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Metabolic syndrome and C-reactive protein in stroke prediction: a prospective study in Taiwan

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Abstract

The authors evaluated whether stroke was associated with the metabolic syndrome (MetS) and C-reactive protein (CRP) levels in an ethnic Chinese population, and whether these 2 factors add to traditional risk factors in predicting stroke risk. This study identified 65 subjects who had a stroke for the first time and 109 subjects in the control group free of stroke from a community cohort in a 10-year follow-up period until 2005. Metabolic syndrome, CRP levels, and traditional risk factors were measured in 1994-1995. The multivariate logistic regression adjusted stroke odds ratio was 2.55 (95% confidence interval, 1.05-6.23) for subjects in the top tertile CRP levels compared with the bottom tertile levels in the controls. The risk was not attenuated after further adjustment for MetS. The risk for stroke associated with MetS was eliminated after including hypertension and diabetes in the model. The area under receiver operating characteristic curves for traditional risk factors (0.676) improved little by adding CRP (0.691), MetS (0.688), or the combination of these 2 variables (0.702). In conclusion, both CRP and MetS are independent factors associated with stroke among ethnic Chinese.

1. Introduction

An elevated level of C-reactive protein (CRP), measured using a high-sensitivity assay, reflects a low-grade inflammation that plays a role in the atherosclerotic process [1]. A meta-analysis of 22 prospective studies has associated CRP with a moderate risk for coronary heart disease [2]. Several studies have also associated incident strokes with elevated CRP [3-6], but this association was not confirmed by other studies [7,8].

C-reactive protein is a prevalent element in persons with metabolic syndrome (MetS) and has been recommended as an additional measure in the management of MetS associated with cardiovascular risk [9-11]. Two population-based studies have linked the combined effect of CRP and MetS to predict incident cardiovascular events [9,12]. One study showed that CRP has an additive effect for those with 4 or 5 MetS characteristics on cardiovascular disease [9]. The other study found that using both MetS and CRP does not increase the ability to discriminate cardiovascular events rather than using either one alone [12].

Recently, investigators emphasized the importance of CRP predictive utility and performance in the risk for cardiovascular disease [8,13,14]. The positive association between CRP and cardiovascular disease, independent of the traditional risk factors, has not yet been concluded for use in screening, particularly for cardiovascular disease subtypes [13,14]. To our knowledge, only the Rotterdam Study reported relevant data for the general population that focused only on stroke and suggested a limited improvement in risk assessment [8]. Whether combining CRP with MetS improves risk prediction for stroke as a specific end point remains unexplored.

We undertook a study to determine the risk for stroke in relation to CRP levels and MetS among ethnic Chinese in

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Taiwan. We investigated whether CRP, MetS, or the combination adds to the ability to discriminate stroke risk from the traditional risk factors.

2. Methods

2.1. Subjects

The Chin-Shan Community Cardiovascular Cohort study is a community-based prospective study initiated in 1990 in a suburban township outside of Taipei City, Taiwan. The detailed study design and data collection have been reported elsewhere [15]. Residents in the community aged at least 35 years identified by household visits (excluding those at institutions) were invited to the baseline survey in 1990 (N = 4349). A total of 3602 participants who consented to complete the structured questionnaire interview conducted by trained medical students formed the original cohort. They were able to come to the clinic by themselves for a health checkup conducted by cardiologists. The health checkup included laboratory tests and biochemical examinations of urine and blood samples. The study team subsequently conducted follow-up visits approximately every other year in the same manner, monitored health status, and provided care or consultation for the participants. By the year 2005, the response rate to follow-up was generally 86% or higher for the study population that remained in the cohort. The Institutional Review Board at National Taiwan University Hospital has approved this study.

2.2. Stroke cases and controls

The follow-up and verification for events and deaths have been detailed elsewhere [15,16]. In brief, cardiologists in the study team reviewed the information collected from medical records, annual questionnaires, official death certificates, and household visits to verify the causes of deaths and events. *Stroke* was defined as a sudden neurologic deficit of vascular origin persisting for more than 24 hours that was supported by data from imaging studies. All types of stroke including subarachnoid hemorrhages were included in this study.

The study subjects included in the present nested case-control study were individuals who participated in the follow-up examination in 1994-1995 because the data on MetS components had been documented. Among 2897 participants free of coronary heart disease and stroke in the 1994-1995 examination, 124 of the subjects experienced their first stroke during the 10-year follow-up period until 2005. Of these, 75 subjects provided sufficient blood samples for CRP measurements in the 1994-1995 checkup. After excluding stroke cases with the log-transformed CRP level higher than 3 standard deviations (SDs) of the control distribution (>13.9 mg/L, n = 2) or incomplete information on MetS (n = 8), 65 cases were available with completed data for analysis in this study. The 2 subjects with extreme CRP levels were excluded because they may present an acute or active inflammatory status [1]. We randomly selected 210 individuals from subjects with no history of stroke and coronary heart disease during the follow-up period as controls. A total of 109 controls with available data were eligible for data analyses. Demographic and clinical characteristics, including sex, age, education, lifestyle, body mass index, waist circumference, and blood pressure, were not significantly different between individuals selected for this study and individuals not selected, for either stroke group or control group.

2.3. CRP and biochemical variables

The overnight fast venous blood samples obtained from the participants were immediately refrigerated and transported within 6 hours to National Taiwan University Hospital and stored at −70°C until analysis for measurements. Blood samples were thawed, and CRP levels in the plasma were determined using a high-sensitivity immunoturbidimetric assay (Denka Seiken, Tokyo, Japan) on a Hitachi 911 analyzer (Roche Diagnostics, Indianapolis, IN) [17]. Baseline serum levels of lipids and fasting glucose were determined as described elsewhere [15,16]. All measurements were performed in a central laboratory blinded to the case status at the hospital.

2.4. MetS and risk factors

We defined *MetS* using the criteria from the US National Cholesterol Education Program Adult Treatment Panel III [18], with modified waist circumference cutoff points for Asians [11,19]. The MetS was determined for individuals with 3 or more of the components of triglycerides of at least 150 mg/dL (1.7 mmol/L), systolic blood pressure of at least 130 mm Hg or diastolic blood pressure of at least 85 mm Hg or taking antihypertensive drugs, high-density lipoprotein (HDL) cholesterol less than 40 mg/dL (1.0 mmol/L) in men or less than 50 mg/dL (1.3 mmol/L) in women, fasting glucose of at least 110 mg/dL (6.1 mmol/L), and waist circumference of at least 90 cm in men or at least 80 cm in women. *Hypertension* was defined as systolic blood pressure higher than 140 mm Hg and/or diastolic blood pressure higher than 90 mm Hg and/or taking antihypertensive medication. *Diabetes mellitus* was defined as a fasting serum glucose level greater than 126 mg/dL (7.0 mmol/L) and/or a history of using hypoglycemic agents or insulin injections. The waist circumference was measured by using a tape positioned midway between the lowest rib and the iliac crest in all of the participants in minimal respiration status.

2.5. Statistical analysis

Baseline clinical characteristics were compared between stroke cases and controls using Student *t* test for continuous variables and χ^2 test for categorical variables. Because of the skewed CRP distribution, the difference in medians between the 2 groups was examined using the Wilcoxon rank sum test.

We used 4 multiple logistic regression models to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for assessing the effects of CRP and MetS on the stroke risk. Model 1 evaluated CRP effect based on tertile distribution of controls (≤0.7, >0.7-1.3, >1.3 mg/L). Model 2 assessed MetS effect classified as groups of 0 to 1, 2, and 3 to 5 components. Models 3 and 4 were exclusively adjusted models that included both CRP and MetS categories in the analyses. All the regression models were adjusted for age (continuous variable), sex, waist circumference, total cholesterol (continuous variables for both), and history of hypertension and diabetes mellitus (yes vs no), except that hypertension and diabetes were excluded in model 3 to evaluate their impact on the associations of CRP and MetS with stroke. These covariates selected were those significant at a P value of less than .2 in the univariate analyses. The linear trends across CRP and MetS categories were examined by defining a median CRP value in each tertile and a continuous MetS variable. These 4 models examined the significance of CRP and MetS categories incorporated into the models with traditional risk factors, that is, all selected covariates, using the likelihood ratio test with 2 degrees of freedom. The adequacy for goodness of fit for all models was determined using Hosmer and Lemeshow [20] statistics. These models were also performed using Cox proportional hazard regression analysis to account for time of follow-up.

The joint effect of CRP and MetS on stroke risk was also evaluated by combining them into 4 categories (CRP ≤ top tertile with no MetS, CRP ≤ top tertile with MetS, CRP > top tertile with no MetS, CRP > top tertile with MetS) in multiple logistic regression models. We used 3 models to adjust covariates illustrating the effects of the covariates. Age and sex were adjusted in model A. In model B, waist circumference and total cholesterol were also included. Model C contained the history of diabetes mellitus and hypertension as well as the variables of model B.

To compare the discriminative ability of these models in stroke prediction, we calculated areas under the receiver operating characteristic (ROC) curves for models with traditional risk factors alone and for models including CRP and/or MetS variables. The area under the ROC curve explains the probability of a model to generate a higher estimated value for a randomly selected diseased person than for a nondiseased one [13]. The difference between the 2 areas under correlated ROC curves was compared using the nonparametric method [21]. A two-sided P less than .05 was considered statistically significant. All analyses were performed using SAS 9.1 (SAS Institute, Cary, NC).

3. Results

The follow-up periods to the occurrence of stroke among cases ranged from 0.3 to 10.5 years, with a median of 5.3 years. Table 1 shows that cases were older than controls at the time of collecting specimens for CRP measurement. Cases also had a higher prevalence of hypertension, diabetes, and MetS, and had a higher median level of CRP than controls (1.5 vs 1.0 mg/L, P = .007).

Table 1
Baseline characteristics for incident stroke cases and control subjects

	Cases (n = 65)		Controls (n = 109)		P
	Mean	(SD)	Mean	(SD)	
Sex, men, %	64.6		61.5		.68
Age, y	68.0	(9.2)	65.1	(9.7)	.047
Body mass index, kg/m^2	24.2	(3.2)	24.0	(3.6)	.60
Waist circumference, cm	86.6	(8.9)	84.5	(10.6)	.19
Current smoking, %	33.9		34.3		.95
Current drinking, %	32.8		26.2		.35
Family history of CVD, %	32.2		24.0		.26
History of hypertension, %	58.5		36.7		.005
History of diabetes, %	29.2		18.4		.096
Systolic blood pressure, mm Hg	138.2	(20.0)	128.6	(18.6)	.002
Diastolic blood pressure, mm Hg	79.6	(11.1)	75.7	(10.7)	.023
Total cholesterol, mmol/L	5.3	(1.2)	5.4	(1.0)	.57
HDL cholesterol, mmol/L	1.02	(0.27)	1.04	(0.32)	.64
Triglycerides, mmol/L[a]	1.08	(0.89-1.59)	1.07	(0.76-1.71)	.63
MetS, %	58.5		42.2		.038
High waist circumference, %	52.3		45.9		.41
Elevated blood pressure, %	81.5		53.2		<.001
Impaired fasting glucose, %	53.9		38.5		.049
Lower HDL cholesterol, %	63.1		65.1		.78
Elevated triglycerides, %	20.0		25.7		.39
CRP, mg/L[a]	1.5	(0.7-2.9)	1.0	(0.6-1.5)	.007

Values are mean and SD unless indicated. CVD indicates cardiovascular disease.

[a] Data are medians (interquartile ranges).

The multivariate logistic regression models in Table 2 shows that stroke was significantly associated with hypertension (OR = 2.12; 95% CI, 1.09-4.12) and individuals in the top CRP tertile compared with the bottom tertile of control subjects (OR = 2.55; 95% CI, 1.05-6.23; *P* for trend = .038) after controlling for covariates (model 1). Metabolic syndrome was not a significant independent factor associated with stroke if hypertension was in the model (model 2). The OR associated with the top CRP increased slightly if hypertension and diabetics status were excluded from the regression analysis, whereas MetS became a significant factor associated with stroke (model 3). The OR for stroke associated with the top CRP tertile decreased slightly to 2.63 (95% CI, 1.06-6.53) by including the MetS categories and hypertension in the regression analysis (model 4), and the OR for hypertension decreased to a moderate significant level.

The CRP contribution for the model fit improvement was greater than that for MetS (likelihood ratio tests [P_{LRT}] *P* values were .10 for CRP in model 1 and .44 for MetS in model 2). The P_{LRT} for CRP remained smaller than that for MetS in the analyses simultaneously assessing CRP and MetS as stroke predictors (models 3 and 4). The estimated risks were weaker but remained significant in the Cox regression analyses, except that the likelihood ratio statistics were significant, for both CRP and MetS, in the model without controlling for hypertension (data not shown).

Fig. 1 shows the adjusted joint effects for stroke associated with the top tertile CRP levels and the presence of MetS in the multivariate analyses. Compared with the subjects with low CRP levels and non-MetS, subjects with high CRP levels and MetS had a high risk for stroke after controlling for only age and sex (model A), or for waist circumference and total cholesterol (model B; OR = 3.17; 95% CI, 1.26-7.97). Only individuals with high CRP levels and free of MetS were at a significant risk of having stroke (OR = 2.95; 95% CI, 1.07-8.15) if hypertension and diabetes were also included in the regression (model C).

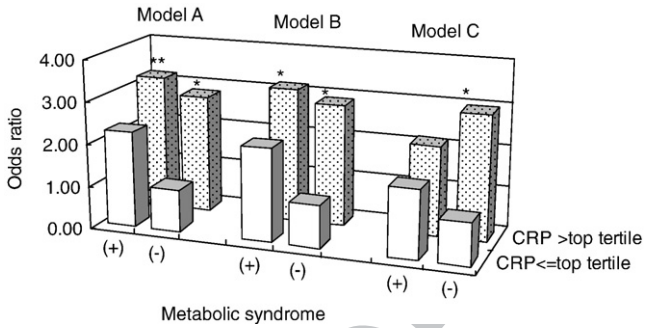

Fig. 1. Odds ratios of incident stroke in 10-year follow-up associated with baseline CRP levels and MetS, the Chin-Shan Community Cardiovascular Cohort Study, Taiwan, 1994-2005. The top tertile value of CRP was 1.3 mg/L. Metabolic syndrome (+) presence; (−) absence. Model A: adjusted for age and sex. Model B: adjusted for age, sex, waist circumference, and total cholesterol. Model C: adjusted further by adding history of diabetes mellitus and hypertension. *$P < .05$. **$P < .01$.

The area under the ROC curves was 0.676 for the model with only traditional risk factors (95% CI, 0.594-0.759) (Table 3). The ability to discriminate was not significantly increased after adding CRP (0.691, *P* = .53), MetS (0.688, *P* = .43), or the combination of CRP and MetS (0.702, *P* = .29) to the model. However, areas under the ROC curves were also not sufficiently different when adding hypertension (0.654), MetS (0.652), CRP (0.639), or joint effect of CRP and MetS (0.669) to the age- and sex-adjusted models.

4. Discussion

This study is the first prospective validation of the association between baseline CRP levels and stroke for a

Table 2
Odds ratios (95% CIs) of incident stroke associated with CRP levels and MetS

	Cases/controls, n	Model 1		Model 2		Model 3		Model 4	
		OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI
CRP tertiles, mg/L									
≤0.7	11/34	1.00	Referent			1.00	Referent	1.00	Referent
>0.7-1.3	20/39	1.57	0.63, 3.90			1.78	0.71, 4.45	1.70	0.67, 4.30
>1.3	34/36	2.55	1.05, 6.23			2.79	1.13, 6.86	2.63	1.06, 6.53
P for trend[a]		0.038				0.031		0.043	
P_{LRT}[b]		0.10				0.070		0.099	
Hypertension		2.12	1.09, 4.12						
MetS, no. of components									
0-1	11/36			1.00	Referent	1.00	Referent	1.00	Referent
2	16/27			1.77	0.66, 4.78	2.32	0.86, 6.26	1.91	0.69, 5.29
3-5	38/46			1.88	0.66, 5.37	2.66	1.03, 6.89	1.75	0.60, 5.13
P for trend[a]				0.30		0.056		0.36	
P_{LRT}[b]				0.44		0.11		0.44	
Hypertension				2.01	1.02, 3.98			1.92	0.96, 3.84

These models were adjusted for age, sex, waist circumference, total cholesterol, and history of hypertension and diabetes mellitus, except that hypertension and diabetes were excluded in model 3.

[a] Test for trend across CRP tertiles and categories of MetS.

[b] Likelihood ratio χ^2 test compares models with the components and without the components with 2 degrees of freedom.

t3.1 Table 3
t3.2 The ROC curve models with traditional risk factors, CRP, and MetS

t3.3		ROC area[a]	95% CI	$P_{ROC\ area}$[b]
t3.4	Traditional risk factors	0.676	0.594, 0.759	
t3.5	+CRP	0.691	0.611, 0.771	.53
t3.6	+MetS	0.688	0.607, 0.769	.43
t3.7	+Combination of CRP and MetS[c]	0.702	0.623, 0.782	.29
t3.8	Age and sex	0.591	0.503, 0.678	
t3.9	+Hypertension	0.654	0.570, 0.738	.10
t3.10	+CRP	0.639	0.554, 0.724	.21
t3.11	+MetS	0.652	0.568, 0.735	.12
t3.12	+Combination of CRP and MetS[c]	0.669	0.585, 0.752	.054

Both CRP and MetS were included as 2 dummy variables. Traditional risk factors include age, sex, waist circumference, total cholesterol, diabetes
t3.13 mellitus, and hypertension.
t3.14 [a] The area under ROC curves.
[b] Each P value compared the difference between ROC area of traditional risk factors alone and the area of adding each corresponding
t3.15 CRP and/or MetS variable.
[c] ~~C-reactive protein~~ and MetS were combined into the following 4 categories: CRP less than or equal to top tertile with no MetS, CRP less than or equal to top tertile with MetS, CRP greater than top tertile with no
t3.16 MetS, and CRP greater than top tertile with MetS.

Chinese community cohort with a 10-year follow-up. This study further extended the observation of previous studies [3-8] to depict the influence of MetS on the association. The Healthy American Women Study [9] and Framingham Offspring Cohort [12] have dealt with this issue but focused on multiple forms of cardiovascular events instead of stroke alone as a unique end point. Our study showed that elevated CRP is a risk factor of stroke independent of the traditional risk factors and MetS.

Based on 498 first-ever strokes, the Rotterdam Study found that high CRP levels were significantly associated with incident stroke assessed with Cox proportional hazards models [8]. They also showed that CRP improved little on traditional risk factors in overall stroke risk prediction. Another large study, the Prospective Study of Pravastatin in the Elderly at Risk, with 865 cases of cardiovascular events, obtained similar findings. The CRP levels were higher in subjects with these events, but the CRP added limited risk prediction value [14]. Our study confirmed the findings of both studies. Furthermore, this study showed that CRP and MetS together do not significantly improve stroke risk prediction beyond the extent obtained by traditional risk factors. The analysis combining CRP and MetS showed significant associations between high CRP levels and the stroke risk regardless of the presence of MetS. It may not be valuable to use both CRP and MetS in stroke prediction when information on traditional risk factors is known.

Including MetS, hypertension, and diabetes as independent variables in the same regression model may cause overadjustment because hypertension and diabetes are components of MetS. However, rather than measuring the MetS-stroke relationship alone, this study evaluated the ability of MetS in risk discrimination in addition to the traditional risk factors. Furthermore, subjects with MetS had a much higher prevalence of hypertension than those with no MetS (56.5% vs 22.2%) in this study. We used 4 models to measure the strength of MetS counts in the association with stroke other than the traditional risk factors. Previous studies that dealt with this issue did not make adjustments for hypertension, although high blood pressure was prevalent in their study populations (38.5% to 78.5%) [22,23]. The Framingham Offspring Cohort considered the influence of hypertension and showed a positive association between MetS and stroke after adjusting for the systolic blood pressure and treatment of hypertension [24]. Our findings revealed that the risk of stroke associated with MetS was removed by adding diabetes and hypertensive status in the model, whereas hypertension remained a significant risk factor for stroke. This observation can be supported by a Japanese cross-sectional study, which showed that, in people without hypertension, MetS was not associated with carotid atherosclerosis after adjusting for traditional risk factors [25]. Our observation suggests that hypertension seems to play a more important role than MetS does in the stroke risk in this study population. The role of hypertension in the MetS-stroke association may need to be considered in further studies.

Evidence has shown ethnic differences in levels of cardiovascular risk factors. Compared with the US and European population, the Chinese population has a higher stroke incidence, with lower lipid levels and smaller body mass indexes, but more prevalent hypertension [26]. Race differences in the CRP levels may be also attributable to the multiethnic disparities for the stroke risk [27-29]. Compared with the US ethnic groups, the median CRP level was the lowest in Asians [27]. The disparity was also observed in people of Asian ethnic origins, among whom the mean CRP level is lower in the Chinese population than in the South Asian population [28]. Using a uniform CRP cut point to distinguish the high-risk group from the low-risk groups of cardiovascular disease in various races has been questioned [13]. We indeed found a lower CRP level associated with increased risk for stroke in our population than in whites [3,4], and the level is similar to that observed in Japanese [6] and American Japanese [5]. Our further analysis using ROC curves also revealed a lower discriminating ability with the US Centers for Disease Control and Prevention–recommended categories (<1, 1-3, and >3 mg/L) than with tertile of CRP.

This study had some limitations. First, our study did not separate stroke types because a few cases were lacking in data on imaging studies. After extensive inquiry, 30% of stroke cases were still unclassified because of lack of adequate medical documentation, particularly for the sudden deaths with the unspecified stroke cases. However, our additional analysis, with 10 hemorrhagic stroke cases excluded, showed no change in the findings. Second, about half of the selected cases and controls were excluded from data analysis in this study because of insufficient quantity of blood samples and incomplete information on MetS

components. However, we further compared the baseline data between subjects included in this study and those not included, for cases and controls separately. Results showed no significant differences in both demographic and clinical characteristics, including lipid and fasting glucose levels. Additional analysis using Cox regression model to compare all stroke cases with original cohort showed the risks associated with MetS in hazard ratios to be similar to the present study, indicating no selection bias. This study revealed an apparent significant finding in the CRP and stroke association in cooperating with MetS, regardless of a relatively small sample size. Third, because only 3 stroke cases and 2 control subjects had atrial fibrillation at baseline, we did not make adjustment using atrial fibrillation to avoid unstable estimates and broad CI. However, the results showed that the model fit was improved (data not shown). Finally, the participants with extreme CRP values were excluded because of suspected conditions of acute or active inflammation; but analyses including these subjects made no difference in the results.

In conclusion, our findings suggest that MetS and the elevated CRP level are important factors that may increase the stroke risk in the study population. This population may be at a higher risk even if the CRP levels are not as high as those found in whites. However, CRP, MetS, or the combination of these 2 measurements adds limited utility in the risk screening to the traditional risk factors because of economic consideration. The management of established risk factors, particularly hypertension, for the patients at an elevated risk remains as important as that of CRP and MetS in the primary stroke prevention. The blood pressure measurement is noninvasive and easy to conduct.

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References

[1] Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon III RO, Criqui M, et al. Centers for Disease Control and Prevention; American Heart Association. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107:499-511.

[2] Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med 2004;350:1387-97.

[3] Rost NS, Wolf PA, Kase CS, Kelly-Hayes M, Silbershatz H, Massaro JM, et al. Plasma concentration of C-reactive protein and risk of ischemic stroke and transient ischemic attack: the Framingham study. Stroke 2001;32:2575-9.

[4] Cao JJ, Thach C, Manolio TA, Psaty BM, Kuller LH, Chaves PH, et al. C-reactive protein, carotid intima-media thickness, and incidence of ischemic stroke in the elderly: the Cardiovascular Health Study. Circulation 2003;108:166-70.

[5] Curb JD, Abbott RD, Rodriguez BL, Sakkinen P, Popper JS, Yano K, Tracy RP. C-reactive protein and the future risk of thromboembolic stroke in healthy men. Circulation 2003;107:2016-20.

[6] Wakugawa Y, Kiyohara Y, Tanizaki Y, Kubo M, Ninomiya T, Hata J, et al. C-reactive protein and risk of first-ever ischemic and hemorrhagic stroke in a general Japanese population: the Hisayama Study. Stroke 2006;37:27-32.

[7] Cesari M, Penninx BW, Newman AB, Kritchevsky SB, Nicklas BJ, Sutton-Tyrrell K, et al. Inflammatory markers and onset of cardiovascular events: results from the Health ABC study. Circulation 2003;108:2317-22.

[8] Bos MJ, Schipper CM, Koudstaal PJ, Witteman JC, Hofman A, Breteler MM. High serum C-reactive protein level is not an independent predictor for stroke: the Rotterdam Study. Circulation 2006;114:1591-8.

[9] Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. Circulation 2003;107:391-7.

[10] Ridker PM, Wilson PW, Grundy SM. Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? Circulation 2004;109:2818-25.

[11] Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735-52.

[12] Rutter MK, Meigs JB, Sullivan LM, D'Agostino Sr RB, Wilson PW. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. Circulation 2004;110:380-5.

[13] Lloyd-Jones DM, Liu K, Tian L, Greenland P. Narrative review: assessment of C-reactive protein in risk prediction for cardiovascular disease. Ann Intern Med 2006;145:35-42.

[14] Sattar N, Murray HM, McConnachie A, Blauw GJ, Bollen EL, Buckley BM, et al, PROSPER Study Group. C-reactive protein and prediction of coronary heart disease and global vascular events in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). Circulation 2007;115:981-9.

[15] Lee Y, Lin RS, Sung FC, Yang C, Chien K, Chen W, et al. Chin-Shan Community Cardiovascular Cohort in Taiwan—baseline data and five-year follow-up morbidity and mortality. J Clin Epidemiol 2000;53:838-46.

[16] Chien KL, Sung FC, Hsu HC, Su TC, Lin RS, Lee YT. Apolipoprotein A-I and B and stroke events in a community-based cohort in Taiwan: report of the Chin-Shan Community Cardiovascular Study. Stroke 2002;33:39-44.

[17] Vukovich TC, Mustafa S, Rumpold H, Wagner O. Evaluation of a turbidimetric Denka Seiken C-reactive protein assay for cardiovascular risk estimation and conventional inflammation diagnosis. Clin Chem 2003;49:511-2.

[18] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.

[19] Internal Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome. Available at: http://www.idf.org/webdata/docs/IDF_Meta_def_final.pdf. Accessed June 28, 2008.

[20] Hosmer Jr DW, Lemeshow S. Applied logistic regression. New York: John Wiley & Sons press; 1989.

[21] DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837-45.

[22] McNeill AM, Rosamond WD, Girman CJ, Golden SH, Schmidt MI, East HE, et al. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. Diabetes Care 2005;28:385-90.

[23] Wannamethee SG, Shaper AG, Lennon L, Morris RW. Metabolic syndrome vs Framingham risk score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. Arch Intern Med 2005; 165:2644-50.

[24] Najarian RM, Sullivan LM, Kannel WB, Wilson PW, D'Agostino RB, Wolf PA. Metabolic syndrome compared with type 2 diabetes mellitus as a risk factor for stroke: the Framingham Offspring Study. Arch Intern Med 2006;166:106-11.

[25] Ishizaka N, Ishizaka Y, Hashimoto H, Toda E, Nagai R, Yamakado M. Metabolic syndrome may not associate with carotid plaque in subjects with optimal, normal, or high-normal blood pressure. Hypertension 2006;48:411-7.

[26] Forouhi NG, Sattar N. CVD risk factors and ethnicity–a homogeneous relationship? Atheroscler Suppl 2006;7:11-9.

[27] Albert MA, Glynn RJ, Buring J, Ridker PM. C-reactive protein levels among women of various ethnic groups living in the United States (from the Women's Health Study). Am J Cardiol 2004;93:1238-42.

[28] Anand SS, Razak F, Yi Q, Davis B, Jacobs R, Vuksan V, et al. C-reactive protein as a screening test for cardiovascular risk in a multiethnic population. Arterioscler Thromb Vasc Biol 2004;24: 1509-15.

[29] Khera A, McGuire DK, Murphy SA, Stanek HG, Das SR, Vongpatanasin W, et al. Race and gender differences in C-reactive protein levels. J Am Coll Cardiol 2005;46:464-9.