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Original article

Association of high sensitivity C-reactive protein concentrations and metabolic syndrome among Thai adults

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Background: Limited information is available regarding associations of metabolic syndrome with C-reactive protein (CRP) concentrations among Asian populations.

Objective: Investigate the association of high sensitivity CRP (hsCRP) concentrations and metabolic syndrome among Thai adults.

Methods: This cross-sectional study was comprised of 467 Thai participants (209 men and 258 women) receiving annual health check-up. Spearman's rank correlation coefficients were used to assess the associations between metabolic parameters (age, waist circumference, blood pressure, triglycerides, HDL-C, fasting plasma glucose, fasting insulin and uric acid) with hsCRP concentrations for men and women, respectively. Multivariable logistic regression procedures were used to estimate the risk (odds ratios (OR), and 95% confidence intervals (CI) of metabolic syndrome according to low, moderate, and high hsCRP concentrations (<1.0, 1.0-3.0, and >3.0 mg/L, respectively).

Results: Measures of adiposity and fasting insulin were positively and significantly correlated with hsCRP concentrations among women with and without metabolic syndrome. Similar associations were observed among men without metabolic syndrome. After controlling for confounders, moderately elevated hsCRP concentrations were associated with a 2.38-fold increased risk of metabolic syndrome (OR=2.38, 95%CI=1.20-4.72) among men. Men with high hsCRP concentrations had a 5.45-fold increased risk of metabolic syndrome (OR=5.45, 95%CI=2.24-13.27) when compared with those who had low hsCRP concentrations. The corresponding OR for women with moderately elevated and high hsCRP concentrations were 4.92 (OR=4.92, 95%CI=2.34-10.35) and 11.93 (OR=11.93, 95%CI=5.54-25.72), respectively.

***Conclusions*:** These findings are consistent with the literature suggesting a role of hsCRP as a biomarker for metabolic syndrome.

Keywords: C-reactive protein, inflammation, metabolic syndrome, obesity

Cardiovascular disease (CVD) has been a leading cause of death in Thailand since 1987 [1, 2]. The prevalence of heart disease has tripled in Thailand, increasing to 168 per 100,000 population, between 1985 and 1997 [1, 3]. Several clinical and metabolic risk factors have been identified for heart disease and other cardiovascular disorders. These risk factors include dyslipidemias (hypertriglyceridemia and low HDL cholesterol), insulin resistance, hypertension, and central obesity [4-6]. The clustering of these risk factors, also known as metabolic syndrome, have been shown to be associated with prevalent and incident CVD worldwide [7, 8].

Metabolic syndrome is regarded as a risk factor for cardiovascular disorders by some

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researchers [7, 8], whilst others view the syndrome as a clustering of metabolic impairments or a pre-disease state [9]. The prevalence of metabolic syndrome is increasing worldwide thus creating an urgent need for evaluating risk and prognostic biomarkers. Identification of prognostic and risk factors is fundamental to establishing screening programs, preventive and therapeutic strategies most appropriate attenuating morbidity and mortality associated with CVD.

Chronic systemic inflammation is regarded as an important pathophysiological characteristic consistent with many of the individual components of metabolic syndrome. It is predictive of incident myocardial infarction, stroke, peripheral arterial disease, sudden cardiac death, and type-2 diabetes [10-12]. C-reactive protein (CRP), an acute phase protein, is synthesized and released by the liver under the stimulation of cytokines that included TNF-α and interleukin-6 (IL-6) [6, 13]. There is evidence to indicate that adipose tissue contributes to the production and release of cytokines [14]. This suggests a strong biological interrelation between CRP concentrations in peripheral circulation and adiposity. These inflammatory factors (e.g. cytokines and CRP) have also been associated with dyslipidemia, hypertension, and insulin action in previous studies [15]. Hence, several lines of evidence have provided plausible biochemical mechanisms for the suggested role of inflammation in the pathophysiology of insulin resistance, metabolic syndrome, and cardiovascular disorders among many populations [10].

The American Heart Association (AHA) and US Centers for Disease Control and Prevention (CDC) have advocated classification of individuals into three categories according to their respective CRP concentrations: low (<1.0 mg/L), intermediate (1.0-3.0 mg/L), and high (>3.0 mg/L). At least 34 large-scale prospective studies have analyzed association of CRP concentrations with metabolic syndrome [8]. However limited information is available regarding associations of metabolic syndrome with CRP concentrations among non-European populations [16]. Notably, few studies have been conducted among Southeast Asians. In this study, we sought to examine the association of CRP concentrations and metabolic syndrome among Thai adults.

Methods

Study population and data collection

We conducted a cross-sectional study of 451 men and 940 women who participated in annual health examinations at the Mobile Health Checkup Unit of King Chulalongkorn Memorial Hospital in Bangkok, Thailand between December 2006 and February 2007.

Participants were those with no current use of antibiotic, anti-hypertensive, anti-diabetic, or lipid lowering medications. Given that blood chemistry evaluations are not routinely measured on all participants under the age of 35 years, this research was restricted to those participants who were $\geq$35 years of age at the time of annual health examination. Eligible participants were asked to provide information about their age, marital status, occupation, educational attainment, medical history, smoking status, alcohol consumption habits, and physical activity. Participants underwent routine clinical physical examinations that included collection of venous blood samples after an overnight fast, and measurement of height, weight, waist circumference, and resting blood pressures. Standing height was determined without shoes and measured to the nearest 0.5 centimeter. Weight was determined without shoes and with participants lightly clothed. Weight was measured using an automatic electronic scale (Seca, Inc., Hamburg, Germany) to the nearest 100 grams. Waist circumference was measured with a heavy-duty inelastic plastic fiber tape measure to the nearest 0.5 centimeter while the subject stood balanced on both feet, with the feet touching each other and both arms hanging freely. Measurement was taken midway between the inferior margin of the last rib and the iliac crest at the end of expiration [17]. Percent body fat (%BF) estimates were determined using the Tanita bioelectrical impedance analysis (BIA) system (Tanita Model BC 532, Tokyo, Japan). The BIA system was routinely calibrated, and quality control measures were followed as recommended by manufacturers. Systolic and diastolic blood pressures, measured using an automatic sphygmomanometer (UDEX-II , UEDA, Tokyo, Japan), were taken in the seated position after participants rested for at least five minutes.

Laboratory analyses

Serum triglyceride (TG) concentrations were determined using standardized enzymatic glycerol phosphate oxidase assay procedures. High-density lipoprotein-cholesterol (HDL-C) was measured by a chemical precipitation technique using dextran sulfate. Fasting plasma glucose (FPG) concentrations were

determined using the hexokinase method. All assays were completed without knowledge of participants' medical history. Plasma lipids, lipoproteins and glucose concentrations were reported as mg/dL.

Analytical variable specification

Metabolic syndrome was defined using a modified version of the ATP III criteria [18]. Briefly, four of the five metabolic syndrome components were defined using the following ATP III categorizations: 1) raised blood pressure ≥130/85 mmHg; 2) raised triglyceride ≥150 mg/dL; 3) reduced high-density lipoprotein-cholesterol (HDL-C) <40 mg/dL in men and <50 mg/dL in women; 4) raised fasting plasma glucose ≥100 mg/dL. The fifth component, waist circumference (WC) was defined based on specific values specified for South Asians [19]. Men with WC ≥90 cm and women with WC ≥80 cm were classified as having a central obesity in this study population. Consistent with the ATP III diagnostic criteria for metabolic syndrome, participants with three of any of the five components were classified as having metabolic syndrome.

Selection of subjects for laboratory analyses of serum hsCRP concentrations

Among 451 men, we identified 108 participants who met the diagnostic criteria for metabolic syndrome. A random sample of 108 participants not meeting the metabolic syndrome diagnostic criteria was selected to serve as controls. Among 940 women, we sampled all those meeting the metabolic syndrome diagnostic criteria (n=133), and an equal number of women without metabolic syndrome were selected to serve as controls. Serum samples for selected participants were submitted to King Chulalongkorn University Immunology Laboratory for determining hsCRP concentrations by means of particle-enhanced immunonephelometry (Dade Behring, Marburg, Germany) with inter and intra-assay coefficients of variation (CV) both <5%. All laboratory tests were completed without knowledge of participants' metabolic syndrome status.

All participants provided informed consent. All research protocols were reviewed and approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University, and the Human Subjects Division, University of Washington.

Statistical analyses

Subjects with serum hsCRP concentrations exceeding 10 mg/L (seven men and eight women) were excluded as markedly elevated concentrations are likely to reflect non-cardiovascular pathophysiologic processes such as autoimmune disorders, cancer, and infections. Hence, 209 men and 258 women remained for statistical analyses. All statistical analyses were performed separately for men and women. Frequency distributions of socio-demographic, behavioral and clinical characteristics were examined. Associations of serum hsCRP concentrations with each component of metabolic syndrome were determined using the Spearman's rank correlation coefficients. Univariate and multivariable logistic regression procedures were employed to calculate unadjusted odds ratios (OR) to assess the risk of metabolic syndrome according to varying concentrations of hsCRP. Confounding factors were evaluated on the basis of their hypothesized relationship with the covariates of interest and with metabolic syndrome [20]. Confounding was empirically assessed by entering covariates into a logistic regression model one at a time, and by comparing the adjusted and unadjusted ORs. Final logistic regression models included those covariates that altered unadjusted ORs by at least 10% [20]. All statistical analyses were performed using SPSS (version 17.0, SPSS Inc. Chicago, USA) software. All reported p-values are two tailed, and confidence intervals (CIs) were calculated at the 95% level.

Results

As shown in **Table 1A**, men with metabolic syndrome were more likely to be overweight or obese, past or current smokers and less likely to be physically active than those without metabolic syndrome. Both groups were largely similar concerning educational attainment, alcohol consumption. The median concentrations of serum hsCRP in men with metabolic syndrome was higher than those without metabolic syndrome (1.50 *vs.* 0.80 mg/L, p <0.001)

Compared with those women who did not have metabolic syndrome, those with the syndrome were more likely to be overweight or obese, were less well educated, and were less physically active. However, the association for this latter covariate did not reach statistical significance (**Table 1B**). Both groups were largely similar concerning smoking status and alcohol consumption. The median concentrations of serum hsCRP among women with metabolic syndrome were statistically significantly higher than values observed among those women without metabolic syndrome (3.10 *vs.* 0.70 mg/L, p<0.001).

Table 1. Socio-demographic and clinical characteristics of men (**A**) and women (**B**) with and without metabolic syndrome (MetS) (Bangkok, 2006-2007).

(A) Men

Characteristic	Non-MetS (n=105)		MetS (n=104)		P-value[a]
	n	%	n	%	
Age (years)					0.001
35-39	38	36.2	19	18.3	
40-44	28	26.7	19	18.3	
45-49	18	17.1	20	19.2	
50-54	12	11.4	21	20.2	
≥55	9	8.6	25	24.0	
Education					0.166
< Bachelor degree	31	29.5	44	42.3	
Bachelor degree	17	16.2	19	18.3	
Master degree	19	18.1	15	14.4	
PhD degree	38	36.2	26	25.0	
Smoking status					0.003
Never smoker	73	69.5	49	47.1	
Previous smoker	15	14.3	31	29.8	
Current smoker	17	16.2	24	23.1	
Alcohol drinking status					0.238
Never drinker	54	51.4	45	43.3	
Ever drinker	51	48.6	59	56.7	
Physical activity levels					0.005
Low	39	37.1	57	54.8	
Moderate	29	27.6	30	28.8	
High	37	35.2	17	16.3	
	Mean (SD)		Mean (SD)		
Waist circumference (cm)	82.0 (7.9)		93.4 (8.7)		<0.001
Body mass index (kg/m^2)	23.8 (2.9)		27.8 (3.5)		<0.001
Body fat percentage (%)	20.9 (4.1)		26.8 (4.1)		<0.001
Systolic blood pressure (mmHg)	120.8 (13.0)		139.2 (17.3)		<0.001
Diastolic blood pressure (mmHg)	75.9 (8.6)		85.5 (11.7)		<0.001
HDL-Cholesterol (mg/dL)	55.7 (11.5)		43.1 (11.1)		<0.001
	Median (IQR)		Median (IQR)		
Triglyceride (mg/dL)	101.0 (62.0)		212.0 (144.0)		<0.001
Fasting plasma glucose (mg/dL)	86.8 (7.9)		113.5 (43.8)		<0.001
Fasting insulin (μIU/mL)	4.9 (3.3)		10.6 (10.5)		<0.001
High sensitivity C-reactive protein (mg/L)	0.8 (1.3)		1.5 (2.3)		<0.001

[a]p-values are from Chi-square test for categorical variables, from Student's t-test for normally distributed continuous variables, or from rank sum test for non-normally distributed continuous variables.

Table 1. Socio-demographic and clinical characteristics of men (A) and women (B) with and without metabolic syndrome (MetS) (Bangkok, 2006-2007).

(B) Women

Characteristic	Non-MetS (n=133)		MetS (n=125)		P-value[a]
	n	%	n	%	
Age (years)					<0.001
35-39	37	27.8	6	4.8	
40-44	34	25.6	22	17.6	
45-49	32	24.1	31	24.8	
50-54	19	14.3	27	21.6	
≥55	11	8.3	39	31.2	
Education					<0.001
< Bachelor degree	20	15.0	45	36.0	
Bachelor degree	63	47.4	51	40.8	
Master degree	26	19.5	23	18.4	
PhD degree	24	18.0	6	4.8	
Smoking status					0.573[b]
Never smoker	129	97.0	118	94.4	
Previous smoker	2	1.5	4	3.2	
Current smoker	2	1.5	3	2.4	
Alcohol drinking status					0.458
Never drinker	114	85.7	111	88.8	
Ever drinker	19	14.3	14	11.2	
Physical activity levels					0.077
Low	65	48.9	75	60.0	
Moderate	45	33.8	39	31.2	
High	23	17.3	11	8.8	
	Mean (SD)		Mean (SD)		
Waist circumference (cm)	72.5 (7.8)		88.2 (8.9)		<0.001
Body Mass Index (kg/m^2)	22.9 (3.3)		29.3 (5.0)		<0.001
Body fat percentage (%)	31.9 (5.3)		41.0 (6.0)		<0.001
Systolic blood pressure (mmHg)	117.5 (14.8)		135.5 (17.3)		<0.001
Diastolic blood pressure (mmHg)	70.7 (9.5)		79.8 (10.0)		<0.001
HDL-Cholesterol (mg/dL)	65.5 (14.9)		49.8 (11.1)		<0.001
	Median (IQR)		Median (IQR)		
Triglyceride (mg/dL)	69.0 (34.0)		155.0 (77.0)		<0.001
Fasting plasma glucose (mg/dL)	85.0 (9.0)		99.0 (23.0)		<0.001
Fasting insulin (μIU/mL)	3.9 (4.1)		8.8 (8.2)		<0.001
High sensitivity C-reactive protein (mg/L)	0.7 (1.1)		3.1 (4.4)		<0.001

[a]p-values are from Chi-square test for categorical variables, from Student's t-test for normally distributed continuous variables, or from rank sum test for non-normally distributed continuous variables.
[b]p-value is from Fisher's exact test.

Spearman's correlation coefficients for metabolic parameters (age, waist circumference, triglycerides, HDL-C, fasting plasma glucose, fasting insulin, uric acid, systolic and diastolic blood pressures) in relation to hsCRP concentrations are presented in **Table 2**. Analyses were completed for men and women, with and without metabolic syndrome. Serum hsCRP concentrations were positively associated with measures of adiposity (correlation coefficients, r, ranged from 0.308 to 0.422, p-values all <0.01) and fasting insulin (r=0.339, p-value <0.001) among men without metabolic syndrome. However, no similar associations were observed among men with metabolic syndrome. Measures of adiposity and fasting insulin concentrations were positively and significantly correlated with hsCRP concentrations among women with and without metabolic syndrome. Systolic (r=0.227) and diastolic blood pressures (r=0.197) as well as age (r=0.188), triglycerides (r=0.370) and uric acid concentrations (r=0.299) were positively correlated with CRP in women without metabolic syndrome.

Results from multivariable logistic regression analyses of the risk of metabolic syndrome according to low, moderate and high hsCRP concentrations (<1.0, 1.0-3.0 and >3.0 mg/L, respectively) are presented in **Table 3**. After adjusting for confounding by age, educational attainment, and smoking status, we noted that the risk of metabolic syndrome increased across categories of hsCRP concentrations (p-value for trend <0.001). Moderately elevated hsCRP concentrations were associated with a 2.38-fold increased risk of metabolic syndrome (adjusted OR=2.38, 95%CI: 1.20-4.72). Men with hsCRP concentrations >3.0 mg/L, as compared with those who had concentrations <1.0 mg/L, had a 5.45-fold increased risk of metabolic syndrome (adjusted OR=5.45, 95% CI: 2.24-13.27).

Similar, yet stronger magnitudes of associations were observed between varying CRP concentrations and metabolic syndrome risks among women. When compared with the referent group (<1.0 mg/L), those with moderately elevated hsCRP concentrations had a 4.92-fold increased risk of metabolic syndrome (adjusted OR=4.92, 95%CI=2.34-10.35). The corresponding metabolic syndrome relative risk was 11.93 (adjusted OR=11.93, 95%CI=5.54-25.72) among women with CRP concentrations >3.0 mg/L.

Table 2. Spearman's rank correlation coefficients for each metabolic parameter in relation to high sensitivity C-reactive protein concentrations (Bangkok, 2006-2007).

Covariates	Among Men		Among Women	
	Non-MetS (n=105)	MetS (n=104)	Non-MetS (n=133)	MetS (n=125)
Age (years)	0.069	-0.031	0.188*	0.045
Waist circumference (cm)	0.415**	0.171	0.462**	0.528**
Body mass index (kg/m²)	0.308**	0.121	0.481**	0.497**
Body fat percentage (%)	0.422**	0.127	0.524**	0.489**
Systolic Blood Pressure (mmHg)	0.145	-0.063	0.227**	0.102
Diastolic Blood Pressure (mmHg)	0.032	0.040	0.197*	0.055
HDL-Cholesterol (mg/dL)	-0.171	0.022	-0.226**	-0.014
Triglyceride (mg/dL)	0.128	-0.065	0.370**	-0.140
Fasting Plasma Glucose (mg/dL)	0.157	0.040	0.116	0.135
Fasting Insulin (μIU/mL)	0.339**	0.095	0.271**	0.261**
Uric acid (mg/dL)	0.122	0.137	0.299**	0.114

*p<0.05, **p<0.01

Table 3. Odds ratios (ORs) and 95% confidence intervals (95%CIs) of metabolic syndrome (MetS) according to high sensitivity C-reactive protein (hsCRP) concentrations (Bangkok, 2006-2007).

hsCRP concentration (mg/L)	Controls		MetS cases		Unadjusted OR (95% CI)	Adjusted OR (95% CI)
	n	%	n	%		
Among men[a]						
<1.0	63	60.0	33	31.7	1.00 (Reference)	1.00 (Reference)
1.0-3.0	31	29.5	42	40.4	2.59 (1.38, 4.84)	2.38 (1.20, 4.72)
>3.0	11	10.5	29	27.9	5.03 (2.23, 11.33)	5.45 (2.24, 13.27)
P for trend					*<0.001*	*<0.001*
Among women[b]						
<1.0	89	66.9	20	16.0	1.00 (Reference)	1.00 (Reference)
1.0-3.0	27	20.3	42	33.6	6.92 (3.49, 13.73)	4.92 (2.34, 10.35)
>3.0	17	12.8	63	50.4	16.49 (8.01, 33.97)	11.93 (5.54, 25.72)
P for trend					*<0.001*	*<0.001*

[a]Odds ratios were adjusted for age (continuous), educational attainment and smoking status. [b]Odds ratios were adjusted for age (continuous) and educational attainment.

Discussion

A number of prospective studies have investigated the relationship between CVD risk factors and metabolic syndrome according to concentrations of hsCRP [8, 12, 21-23]. An enhanced understanding of how inflammatory processes are associated with CVD risk factors and metabolic syndrome has allowed for greater insights into the pathophysiology of CVD events in many populations. However, at present, a limited amount of information is available regarding associations of hsCRP concentrations with metabolic syndrome among non-European populations, particularly among ethnic groups of Southeast-Asia. In our study, we found hsCRP concentrations and metabolic syndrome to be correlated in both men and women. In addition, we noted that risk of metabolic syndrome increased across categories of hsCRP concentrations with stronger, more positive associations observed among women. These findings are in accordance with literature analyzing the association of hsCRP concentrations and metabolic syndrome among North American and European populations [4, 8, 11].

Other cross-sectional studies have investigated the association of CRP and metabolic syndrome [24-28]. In the study of 3,037 subjects, Rutter et al. [27] noted that CRP concentrations were significantly elevated with increasing numbers of components of metabolic syndrome. Mean age-adjusted CRP concentrations for those with 0, 1, 2, 3, 4, or 5 metabolic syndrome traits were 2.2, 3.5, 4.2, 6.0, or 6.6 mg/L, respectively (p for trend=0.0001). Additionally, the authors noted that age-adjusted CRP concentrations were higher among women than men (7.8 compared to 4.6 mg/L; p<0.0001). Ford et al. [25], in the study of 1,366 American participants aged between 12-17 years from the National Health and Nutrition Examination Survey, reported that mean and geometric mean concentrations of CRP were higher among participants who had metabolic syndrome (mean 3.8 mg/L, geometric mean 1.8 mg/L) than among those who did not (mean 1.4 mg/L, geometric mean 0.4 mg/L). In addition, the authors noted that the percentage of participants with a concentration of CRP >3.0 mg/L was significant higher among those with metabolic syndrome than those without the syndrome (38.4% *vs.* 10.3%, p=0.007).

This study has several potential limitations. First, the study population is comprised of highly educated middle-aged office workers; hence, results may not be generalizable to the entire Thai population. However, associations of CRP concentrations with metabolic syndrome observed among our study population are largely comparable to estimates from other studies conducted among other Asian [26], and American [8] populations. Second, we do not have detailed information on other medications that may have influenced hsCRP concentrations; however, the proportion of subjects who use such medications is expected to be low. Third, because of self-reporting and the lack of quantitative measures of behavioral characteristics such as cigarette smoking, alcohol consumption, and leisurely physical activity, some error due to residual confounding by these covariates cannot

be excluded. Fourth, the cross-sectional design of our study does not allow us to determine elevated hsCRP as a cause or consequence of metabolic syndrome. However, available literature suggests that chronic systemic inflammation among subjects without metabolic syndrome precede the development of metabolic syndrome [8, 29]. Ridker et al. [8], in the prospective study with eight years of follow-up study, reported that elevated CRP concentrations predicted subsequent development of metabolic syndrome. Lastly, causal inferences from our study are limited given that assessment of CRP was made at a single time-point and may have led to some misclassification. Future prospective studies with serial measures of CRP concentrations along with a more comprehensive assessment of participants' chronic inflammatory status will overcome these limitations.

In conclusion, hsCRP concentrations were associated with clustered components of metabolic syndrome among Thai professional and office workers who received annual health examinations in Bangkok.

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