0.001
DBP (mmHg)	76.1 ± 9.8	85.2 ± 10.2	<0.001
WC (cm)	81.1 ± 9.4	91.5 ± 7.8	<0.001
BMI (kg/m^2)	22.8 ± 3.29	25.7 ± 2.87	<0.001
TG (mM)	1.25 ± 0.74	2.58 ± 1.59	<0.001
LDL (mM)	3.24 ± 0.89	3.22 ± 0.98	0.78
HDL (mM)	1.59 ± 0.33	1.41 ± 0.32	<0.001
eGFR (mL/min/1.73 m^2)	93.0 ± 15.7	85.7 ± 16.2	<0.001
hs-CRP (mg/L)	1.42 ± 1.67	2.38 ± 1.94	<0.001
FBG (mM)	4.78 ± 0.66	5.95 ± 1.88	<0.001
UA (mM)	333.3 ± 85.7	400.9 ± 97.6	<0.001
ACR (mg/g)	8.0 (5.7–12.0)	11.3 (7.4–20.8)	<0.001

Notes: Data are presented as the mean ± standard deviation or n (%) for categorical variables.

Abbreviations: MetS, metabolic syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; FBG, fasting blood glucose; UA, uric acid; ACR, urinary albumin-to-creatinine ratio.

plausibility and the statistical significance. Model 1 was adjusted for sex and age; model 2 was additionally adjusted for socioeconomic and lifestyle factors (education, exercise, smoking, and alcohol consumption). Model 3 was the final model including all of the variables in model 2 plus clinical biomarkers (UA, albumin-to-creatinine ratio [ACR], and estimated glomerular filtration rate [eGFR]). Since all three of these variables are biomarkers for kidney function and had high correlations, we included eGFR in the final model (Model 3). We did not include WC, glucose levels, blood pressure, or lipids in the final model because they were used to define the outcome of MetS. Statistical analyses were performed using the SPSS software version 20.0 (IBM Corp., Armonk, NY, USA). A two-sided *P* value of <0.05 was considered statistically significant.

Results

Baseline Characteristics

After a mean follow-up period of 5.4 years, 116 out of the 886 participants developed incident MetS in the current study. The baseline characteristics of the participants included in this study and those excluded due to prevalent disease are shown in Table 1. The average age of those who developed incident MetS was 52.0 ± 12.7 years old, and 68.7% were female. The average body mass index (BMI) was 22.8 ± 3.29 kg/m^2. Compared to the recruited participants, those excluded from the study due to prevalent MetS were more likely to be men and older, and have higher levels of blood pressure (SBP and DBP), BMI, WC, total cholesterol (TC), TG, very-low-density lipoprotein (VLDL), hs-CRP, and FBG ($P < 0.001$) and lower levels

Table 2 Baseline Characteristics According to the Quartile Distribution of hs-CRP Levels

Characteristic	Quartile 1 (≤0.39 mg/L) n = 229	Quartile 2 (0.39 mg/L to ≤0.79 mg/L) n = 216	Quartile 3 (0.79 mg/L to ≤1.73 mg/L) n = 222	Quartile 4 (1.73 mg/L to ≤10 mg/L) n = 219	*P*
Sex, male (%)	31.0	36.1	32.0	26.0	0.16
Age	49.0 ± 12.3	52.0 ± 12.4★	53.3 ± 12.6★	53.8 ± 12.2★	
History of hypertension (%)	11.1	13.0	13.1	17.8	0.20
History of diabetes (%)	2.7	4.7	0.9▲	1.8	0.08
History of coronary heart disease (%)	0.4	3.3	2.7	1.4	0.13
History of stroke (%)	0.4	0.5	0	0.5	0.80
Education of high school or above (%)	46.0	42.8	34.4	28.2★	<0.001
Physical inactivity (%)	47.4	52.4	52.9	59.3	0.11
Smoking status (%)					
Nonsmoker	84.2	87.9	85.9	87.7	
Current smoker	11.3	9.3	10.5	7.8	0.63
Current alcohol use (%)	21.1	22.5	17.3	22.1	0.54
SBP (mmHg)	120.8 ± 16.4	124.7 ± 17.5★	127.0 ± 19.4★	126.4 ± 20.1★	<0.001
DBP (mmHg)	75.2 ± 9.5	75.8 ± 9.8	76.9 ± 9.7	76.5 ± 10.1	0.29
WC (cm)	76.1 ± 8.2	80.37 ± 8.7★	82.8 ± 8.9★▲◆	85.3 ± 9.3★▲◆	<0.001
BMI (kg/m^2)	21.4 ± 3.0	22.5 ± 3.0★	23.3 ± 3.0★▲	24.2 ± 3.5★▲◆	<0.001
TG (mM)	1.07 ± 0.61	1.22 ± 0.74★	1.39 ± 0.87★▲	1.31 ± 0.67★	<0.001
LDL (mM)	3.11 ± 0.92	3.12 ± 0.82	3.28 ± 0.87★▲	3.46 ± 0.89★▲◆	<0.001
HDL (mM)	1.68 ± 0.35	1.59 ± 0.33★	1.57 ± 0.32★	1.51 ± 0.29★▲	<0.001
eGFR (mL/min/1.73 m^2)	94.8 ± 14.7	93.6 ± 15.7	91.1 ± 15.5	92.3 ± 16.8	0.07
hs-CRP (mg/L)	0.25 ± 0.10	0.58 ± 0.11★	1.18 ± 0.27★▲	3.69 ± 1.97★▲◆	<0.001
FBG (mM)	4.69 ± 0.55	4.79 ± 0.60	4.77 ± 0.48▲	4.90 ± 0.91★◆	0.01
UA (mM)	311.5 ± 77.8	329.6 ± 81.1★	341.6 ± 84.8★	351.3 ± 93.8★	<0.001
ACR (mg/g)	7.2 (5.5–11.0)	8.1 (5.6–12.0)	8.3 (5.6–12.4) ★	8.5 (6.3–13.0)★	0.01

Notes: Data are presented as the mean ± standard deviation or % for categorical variables. ★Compared with quartile 1, $P < 0.05$. ▲Compared with quartile 2, $P < 0.05$. ◆Compared with quartile 3, $P < 0.05$.

Abbreviations: MetS, metabolic syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; BMI, body mass index; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; FBG, fasting blood glucose; UA, uric acid; ACR, urinary albumin-to-creatinine ratio.

of HDL. The proportion of participants with a high-school education or above in the non-MetS group was higher than that in the MetS group ($P < 0.001$). The LDL levels were similar between the two groups ($P = 0.78$).

The distribution of baseline characteristics according to the quartiles of hs-CRP levels is shown in Table 2. Compared to quartile 1, the participants in quartile 4 were older, heavier, less educated, and more likely to be female, have a history of hypertension and coronary heart disease, and be nonsmokers. The levels of blood biomarkers, including SBP, TC, TG, LDL, VLDL, FBG, insulin, UA, and ACR, were higher and the level of HDL was lower in quartile 4 vs 1 (Table 2).

The incidence of MetS in the total study population as well as stratified by sex is shown in Table 3. The overall incidence of MetS was 13.3%, and it increased from 5.8% in quartile 1 to 10.8%, 16.6%, and 20.5% in quartiles 2–4, respectively ($P < 0.001$) (Table 3). When stratified by sex, the incidence in men was higher than that in women (16.1% vs 12.1%); however, a statistically significant trend was observed of the increment of MetS incidence across quartiles in women ($P < 0.001$) but not in men ($P = 0.26$) (Table 3).

The multivariate logistic regression analyses showed consistent results (Table 3). In the total study population, a positive association between hs-CRP and MetS was observed in all three models. In the final model (model 3), the OR comparing the extreme quartiles of hs-CRP was 4.06 (95% CI: 1.91–8.65; P-trend < 0.001) (Table 3 and Figure 2). When stratified by sex, the positive association persisted in women (OR 4.82 [1.89–12.3]; P-trend< 0.001) but disappeared in men (OR 3.15 [0.82–12.1]; P-trend= 0.08) (Table 3 and Figure 2). The interaction between sex and the hs-CRP–MetS association was statistically significant (P-interaction = 0.039).

To test the robustness of the sensitivity analysis results, we further categorized hs-CRP into a binary variable using the sex-specific median value as the cut-off value and evaluated its association with MetS. Similar to the main analysis, higher levels of hs-CRP were significantly associated with incident MetS (OR 2.30 [1.42–3.72]). When stratified by sex, the positive association was only observed in women (OR 2.47 [1.39–4.37]) but not in men (OR 2.05 [0.85–4.93]) (Table 4).

Table 3 Logistic Regression Analysis of hs-CRP and Incident MetS in the Total Study Population and Stratified by Sex

Characteristic	Total	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P*-Trend
		n = 229	n = 216	n = 222	n = 219	
Total population						
Incident MetS/non-MetS (n)	116/753	13/211	23/190	36/181	44/171	
Incidence rate of MetS (%)	13.3	5.8	10.8	16.6	20.5	<0.001
Model 1[a]		1.00	1.73 (0.85–3.54)	2.82 (1.44–5.53)	3.74 (1.93–7.23)	<0.001
Model 2[b]		1.00	1.78 (0.79–3.99)	2.59 (1.19–5.62)	4.05 (1.91–8.61)	<0.001
Model 3[c]		1.00	1.81 (0.81–4.07)	2.57 (1.18–5.58)	4.06 (1.91–8.65)	<0.001
Men						
Incident MetS/non-MetS (n)	44/230	7/62	10/67	14/56	13/44	
Incidence rate of MetS (%)	16.1	10.0	13.0	20.2	22.8	0.03
Model 1[d]		1.00	1.54 (0.55–4.33)	1.71 (0.62–4.67)	2.50 (0.95–6.62)	0.04
Model 2[e]		1.00	1.29 (0.33–5.08)	1.93 (0.52–7.09)	2.78 (0.73–10.6)	0.11
Model 3[f]		1.00	1.34 (0.34–5.34)	1.94 (0.52–7.17)	3.15 (0.82–12.1)	0.08
Women						
Incident MetS/non-MetS (n)	72/523	6/148	13/123	22/125	31/127	
Incidence rate of MetS (%)	12.1	3.9	9.6	15.0	19.6	<0.001
Model 1[d]		1.00	2.06 (0.76–5.60)	3.67 (1.42–9.49)	5.15 (2.05–12.9)	<0.001
Model 2[e]		1.00	2.13 (0.78–5.81)	3.07 (1.15–8.17)	4.83 (1.89–12.4)	<0.001
Model 3[f]		1.00	2.15 (0.79–5.84)	3.06 (1.15–8.15)	4.82 (1.89–12.3)	<0.001

Notes: [a]Model 1: adjusted for age and sex. [b]Model 2: adjusted for age, sex, education, exercise, smoking, and alcohol consumption. [c]Model 3: adjusted for age, sex, education, exercise, smoking, alcohol consumption, and eGFR. [d]Model 1: adjusted for age. [e]Model 2: adjusted for age, education, exercise, smoking, and alcohol consumption. [f]Model 3: adjusted for age, education, exercise, smoking, alcohol consumption, and eGFR.

Abbreviations: MetS, metabolic syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; BMI, body mass index; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; UA, uric acid; ACR, urinary albumin-to-creatinine ratio.

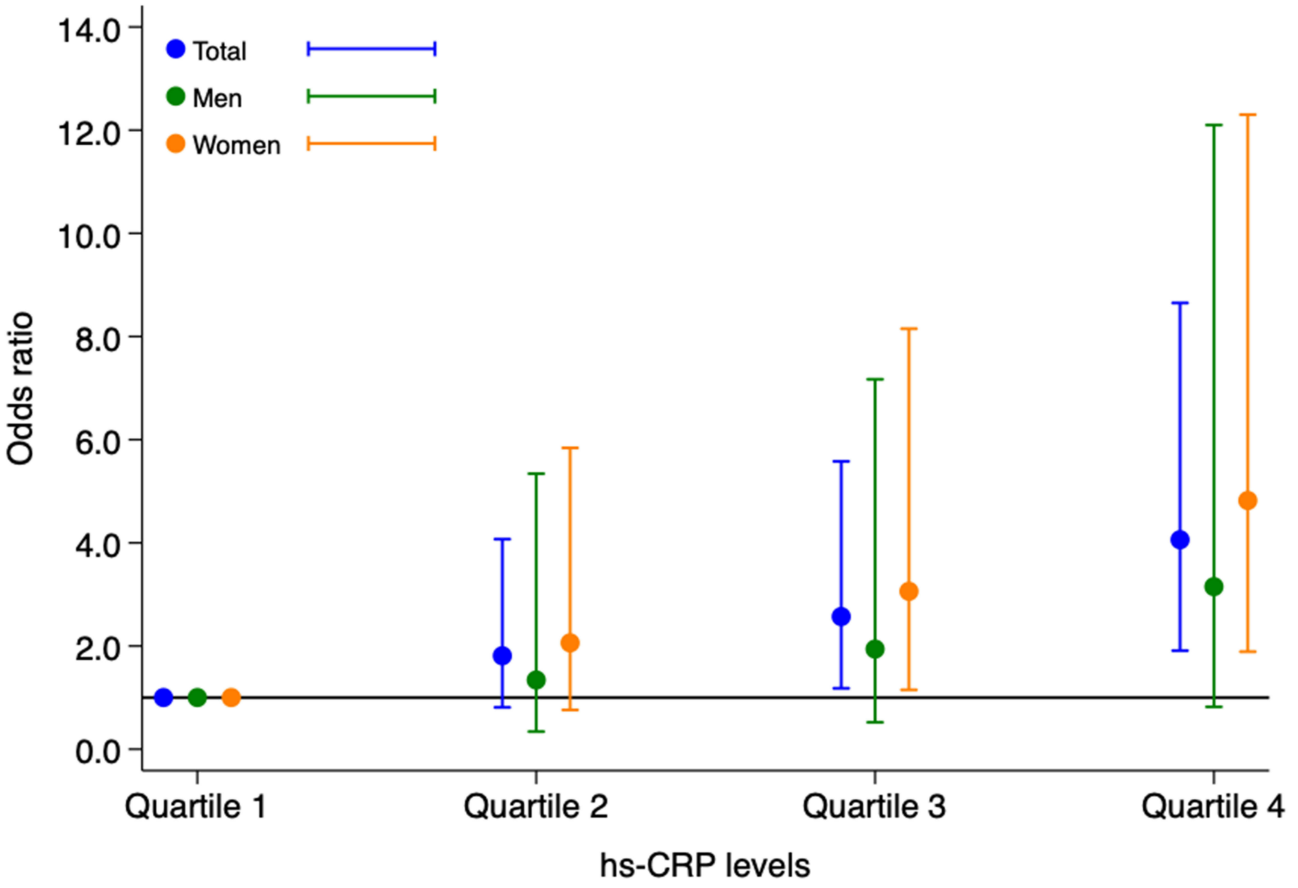

Figure 2 Associations between hs-CRP and MetS in the general population (total) as well as in men and women, separately. The odds ratio and 95% confidence interval of hs-CRP associated with MetS were based on Model 3 from Table 3.
Abbreviations: hs-CRP, high-sensitivity C-reactive protein; MetS, metabolic syndrome.

Discussion

In this Chinese population-based cohort study, we found a positive association between hs-CRP levels and the risk of developing MetS. We also observed a significant sex interaction, where the positive association was only observed in women but not in men. To the best of our knowledge, this is the first prospective study among a Chinese population to examine the association between hs-CRP and incident MetS in the general population as well as the potential sex heterogeneity.

The positive association between hs-CRP and MetS observed in the current study was largely consistent with the positive correlations that have been reported from cross-sectional studies.[7–15] Among the few prospective cohort studies conducted in Finland,[22,23] Mexico,[24] and Korea,[25] the results have not been entirely consistent. Among the three prospective studies conducted in men only,[22,24,25] two studies observed a positive association between CRP and MetS,[22,24] while the other study found no association.[25] The observed difference may be due to the difference in sampling methods, genetic makeups, diagnostic criteria for MetS, measurements for hs-CRP, and model adjustment.[22,24,25] For example, the Mexican study lacked information on the population sources and sampling methods, and the age range (35–64 years) did not represent the general population;[24] in addition, the diagnostic criteria did not include WC in that study. The study conducted in Finland had a relatively low follow-up rate (26.4%), and the association between hs-CRP and MetS disappeared in the final model after including factors associated with insulin resistance.[22] Furthermore, another study from Finland included a small sample size of 103 women with a narrow age range (60–70 years).[23] Among the other two prospective studies that included women, a consistent positive association was observed between CRP and MetS,[20,23] which corroborated with the results found in the current study. The sex heterogeneity also has been observed in various cross-sectional studies.[26–29] Of

Table 4 Logistic Regression Analysis of Binary hs-CRP and Incident MetS in the Total Study Population and Stratified by Sex

Characteristic	Total	Low hs-CRP (≤Median)	High hs-CRP (>Median)
		n = 445	n = 441
Total population		(≤0.79 mg/L)	(0.79 mg/L to ≤10 mg/L)
Incident MetS/non-MetS (n)	116/753	36/401	80/352
Incidence rate of MetS (%)	13.3	8.2	18.5
Model 1[a]		1.00	2.38 (1.56–3.64)
Model 2[b]		1.00	2.33 (1.44–3.77)
Model 3[c]			2.30 (1.42–3.72)
Men		(≤0.74 mg/L)	(0.74 mg/L to ≤10 mg/L)
Incident MetS/non-MetS (n)	44/230	17/120	27/110
Incidence rate of MetS (%)	16.1	12.4	19.7
Model 1[d]		1.00	1.65 (0.85–3.21)
Model 2[e]		1.00	1.97 (0.83–4.71)
Model 3[f]			2.05 (0.85–4.93)
Women		(≤0.83 mg/L)	(0.83 mg/L to ≤10 mg/L)
Incident MetS/non-MetS (n)	72/523	20/284	52/239
Incidence rate of MetS (%)	12.1	6.6	17.9
Model 1[d]		1.00	2.84 (1.63–4.94)
Model 2[e]		1.00	2.48 (1.40–4.38)
Model 3[f]			2.47 (1.39–4.37)

Notes: [a]Model 1: adjusted for age and sex. [b]Model 2: adjusted for age, sex, education, exercise, smoking, and alcohol consumption. [c]Model 3: adjusted for age, sex, education, exercise, smoking, alcohol consumption, and eGFR. [d]Model 1: adjusted for age. [e]Model 2: adjusted for age, education, exercise, smoking, and alcohol consumption. [f]Model 3: adjusted for age, education, exercise, smoking, alcohol consumption, and eGFR.

Abbreviations: MetS, metabolic syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; BMI, body mass index; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; UA, uric acid; ACR, urinary albumin-to-creatinine ratio.

note, a study in Japan has identified a lower cut-off point for the identification of MetS in women compared to men (0.25 mg/L vs 0.45 mg/L).[26]

Inflammation has been hypothesized to be pivotal in several components of MetS, such as obesity[40–43] and insulin resistance,[42,43] which could explain the observed association between hs-CRP and MetS. Although the underlying mechanism behind the observed sex heterogeneity is not clear yet, two possible explanations are proposed. First of all, compared to men, women have a higher visceral fat level,[44] which has been shown to be associated with MetS risk.[45] Second, the sex hormone estrogen may exhibit proinflammatory roles;[27,46] therefore, the increment of hs-CRP may have a more pronounced impact in leading to MetS in women compared to men. In addition, the observed sex difference has important clinical and public health implications. This finding suggests that prediction and modulation of the MetS risk by targeting hs-CRP should be focused in women. Future prospective studies and controlled trials are warranted to validate our findings and to evaluate the sex-specific prediction and intervention of MetS via targeting hs-CRP.

The current study used the stratified random sampling method to recruit a representative population of Chinese adults. We chose hs-CRP instead of CRP as a more sensitive marker for inflammation and excluded subjects with hs-CRP levels greater than 10 mg/L to avoid those with acute inflammation. The diagnostic criteria of MetS were based on the most updated Chinese Diabetes Society version (2017) and are similar to the present Adult Treatment Panel III criteria.[47] However, some limitations merit consideration. First of all, the participants included in the current study were all ethnic Han Chinese from Zhuhai City; thus, they may not be representative of other ethnic groups. In addition, the hs-CRP levels were measured only once, and some measurement error is evitable. Residual confounding may also exist as some of the confounding factors may not have been collected in the current study. Furthermore, although this is the first Chinese prospective study, many cross-sectional studies have been conducted

on this topic and the implication of our results is not new. Future studies with larger sample sizes, longer follow-up times, and repeated measurements of hs-CRP are warranted to validate our findings so that detailed subgroup analyses can be performed.

Conclusions

In conclusion, in this prospective cohort study among a Chinese population, we found a positive association between hs-CRP and incident MetS, which was only observed in women and not in men. The results may facilitate the sex-specific prediction and treatment of MetS by targeting hs-CRP. However, future studies are warranted to validate our findings and to evaluate related interventions.

Abbreviations

hs-CRP, high-sensitivity C-reactive protein; MetS, Metabolic syndrome; OR, Odds ratio; WC, waist circumference; BMI, body mass index; UA, uric acid; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; UA, uric acid; ACR, urinary albumin-to-creatinine ratio.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of the Third Affiliated Hospital of Southern Medical University and was conducted in accordance with the Declaration of Helsinki. All subjects provided their written informed consent at recruitment.

Consent for Publication

All data published here are under the consent for publication.

Data Sharing Statement

The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

Author Contributions

All authors contributed to data analysis, drafting, or revising the article; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the following sources: (1) Clinical Research Startup Program of Southern Medical University by High-level University Construction Funding of Guangdong Provincial Department of Education (LC2016PY047, 2016, ChiCTR1800016248); (2) Science and Technique Program of Guangzhou (201604020015, 2015); (3) Medical Scientific Research Foundation of Guangdong Province of China (A2017450); (4) South Wisdom Valley Innovative Research Team Program (CXTD-004, 2014); (5) Guangdong Provincial Science and Technique Program (No. 2011B031800386, 2011); (6) The National Natural Science Foundation of China (81873620); (7) ISN Research Committee grant, 2007; (8) EU FP7 Program, UroSense, 2011; (9) ISN Research Committee grant, 2004.

Disclosure

The authors report no conflicts of interest in this work.

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