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Distribution of C-reactive protein and its association with subclinical atherosclerosis in asymptomatic postmenopausal Chinese women

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Abstract

Substantial evidence shows that C-reactive protein (CRP) is associated with atherosclerosis. However, data on the association between CRP and subclinical atherosclerosis are lacking in postmenopausal Chinese women. We aimed to describe the distribution of CRP and its association with metabolic syndrome (MS) and subclinical atherosclerosis in postmenopausal Chinese women in Hong Kong. Between 2002 and 2004, we recruited 518 postmenopausal women aged 50 to 64 years. Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III criteria. Subclinical atherosclerosis was determined by measuring carotid intima-media thickness (IMT) and plaque (focal wall thickening ≥1.5 mm) using high-resolution B-mode ultrasonography. Median CRP level was 1.00 mg/L. Women with MS had higher median CRP levels than those without MS (1.85 vs 0.80 mg/L, $P < .05$), and there was a modest trend toward increasing CRP levels with more metabolic components (P for trend < .05). Adjusted for age, hormonal use, and lifestyle factors, women with CRP levels of 0.5 to less than 1.0 mg/L had significantly higher mean IMT compared with those with CRP levels of less than 0.5 mg/L (0.78 vs 0.74 mm, $P < .05$). Odds ratio for plaque was 1.92 (95% confidence interval, 1.06-3.50) for women with CRP levels of 1.0 to less than 3.0 mg/L compared with those with CRP levels of less than 0.5 mg/L. Further adjustment for MS eliminated the associations. C-reactive protein did not add prognostic value to MS in the prediction of subclinical atherosclerosis. Compared with women without MS and who had CRP levels of less than 3.0 mg/L, those with CRP of at least 3.0 mg/L alone had similar IMT levels (0.75 vs 0.74 mm) and prevalence of plaque (19.4% vs 20.0%). Similarly, women with MS and who had CRP levels of at least 3.0 mg/L had similar IMT levels (0.81 vs 0.81 mm) and prevalence of plaque (30.1% vs 29.7%) compared with those with MS alone. C-reactive protein was strongly associated with MS and its individual components. However, it is not an independent predictor of subclinical atherosclerosis in postmenopausal Chinese women.

1. Introduction

Atherosclerosis progresses silently over a period of time before clinical manifestations of cardiovascular disease (CVD); it is important to identify the risk factors associated with subclinical atherosclerosis for the prevention of CVD. Carotid intima-media thickness (IMT) and plaques serve as markers of subclinical atherosclerosis and can be assessed noninvasively with B-mode ultrasound [1]. Previous studies have found that IMT and plaques correlate with traditional vascular risk factors and are predictive of future cardiovascular risk and mortality [2,3].

Increasing evidence implicates inflammation in the pathogenesis of atherosclerosis [4]. C-reactive protein (CRP), a nonspecific marker of inflammation, has been shown to be an independent predictor of CVD [5,6]. The association between CRP and the metabolic syndrome (MS) is also well established [7-9]. Both CRP and MS have predictive potential regarding future cardiovascular event [7,8,10,11]. However, the contribution of CRP to atherosclerosis is not yet established.

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The Centers for Disease Control and Prevention and the American Heart Association (CDC/AHA) issued the clinical guidelines for CRP as a part of global risk prediction and suggested that levels of CRP of less than 1.0, 1.0 to less than 3.0, and at least 3.0 mg/L be used to represent low, moderate, and high vascular risk [12]. However, CRP levels vary among different populations; and Asian women had significantly lower CRP levels [13,14]. In addition, a recent study has demonstrated that both very low (<0.5 mg/L) and very high (≥10.0 mg/L) levels of CRP provide important prognostic information on cardiovascular risk [15]. Therefore, current cut points may not be satisfactory for certain sex-ethnic subgroups in cardiovascular risk prediction. Yet there have been little data on the distribution of CRP and its association with subclinical atherosclerosis in asymptomatic postmenopausal Chinese women.

In this study, we aimed to investigate the distribution of CRP and its association with MS and subclinical atherosclerosis in a population-based sample of asymptomatic postmenopausal Chinese women in Hong Kong. We also tested whether CRP adds prognostic value to MS in the prediction of subclinical atherosclerosis.

2. Methods

2.1. Study population

From 2002 to 2004, 518 women aged between 50 and 64 years, and within 10 years since *menopause* (defined as 12 months since the cessation of the last menses) were recruited through random telephone dialing based on the most recent residential telephone directory. At least 6 attempts were made at different times of the day and week for each number before it was considered a noncontact. If more than one postmenopausal woman within the household fell into the targeted age range of 50 to 64 years, the member with the most recent birthday was selected. Women with surgical menopause, CVD, and severe disease conditions such as cancer and renal failure were excluded. Eligible women were invited for clinical examinations and ultrasound measurements. A response rate of 62.5% was obtained. Triglycerides level was missing for one woman and CRP levels were missing for another 2 women, thus leaving 515 women for some analyses. All women gave written informed consent, and the study was approved by the Ethics Committee of the Chinese University of Hong Kong.

2.2. Clinical examinations

A structured questionnaire including information on sociodemographic characteristics, medical history, current use of medications, smoking and alcohol intake was administered to participants. Twelve-hour fasting blood samples were drawn for total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and glucose measurements. They were analyzed using commercial kits (Randox, County Antrim, United Kingdom) with standard enzymatic methods on the Alcyon 300 analyzer (Abbott Laboratories, Abbott Park, IL). Blood pressures were measured twice with a mercury sphygmomanometer on the right upper arm with the participant seated quietly for at least 10 minutes. Height and weight were measured with the women wearing light clothing and no shoes. Body mass index was calculated. Waist circumference was measured over the abdomen at the smallest diameter between the costal margin and iliac crest. Hip circumference was measured at the level of the greater trochanters. Waist-to-hip ratio was calculated as the ratio of waist to hip circumferences. Women were also asked to give information about the usual level of participation in occupational, leisure-time physical activity, sport and exercise, and household activity over the previous 12 months with the modified and locally translated Baecke questionnaire [16,17]. A validated food frequency questionnaire containing 60 food items was used to assess dietary intake [18].

2.3. CRP measurements

Serum CRP was measured with a high-sensitivity chemiluminescence immunoassay (Diagnostic Products, Los Angeles, CA) using the IMMULITE analyzer. The between-run and within-run coefficient of variation was 5.6% and 4.6%, respectively.

2.4. Definition of medical disorders

Hypertension was defined as systolic blood pressure of at least 140 mm Hg and/or diastolic blood pressure of at least 90 mm Hg and/or pharmacologic treatment. *Hypercholesterolemia* was defined as total cholesterol of at least 5.2 mmol/L and/or pharmacologic treatment. *Diabetes* was defined as fasting blood glucose of at least 7.0 mmol/L and/or pharmacologic treatment. According to the National Cholesterol Education Program Adult Treatment Panel III guidelines [19] and the revised cutoff value of waist circumference for defining abdominal obesity for Asian populations [20], a woman was considered to have MS if she met at least 3 of the following criteria: (1) waist circumference of at least 80 cm, (2) triglycerides of at least 1.7 mmol/L, (3) high-density lipoprotein cholesterol less than 1.3 mmol/L, (4) blood pressures of at least 130/85 mm Hg and/or taking an antihypertensive medication, and (5) fasting blood glucose of at least 6.1 mmol/L and/or taking an antidiabetic medication.

2.5. Carotid ultrasonography

A 12.5-MHz linear probe of the Philips HDI 5000 ultrasound scanner (Advanced Technology Laboratory, Bothell, WA) was used for measuring IMT at the near and far walls of three 10-mm segments: distal common carotid, bifurcation (bulb), and proximal internal carotid of both the left and right carotid arteries. For each of the 12 segments,

Table 1
Subject characteristics by CRP categories

Characteristics		CRP categories				*P*
	All	<0.5 mg/L	0.5-<1.0 mg/L	1.0-<3.0 mg/L	≥3.0 mg/L	
	N = 518	n = 126	n = 125	n = 182	n = 83	
Sociodemographic characteristics						
Age, y	56.35 ± 3.33	56.48 ± 3.08	56.61 ± 3.38	56.20 ± 3.37	56.08 ± 3.58	.601
YSM, y	5.10 ± 2.76	5.03 ± 2.82	5.54 ± 2.78	4.91 ± 2.64	4.98 ± 2.84	.224
Medical history						
Hypertension, %	23.9	15.1	20.0	29.1	32.5	.006
Hypercholesterolemia, %	18.0	15.1	13.6	19.8	24.1	.181
Diabetes, %	6.9	5.6	4.8	8.8	8.4	.475
Use of medication						
Hormonal therapy, %	5.0	3.2	4.8	5.5	7.2	.592
Antihypertensive, %	17.8	11.1	12.8	22.0	26.5	.006
Lipid lowering, %	3.9	1.6	3.2	3.8	7.2	.225
Antidiabetic, %	5.8	5.6	3.2	6.6	8.4	.381
Blood pressure measurements						
SBP, mm Hg	127.46 ± 21.21	122.26 ± 19.25	125.38 ± 19.77	129.08 ± 21.67	135.71 ± 22.28	.000
DBP, mm Hg	77.71 ± 10.36	75.44 ± 10.20	76.48 ± 9.46	78.48 ± 10.24	81.61 ± 10.96	.000
Anthropometric measurements						
BMI, kg/m^2	23.58 ± 3.67	22.13 ± 3.09	22.88 ± 2.79	24.02 ± 3.47	25.95 ± 4.64	.000
WC, cm	81.03 ± 9.54	77.19 ± 8.28	79.16 ± 7.68	82.14 ± 9.00	87.46 ± 11.24	.000
WHR	0.83 ± 0.06	0.81 ± 0.05	0.83 ± 0.06	0.84 ± 0.06	0.87 ± 0.06	.000
Biochemical measurements						
TC, mmol/L	5.79 ± 1.06	5.72 ± 1.02	5.79 ± 1.10	5.78 ± 1.11	5.91 ± 0.94	.653
HDL-C, mmol/L	1.82 ± 0.46	1.95 ± 0.45	1.91 ± 0.42	1.73 ± 0.46	1.66 ± 0.40	.000
LDL-C, mmol/L	3.34 ± 0.87	3.24 ± 0.91	3.30 ± 0.83	3.34 ± 0.86	3.58 ± 0.87	.044
TG, mmol/L	1.33 ± 0.90[a]	1.08 ± 0.63	1.14 ± 0.65	1.49 ± 1.06	1.66 ± 1.04	.000
FBG, mmol/L	5.82 ± 1.70	5.45 ± 1.28	5.58 ± 1.04	5.93 ± 1.89	6.49 ± 2.32	.000
Lifestyle factors						
Current smokers, %	1.5	2.4	0.8	0.5	3.6	.189
Regular drinkers, %	3.5	4.8	4.8	3.3	0	.171
Physical activity, weighted total index	24 ± 3	24 ± 3	23 ± 3	24 ± 3	24 ± 3	.993
Dietary total energy intake, kcal/d	1379 ± 446	1405 ± 478	1384 ± 435	1389 ± 446	1310 ± 407	.473
Medical disorders						
Hypertension, %	35.5	23.8	31.2	39.0	53.0	.000
Hypercholesterolemia, %	71.2	70.6	73.6	66.5	78.3	.223
Diabetes, %	11.8	6.3	4.8	13.7	26.5	.000
MS, %	23.2	8.7	13.6	30.2	45.1	.000

Data are presented as mean ± SD for continuous variables and percentage for categorical variables. *P* values obtained from ANOVA tests for comparison of mean values, χ^2 tests for proportions, and Fisher exact test when one or more of the cells have an expected frequency of 5 or less. YSM indicates year since menopause; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; FBG, fasting blood glucose.

[a] n = 517.

sonographers measured the maximum IMT thickness free of atherosclerotic plaques. The *final IMT* was defined as the averages of maximum IMT at the 12 preselected sites. Previous studies have indicated that the inclusion of these multiple sites provides the most sensitive and statistically powerful assessment of atherosclerosis, and aggregating data across segments provides measures that are stable and less sensitive to measurement error [21]. The sonographers also identified atherosclerotic plaques along the defined artery segments (common carotid artery, bulb, and internal carotid artery) of both the left and right carotid arteries. *Plaque* was defined as a focal wall thickening of at least 1.5 mm. Based on earlier studies [22,23], the degree of plaque at the 6 segments was graded according to the following criteria: grade 0, no observable plaque; grade 1, one small plaque less than 30% of vessel diameter; grade 2, one medium plaque between 30% and 50% of the vessel diameter or multiple small plaques; and grade 3, one large plaque greater than 50% vessel diameter or multiple plaques with at least one medium plaque. The grades were then totaled to form a plaque index representing the extent and severity of atherosclerosis.

2.6. Statistical analyses

Continuous variables are reported as mean and SD; and categorical variables, as percentages. Differences in characteristics were analyzed using analysis of variance (ANOVA) or χ^2 tests as appropriate. Comparisons of CRP levels were made between women with or without MS and among groups of women classified as having 0, 1, 2, 3, or at

Table 2
Levels of CRP by MS status and number of metabolic components

	n	CRP, mg/L (median)	P^a	P^b
All	516	1.95 ± 4.25 (1.00)	–	–
MS status				
No	395	1.72 ± 4.57 (0.80)	.000	–
Yes	120	2.70 ± 2.89 (1.85)		
No. of metabolic components				
0	130	1.78 ± 6.97 (0.60)	.000	.020
1	126	1.49 ± 3.07 (0.80)		
2	139	1.88 ± 2.37 (1.00)		
3	72	2.41 ± 3.12 (1.60)		
≥4	48	3.14 ± 2.47 (2.50)		

Data are presented as mean ± SD (median).
[a] P values obtained from Mann-Whitney U tests/Kruskal-Wallis tests for comparison of mean values.
[b] P values obtained from ANOVA tests for linear trend.

least 4 components of MS using Mann-Whitney U test and Kruskal-Wallis test, respectively. Relationships between elevated CRP levels (≥3.0 mg/L) and individual components of MS were assessed using multivariate logistic regression analyses. Based on the clinical cut points set by the CDC/AHA guidelines [12] and the cut points including both very low (<0.5 mg/L) and very high levels (≥10 mg/L) of CRP, women were classified into 5 groups of CRP levels, as follows: less than 0.5, 0.5 to less than 1.0, 1.0 to less than 3.0, 3.0 to less than 10.0, and at least 10.0 mg/L. However, the number of women with CRP levels of at least 10.0 mg/L was small; therefore, women with CRP levels of at least 10.0 mg/L were merged into the group of women with CRP levels of at least 3.0 mg/L. Analysis of variance and analysis of covariance (ANCOVA) were used to compute crude and adjusted mean values of IMT among the 4 categories of women. Multivariate logistic regression models were used to estimate the odds ratios for plaque. Potential confounders were adjusted in the regression models. They were age (continuous), hormonal use, smoking, alcohol intake, physical activity (continuous), dietary total energy intake (continuous), and MS. To avoid colinearity, low-density lipoprotein cholesterol was not included in the models. In addition, women were stratified into groups with elevated IMT (≥1.0 mm) vs normal; and comparisons of CRP levels were made between the 2 groups using Mann-Whitney U test. To evaluate whether CRP might add prognostic value to MS in the prediction of subclinical atherosclerosis, women were categorized into 4 groups on the basis of absence or presence of MS and on the basis of CRP levels of less than 3.0 mg/L or at least 3.0 mg/L, that is, MS−CRP−, MS−CRP+, MS+CRP−, and MS+CRP+. Comparisons of IMT and plaque prevalence were made between the 4 groups of women using ANCOVA or χ^2 tests where appropriate. All analyses were carried out using the Windows-based SPSS statistical package (Version 17.0; SPSS, Chicago, IL), and P values < .05 were considered to be significant.

3. Results

3.1. Characteristics of the study population

A total of 518 early postmenopausal Chinese women were examined (mean age, 56 years; range, 50-64 years) (Table 1). The mean number of years since menopause was 5 years. The majority of women (80.3%) were married, and about half had secondary level of education. Around one thirds of women (35.5%) had hypertension. More than 70% had hypercholesterolemia, and 61 women (11.8%) had diabetes. The prevalence of MS was 23.2%. The mean IMT was 0.76 ± 0.12 mm (range, 0.53-1.33 mm), and 21.8% were found to have plaques (plaque index ≥1) of carotid arteries.

3.2. Distribution of CRP levels

The distribution of CRP was highly skewed toward a lower level. Mean CRP level was 1.95 ± 4.25 mg/L (median, 1.00 mg/L; range, 0.01-77.00 mg/L) (Table 2). The quartile ranges for CRP was 0 to 0.5, 0.5 to 1.0, 1.0 to 2.0, and 2.0 to 77.0 mg/L. Eighty-three women (16.1%) had CRP levels of at least 3.0 mg/L ,and 11 (2.1%) had at least 10.0 mg/L. No

Table 3
Crude and adjusted mean IMT according to clinical cut points of CRP

	n	Crude mean value of IMT ± SD, mm	P^a	Adjusted mean value of IMT ± SE, mm					
				Model 1	P^b	Model 2	P^b	Model 3	P^b
CRP, mg/L									
<0.5	126	0.74 ± 0.10	.094	0.74 ± 0.010	.053	0.74 ± 0.010	.044	0.75 ± 0.010	.136
0.5-<1.0	125	0.78 ± 0.12*		0.78 ± 0.010*		0.78 ± 0.010*		0.78 ± 0.010*	
1.0-<3.0	182	0.77 ± 0.11		0.77 ± 0.008*		0.77 ± 0.008*		0.77 ± 0.008	
≥3.0	83	0.77 ± 0.14		0.77 ± 0.012*		0.77 ± 0.012*		0.76 ± 0.013	

Model 1: ANCOVA adjusted for age and hormonal use. Model 2: ANCOVA adjusted for age, hormonal use, and lifestyle factors (smoking, alcohol intake, physical activity, and dietary total energy intake). Model 3: ANCOVA adjusted for age, hormonal use, lifestyle factors (smoking, alcohol intake, physical activity, and dietary total energy intake), and MS.
[a] P values obtained from ANOVA tests for comparison of mean values.
[b] Adjusted P values obtained from ANCOVA tests for comparison of mean values.
* P < .05 when compared with the lowest category (<0.5 mg/L) in multiple comparisons.

Table 4
Percentage of plaque, and crude and adjusted odds ratios of plaque according to clinical cut points of CRP

	n	Percentage of plaque	*P*	Prevalence of plaque, OR (95% CI)			
				Crude model	Model 1	Model 2	Model 3
CRP, mg/L							
<0.5	126	15.1	.201	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
0.5-<1.0	125	23.2		1.70 (0.90-3.23)	1.69 (0.89-3.22)	1.70 (0.89-3.24)	1.66 (0.87-3.18)
1.0-<3.0	182	24.7		1.85 (1.02-3.35)	1.91 (1.05-3.48)	1.92 (1.05-3.50)	1.74 (0.95-3.22)
≥3.0	83	24.1		1.79 (0.89-3.60)	1.87 (0.92-3.79)	1.89 (0.93-3.87)	1.64 (0.78-3.45)

Model 1: multivariate logistic regression adjusted for age and hormonal use. Model 2: multivariate logistic regression adjusted for age, hormonal use, and lifestyle factors (smoking, alcohol intake, physical activity, and dietary total energy intake). Model 3: multivariate logistic regression adjusted for age, hormonal use, lifestyle factors (smoking, alcohol intake, physical activity, and dietary total energy intake), and MS. *P* values obtained from χ^2 tests for comparison of proportions. OR indicates odds ratio.

significant difference in the CRP levels was observed between age groups. Mean CRP levels were 2.36 ± 6.12, 1.51 ± 1.94, and 2.19 ± 3.19 mg/L for ages 50 to 54, 55 to 59, and 60 to 64 years, respectively ($P = .103$) (data not shown).

3.3. Association between CRP and MS

C-reactive protein levels were significantly higher among women with MS (mean, 2.70 ± 2.89 mg/L; median, 1.85 mg/L) than those without (mean, 1.72 ± 4.57 mg/L; median, 0.80 mg/L) ($P< .05$) (Table 2). The number of single components of MS was also associated with an increase in CRP levels (P for trend < .05). Among the 5 components of MS, abdominal obesity was the strongest independent predictor of elevated CRP levels (≥3.0 mg/L) after adjustments for age, lifestyle factors (smoking, alcohol intake, physical activity, and dietary total energy intake), and other components of MS, with an adjusted odds ratio of 2.89 (95% confidence interval [CI], 1.89-5.28). High-density lipoprotein cholesterol less than 1.3 mmol/L (odds ratio, 2.63; 95% CI, 1.33-5.19) and fasting blood glucose at least 6.1 mmol/L and/or taking an antidiabetic medication (odds ratio, 2.18; 95% CI, 1.23-3.88) were both independently associated with elevated CRP levels. However, blood pressures at least 130/85 mm Hg and/or taking an antihypertensive medication (odds ratio, 1.46; 95% CI, 0.84-2.53) and triglycerides at least 1.7 mmol/L (odds ratio, 0.79; 95% CI, 0.42-1.49) were not associated with elevated CRP levels (data not shown).

3.4. Association between CRP and subclinical atherosclerosis

Table 3 presents the mean and adjusted mean value of IMT in analyses in which CRP levels were defined according to the clinical cut points recommended by the CDC/AHA guidelines and cut points with very low levels (<0.5 mg/L) of CRP. C-reactive protein was associated positively but weakly with IMT. Women with CRP levels of 0.5 to less than 1.0 mg/L had significantly higher IMT compared with those with CRP levels of less than 0.5 mg/L ($P < .05$). In a model adjusted for age, hormonal use, and lifestyle factors (as for model 2 in Table 3), mean IMT values across categories of CRP were 0.74, 0.78, 0.77, and 0.77 mm ($P < .05$). However, adjustment for MS (model 3) eliminated the association between CRP and IMT, although women with CRP levels of 0.5 to less than 1.0 mg/L had significantly higher IMT compared with those with CRP levels of less than 0.5 mg/L ($P < .05$). We also stratified women into groups with elevated IMT (≥1.0 mm) vs normal. Women with elevated IMT had higher CRP levels (mean, 3.10 ± 5.04 mg/L; median, 1.0 mg/L) than those with IMT less than 1.0 mm (mean, 1.90 ± 4.21 mg/L; median, 1.1 mg/L), but the difference was not statistically significant.

Analyses of the association of CRP with plaque are shown in Table 4. Women with CRP levels of 0.5 to less than 1.0 mg/L and 1.0 to less than 3.0 mg/L had higher prevalence of plaque compared with those with CRP levels of less than 0.5 mg/L. In logistic regression models, adjusted for age, hormonal use, and lifestyle factors, odds ratio for plaque was 1.92 (95% CI, 1.06-3.50) for women with CRP levels of 1.0 to less than 3.0 mg/L compared with those with CRP levels of less than 0.5 mg/L. After further adjustment for MS, the association was eliminated.

To determine whether measuring CRP added prognostic value to MS in the prediction of subclinical atherosclerosis, women were categorized into 4 groups on the basis of the presence or absence of MS and on the basis of CRP levels of less than 3.0 mg/L or at least 3.0 mg/L. As shown in Table 5, CRP measurement did not provide additional prognostic information for those both with and without MS. Compared with women without MS and had CRP levels of less than 3.0 mg/L (MS−CRP−), those with CRP at least 3.0 mg/L alone (MS−CRP+) had similar IMT levels and prevalence of

Table 5
Mean IMT and prevalence of plaque according to MS status and CRP levels

	n	IMT, mm		Prevalence of plaque		
		Mean ± SD	P^a	n	%	P^b
MS−CRP−	350	0.75 ± 0.11	.000	68	19.4	.114
MS−CRP+	45	0.74 ± 0.11		9	20.0	
MS+CRP−	83	0.81 ± 0.12		25	30.1	
MS+CRP+	37	0.81 ± 0.16		11	29.7	

[a] *P* values obtained from ANOVA tests for comparison of mean values.
[b] *P* values obtained from χ^2 tests for comparison of proportions.

plaque. Compared with those with MS alone (MS+CRP−), those with MS and had CRP levels of at least 3.0 mg/L (MS+CRP+) had similar IMT levels and prevalence of plaque.

4. Discussion

The majority of population-based studies describing the distribution of CRP have been confined to whites [24-26], with few studies of postmenopausal Chinese women. We described the distribution of CRP and its association with MS and subclinical atherosclerosis in a population-based sample of asymptomatic postmenopausal Chinese women in Hong Kong. We additionally examined whether CRP adds prognostic value to MS in the prediction of carotid atherosclerosis.

Previous studies have shown that CRP levels vary between populations and Asian women had significantly lower CRP levels. The Women's Health Study reported that median CRP levels in Asian women (1.12 mg/L) were significantly lower than those in whites (2.02 mg/L), Hispanics (2.06 mg/L), or blacks (2.96 mg/L) in the United States [13]. Similar results were observed in premenopausal women in the Study of Women's Health Across the Nation, where median CRP levels in Japanese (0.5 mg/L) and Chinese (0.7 mg/L) were lower whereas higher levels were observed in Hispanic and African American compared with white women (1.4 mg/L) [14]. Only limited data of distribution of CRP in postmenopausal population have been performed [13]. The CRP level in our postmenopausal Chinese women (median 1.0 mg/L) was similar to the levels found in Asian women of comparable ages and menopausal status in the Women's Health Study [13]. However, the latter study consisted of women with much higher rates of estrogen use. In contrast, Ye et al [9] found that the median CRP among asymptomatic Chinese women aged 50 to 70 years in China was 0.69 mg/L, which was lower than their counterparts in the United States and similar to the level found in premenopausal Chinese women in the Study of Women's Health Across the Nation [14].

In line with the results in other population studies [7-9], CRP was strongly associated with MS and its individual components, where abdominal obesity was largely responsible for the observed association. There is considerable evidence linking elevated CRP with MS and obesity, whereas adipose tissue in obesity overproduces proinflammatory cytokines such as tissue necrosis factor–α and interleukin-6, which stimulated CRP production [27].

Although the CRP levels in our study population were lower than that of the whites, a quarter of our subjects (23.3%) with MS had CRP levels less than 1.0 mg/L, which is considered "low risk" for subsequent development of CVD according to the CDC/AHA criteria. As such, the levels proposed by CDC/AHA may not be the appropriate ranges or cutoffs for risk stratification in Asians. Recently, Ridker and Cook [15] revealed that cardiovascular risks increased linearly from the very low (<0.5 mg/L) to the very high levels (≥10.0 mg/L) of CRP, suggesting that both very low and very high levels of CRP provide important prognostic information on cardiovascular risk. We therefore examined the association between CRP and subclinical atherosclerosis in which CRP levels were defined according to both the clinical cut points set by the CDC/AHA guidelines and the cut points including both very low (<0.5 mg/L) and very high levels (≥10 mg/L) of CRP.

Previous studies relating CRP to carotid atherosclerosis have yielded conflicting results. A positive association has been reported in middle-aged women who have ever smoked [28]. However, other studies have found a weak or nonexistent association after adjustment for age and other cardiovascular risk factors [29-32]. In addition, there are conflicting data regarding the sex difference on the relation between CRP and carotid atherosclerosis [33-35]. Only a few previous studies have examined the relationship between CRP and subclinical atherosclerosis in postmenopausal population. Our study extends the results of previous studies by examining a sample of early postmenopausal Chinese women in Hong Kong. The present study demonstrates a positive but weak association between CRP and IMT. Women with CRP levels between 0.5 and less than 1.0 mg/L, between 1.0 and less than 3.0 mg/L, and at least 3.0 mg/L appeared to have greater carotid atherosclerosis as measured by IMT when compared with those with CRP levels less than 0.5 mg/L; and this was true after adjustment for age, hormonal use, and lifestyle factors. C-reactive protein was also associated positively but weakly with plaque when adjusted for age, hormonal use, and lifestyle factors. However, these associations were eliminated after adjustment for MS. Substantial evidence suggests that MS would lead to a proinflammatory state caused by insulin resistance and abdominal fat [27], promote hepatic fatty acid synthesis, and increase hepatic CRP production [36,37]. Thus, the associations between CRP and subclinical atherosclerosis would be completely eliminated after adjustment for MS, as is the case in our study. These findings are consistent with those found in previous studies [30,32] in that the unadjusted association of CRP with subclinical atherosclerosis was attributable to confounding of cardiovascular risk factors, particularly those associated with inflammation. Possible explanations for the lack of independent predictive value of CRP and subclinical atherosclerosis also include reduced power to detect a difference because of our sample size (N = 518) and multivariable adjustments of several covariates.

Recent evidence has suggested a possible direct pathogenic role of CRP on atherosclerosis including recruitment of monocytes to the atherosclerotic lesion [38], intimal growth [39], and endothelial dysfunction [40-42]. We therefore additionally sought evidence as to whether CRP might add prognostic information to MS in the prediction of carotid atherosclerosis. However, CRP level did not add to the prognostic value of MS in the prediction of subclinical atherosclerosis. Therefore, our results suggest that elevated CRP may merely reflect an exaggerated inflammatory

response associated with MS, which itself is associated with atherosclerosis, independent of CRP.

There are several limitations in this study. Our data are cross-sectional, and the temporal relationship between CRP and MS and subclinical atherosclerosis cannot be assessed. Moreover, our analyses are based on single measurements of CRP; and these data may not reflect their relative contributions over time. However, the findings were based on a population-based sample of asymptomatic and relatively homogeneous midlife women within 10 years since menopause.

In conclusion, CRP level is low among postmenopausal Chinese Hong Kong women when compared with levels reported in postmenopausal white women. There is a strong association between CRP and MS and its individual components. However, CRP is not an independent predictor of carotid atherosclerosis, despite the association of relatively low levels of CRP (0.5 to <1.0 mg/L) with increased atherosclerotic risk. Considering the lower level of CRP and high prevalence of MS in postmenopausal Chinese women, further research is needed to investigate the association of CRP and the subsequent development of atherosclerosis and CVD and to find optimal sex-ethnic–specific CRP cutoffs that most accurately predict cardiovascular risk.

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