

C-Reactive Protein, the Metabolic Syndrome, and Risk of Incident Cardiovascular Events

An 8-Year Follow-Up of 14 719 Initially Healthy American Women

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Background—The metabolic syndrome describes a high-risk population having 3 or more of the following clinical characteristics: upper-body obesity, hypertriglyceridemia, low HDL, hypertension, and abnormal glucose. All of these attributes, however, are associated with increased levels of C-reactive protein (CRP).

Methods and Results—We evaluated interrelationships between CRP, the metabolic syndrome, and incident cardiovascular events among 14 719 apparently healthy women who were followed up for an 8-year period for myocardial infarction, stroke, coronary revascularization, or cardiovascular death; 24% of the cohort had the metabolic syndrome at study entry. At baseline, median CRP levels for those with 0, 1, 2, 3, 4, or 5 characteristics of the metabolic syndrome were 0.68, 1.09, 1.93, 3.01, 3.88, and 5.75 mg/L, respectively ($P_{\text{trend}} < 0.0001$). Over the 8-year follow-up, cardiovascular event-free survival rates based on CRP levels above or below 3.0 mg/L were similar to survival rates based on having 3 or more characteristics of the metabolic syndrome. At all levels of severity of the metabolic syndrome, however, CRP added prognostic information on subsequent risk. For example, among those with the metabolic syndrome at study entry, age-adjusted incidence rates of future cardiovascular events were 3.4 and 5.9 per 1000 person-years of exposure for those with baseline CRP levels less than or greater than 3.0 mg/L, respectively. Additive effects for CRP were also observed for those with 4 or 5 characteristics of the metabolic syndrome. The use of different definitions of the metabolic syndrome had minimal impact on these findings.

Conclusions—These prospective data suggest that measurement of CRP adds clinically important prognostic information to the metabolic syndrome. (*Circulation*. 2003;107:391-397.)

Key Words: protein, C-reactive ■ risk factors ■ prognosis ■ diabetes mellitus ■ inflammation

Patients with the metabolic syndrome are at increased risk for diabetes and cardiovascular events,¹⁻³ and the recently released Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP-III) stresses the importance of targeting prevention strategies for such individuals.⁴ The ATP-III guideline also suggests a working definition of the metabolic syndrome that includes the presence of at least 3 of the following characteristics: abdominal obesity, elevated triglycerides, reduced levels of HDL cholesterol, high blood pressure, and high fasting glucose. However, all of these parameters are associated with elevated levels of C-reactive protein (CRP), an easily measured inflammatory biomarker that has proven to be a strong, independent predictor of both incident diabetes^{5,6} and incident cardiovascular disease.⁷⁻¹⁴ CRP levels also correlate

with several other components of the metabolic syndrome such as fasting insulin, microalbuminuria, and impaired fibrinolysis that are not easily evaluated in usual clinical practice.¹⁵⁻²⁰ We therefore sought to evaluate in a large-scale population cohort the potential interrelationships between CRP, the metabolic syndrome, and incident cardiovascular events. We additionally sought evidence as to whether or not CRP might add prognostic information at all levels of severity of the metabolic syndrome.

Methods

We evaluated the relationship of CRP with components of the metabolic syndrome among apparently healthy women participating in the Women's Health Study (WHS), an ongoing trial of aspirin and vitamin E in primary prevention. Details of the WHS and the methods used to ascertain baseline risk factors and adjudicate clinical outcomes have been described elsewhere.^{8,10} In brief, American

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Dr Ridker is named as a coinventor on patents filed by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes.

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women aged 45 years and over with no prior history of cardiovascular disease or cancer were enrolled between November 1992 and July 1995, at which time they provided detailed information on demographic, lifestyle, and behavioral risk factors. Of these women, 28 345 provided baseline blood samples collected in EDTA, which were stored in liquid nitrogen. Since enrollment, all study participants have been followed up for incident cardiovascular events, including nonfatal myocardial infarction, nonfatal ischemic stroke, coronary revascularization procedures, and cardiovascular death.

Because recent randomized trial evidence indicates a net hazard in association with hormone replacement therapy (HRT), we elected to increase the generalizability of our data by limiting our analysis to the 15 745 WHS participants not using HRT at study entry. Of these, 14 719 were also free of diabetes at study entry and contributed complete data for all 5 components of the metabolic syndrome. Baseline blood samples from these women were thawed and assayed for CRP by a validated high-sensitivity assay (Denka Seiken), whereas triglyceride and HDL cholesterol levels were ascertained with direct measurement assays (Roche Diagnostics).

Women with 3 or more of the following attributes are typically defined as having the metabolic syndrome: (1) triglycerides ≥ 150 mg/dL; (2) HDL cholesterol < 50 mg/dL; (3) blood pressure $\geq 135/85$ mm Hg; (4) obesity as defined by a waist circumference > 88 cm; and (5) abnormal glucose metabolism as defined by a fasting glucose ≥ 110 mg/dL. In the WHS, triglycerides, HDL cholesterol, and blood pressure were directly ascertained as outlined above. However, waist circumference was not measured until year 6 of follow-up. As such, we elected to use as our cutpoint for obesity a body mass index (BMI) > 26.7 kg/m², a value that corresponded to the same percentile cutpoint for BMI at year 6 as did a waist circumference of 88 cm measured at that time. To address whether this choice of BMI affected our results, we repeated our analyses using a BMI cutpoint of 30 kg/m² as suggested in recent European guidelines.²¹ Because fasting glucose levels were not available, we elected to conservatively use the diagnosis of incident type II diabetes during study follow-up as an alternative measure of baseline impairment of glucose metabolism. To address how closely these definitions represented the metabolic syndrome, we compared the proportion of women in the present study categorized according to characteristics of the metabolic syndrome as defined above to that previously published for American women in the National Health and Nutrition Survey (NHANES)²² using categories defined by the ATP-III guideline.

To evaluate for evidence of association between baseline CRP levels and the metabolic syndrome, we first compared the distribution of CRP levels among individuals with or without each of the individual components of the syndrome as defined above. Because levels of CRP are skewed, we evaluated the significance of any differences in median values between groups using the Wilcoxon rank-sum test. We then classified all study subjects as having 0, 1, 2, 3, 4, or 5 components of the metabolic syndrome and assessed for evidence of a relation of median CRP levels across these groups using the Jonckheere-Terpstra test. We then used logistic regression analysis to discern whether elevated CRP levels added prognostic information on risk of subsequent cardiovascular events across the

TABLE 1. Prevalence of Metabolic Syndrome Abnormalities Among Participants in the Women's Health Study

No. of Metabolic Abnormalities	Women's Health Study (n=14 719)	NHANES Survey (n=4549)
≥ 1	72.2(0.4)	70.9(1.2)
≥ 2	45.9(0.4)	42.7(1.3)
≥ 3	24.4(0.4)	23.4(0.9)
≥ 4	8.9(0.2)	9.6(0.5)
5	1.2(0.1)	2.9(0.3)

Data are % (SEM). For comparison, data are also shown from the NHANES survey. See Methods for a description of the criteria used for each component of the metabolic syndrome.

full spectrum of severity of the metabolic syndrome. Consistent with recent recommendations from the Centers for Disease Control and Prevention, a CRP cutpoint of 3 mg/L was used to differentiate high-risk and low-risk groups.²³

To directly compare the clinical utility of CRP alone to that of the metabolic syndrome alone, we constructed 8-year cardiovascular event-free survival curves for those with CRP levels above or below 3.0 mg/L and compared these to survival curves based on the presence or absence of 3 or more components of the metabolic syndrome. Age-adjusted c statistics, analogous to the area under the receiver operator characteristic (ROC) curve, were used to assess the discrimination of cardiovascular prediction models based on CRP alone versus those based on having 3 or more characteristics of the metabolic syndrome. These analyses were then repeated with continuous rather than dichotomous definitions used for components of the metabolic syndrome. Finally, in analysis stratified by those with and without the metabolic syndrome, we sought evidence in terms of cardiovascular event-free survival that CRP levels might have additional prognostic value in the prediction of incident cardiovascular end points.

Results

Mean age of the 14 719 women evaluated in the present study was 54 ± 7.6 years. As defined by the proportion of individuals with increasing numbers of characteristics of the metabolic syndrome, the women participating in the present study were almost identical to those evaluated in the recent NHANES report²² (Table 1). Specifically, the proportion of women in the present cohort with 3 or more characteristics of the metabolic syndrome was 24.4% compared with 23.4% in NHANES.

Table 2 presents median CRP values (with interquartile ranges) for those study participants with and without each individual component of the metabolic syndrome. Consistent with prior cross-sectional data, CRP levels were significantly

TABLE 2. Median CRP Levels (Interquartile Range) Among 14 719 American Women According to the Presence or Absence of Each Component of the Metabolic Syndrome

Characteristic	Present	Absent	P
Obesity (n=5158)	3.13 (1.57–5.63)	0.95 (0.43–2.04)	< 0.0001
Hypertriglyceridemia (n=4297)	2.56 (1.24–4.84)	1.11 (0.48–2.57)	< 0.0001
Low HDL cholesterol (n=7572)	2.02 (0.88–4.26)	1.00 (0.44–2.31)	< 0.0001
High blood pressure (n=4859)	2.38 (1.06–4.78)	1.14 (0.48–2.56)	< 0.0001
Abnormal glucose metabolism (n=568)	4.30 (2.51–7.48)	1.39 (0.57–3.16)	< 0.0001
≥ 3 Characteristics (n=3597)	3.38 (1.76–6.01)	1.08 (0.47–2.37)	< 0.0001

See Methods for a description of the criteria used for each component of the metabolic syndrome.

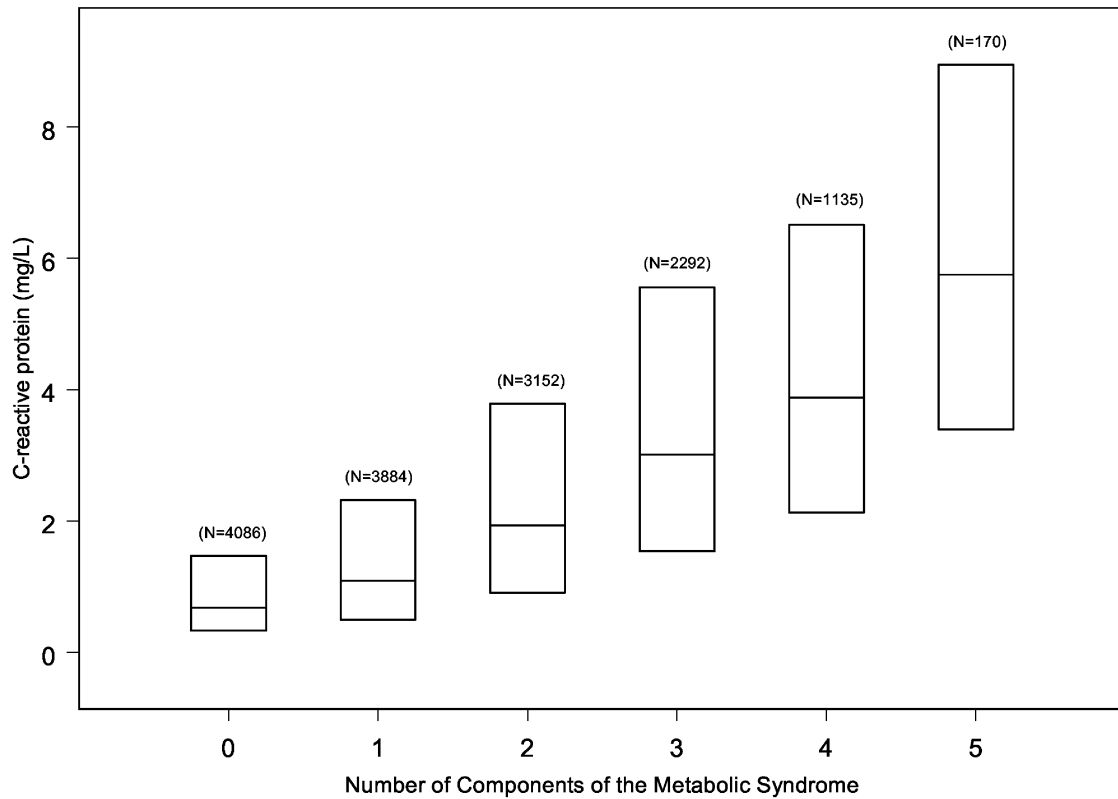


Figure 1. Distribution of CRP levels among 14 719 American women according to presence of 0, 1, 2, 3, 4, or 5 components of metabolic syndrome. Box plots demonstrate median, 25th, and 75th percentile values for CRP.

higher among women who had each component of the metabolic syndrome than among women who did not (all $P < 0.0001$).

Figure 1 displays the distribution of CRP levels after women were classified according to their total number of components of the metabolic syndrome. As shown, there was a strong linear increase in CRP levels as the number of components of the metabolic syndrome increased; median CRP levels for those with 0, 1, 2, 3, 4, or 5 characteristics of the metabolic syndrome were 0.68, 1.09, 1.93, 3.01, 3.88, and 5.75 mg/L, respectively ($P_{\text{trend}} < 0.0001$).

As shown in Figure 2, CRP levels > 3 mg/L at baseline added prognostic information at all levels of severity of the metabolic syndrome. This additive effect was particularly apparent among those with 3, 4, or 5 characteristics of the metabolic syndrome (all $P < 0.001$).

Figure 3 presents results of the survival analyses directly comparing CRP with the metabolic syndrome. As shown, the predictive value of CRP levels above or below 3.0 mg/L in terms of the development of first-ever cardiovascular events was quite similar to the predictive value associated with having or not having 3 or more characteristics of the metabolic syndrome. In age-adjusted analyses, the area under the ROC curve associated with CRP alone was 0.77 versus 0.78 for the metabolic syndrome.

As prespecified, we additionally sought evidence that CRP might have prognostic utility among those with and without the metabolic syndrome. We therefore first performed an analysis limited to the 3597 study participants classified as

having 3 or more characteristics of the metabolic syndrome at study entry. Among these women, we observed significant increases in rates of future cardiovascular disease as levels of baseline CRP increased. Specifically, age-adjusted incidence rates were 3.4 and 5.9 events per 1000 person-years of exposure for those with baseline CRP levels less than or greater than 3.0 mg/L, respectively ($P < 0.001$).

To further explore these interrelationships, we divided the study cohort into 4 groups on the basis of the presence or absence of the metabolic syndrome and on the basis of CRP levels less than or greater than 3.0 mg/L. As shown in Figure 4 (left), CRP evaluation provided additional prognostic information both for those with and without the metabolic syndrome. The age-adjusted relative risks of future cardiovascular events for women in the low-CRP/no metabolic syndrome, high-CRP/no metabolic syndrome, low-CRP/yes metabolic syndrome, and high-CRP/yes metabolic syndrome groups were 1.0 (referent), 1.5 (95% CI 1.0 to 2.2), 2.3 (95% CI 1.6 to 3.3), and 4.0 (95% CI 3.0 to 5.4), respectively.

We performed several additional analyses to address the robustness of these findings. First, because the concept of the metabolic syndrome was developed in part to reflect a secondary target population without hyperlipidemia, we repeated our analyses for the 12 453 women with baseline LDL cholesterol levels < 160 mg/dL and for the 8500 women with LDL cholesterol < 130 mg/dL. As shown in Figure 4 (middle and right), CRP provided prognostic information in addition to the metabolic syndrome in both of these latter analyses. The relative risks and associated CIs for these analyses are presented in Table 3.

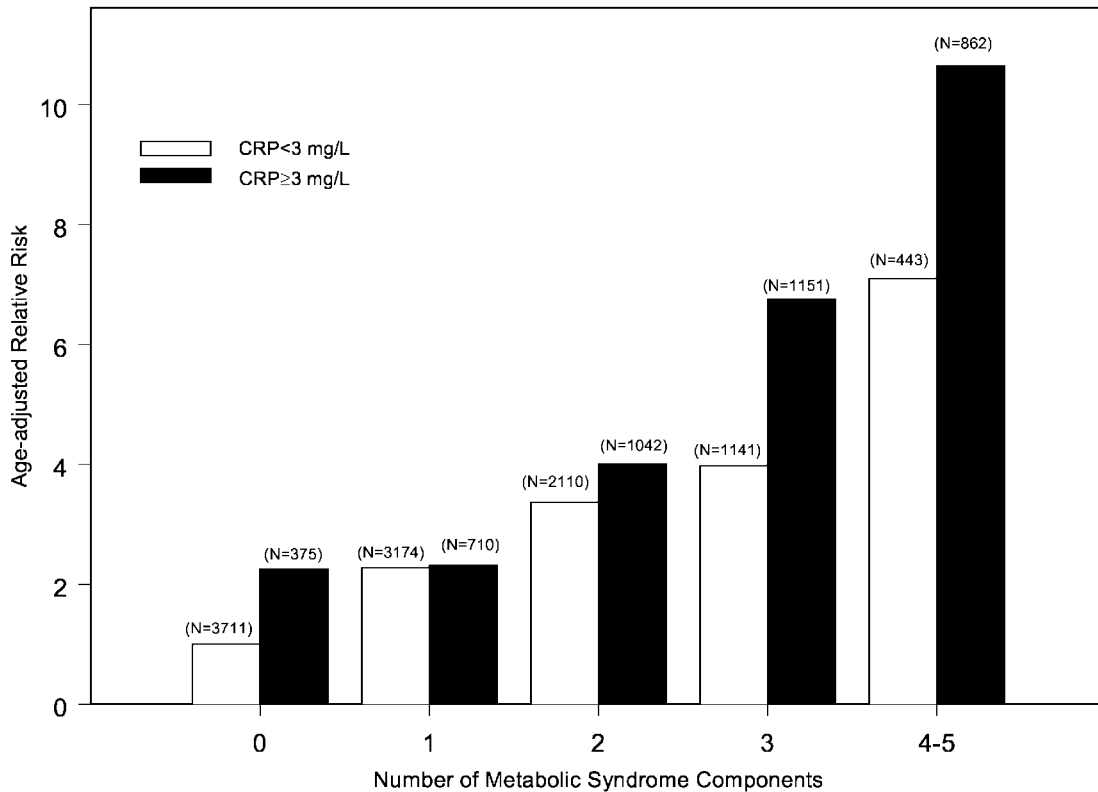


Figure 2. Relative risks of future cardiovascular events according to number of components of metabolic syndrome and according to CRP levels above or below 3.0 mg/L.

Second, and as also shown in Table 3, we repeated our analyses using only the end point of coronary heart disease. For this end point, overall effects were, if anything, larger than that observed with the a priori combined end point that also included thromboembolic stroke.

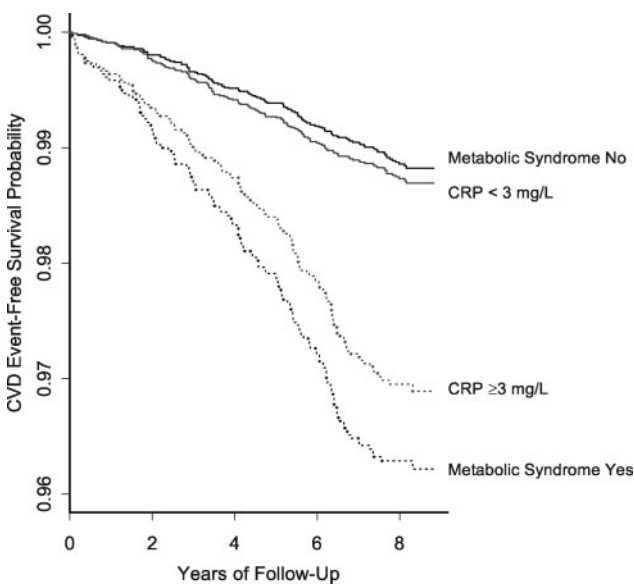


Figure 3. Comparison of cardiovascular event-free survival for those with and without metabolic syndrome to those with baseline CRP levels above or below 3.0 mg/L. CVD indicates cardiovascular disease.

Third, we repeated our analyses using continuous rather than dichotomous variables and found similar effects. In the continuous variable models, the relative risk of future cardiovascular events associated with CRP levels >3.0 mg/L was 1.5 ($P=0.006$), and the area under the ROC curve was 0.82. By contrast, when dichotomous definitions for each component of the metabolic syndrome were used, the corresponding relative risk was 1.6 ($P=0.0003$), and the corresponding area under the ROC curve was 0.79.

Fourth, we repeated our primary analyses using a BMI cutpoint of 30 kg/m² and again found almost identical results in terms of additive predictive value. Use of this cutpoint, however, classified only 17% of the present cohort as obese. By contrast, the use of a BMI cutpoint of 26.7 kg/m² (as done in our primary analyses) classified 32% of the cohort as obese, a value closer to that observed in the NHANES survey.

Finally, we performed an additional analysis limited to those 3597 participants with the metabolic syndrome at study entry and found that CRP levels <1, 1 to 3, and >3 mg/L stratified the population into 3 risk groups such that those with the metabolic syndrome and the highest CRP levels had a relative risk 2.1 times that of those with the metabolic syndrome who had the lowest CRP levels (95% CI 1.1 to 4.2, $P=0.001$; Figure 5). In all these analyses, virtually identical results were observed when we excluded incident diabetes as part of the definition of the metabolic syndrome.

Discussion

Recent guidelines stress the importance of identifying individuals with the metabolic syndrome as a high-risk group for

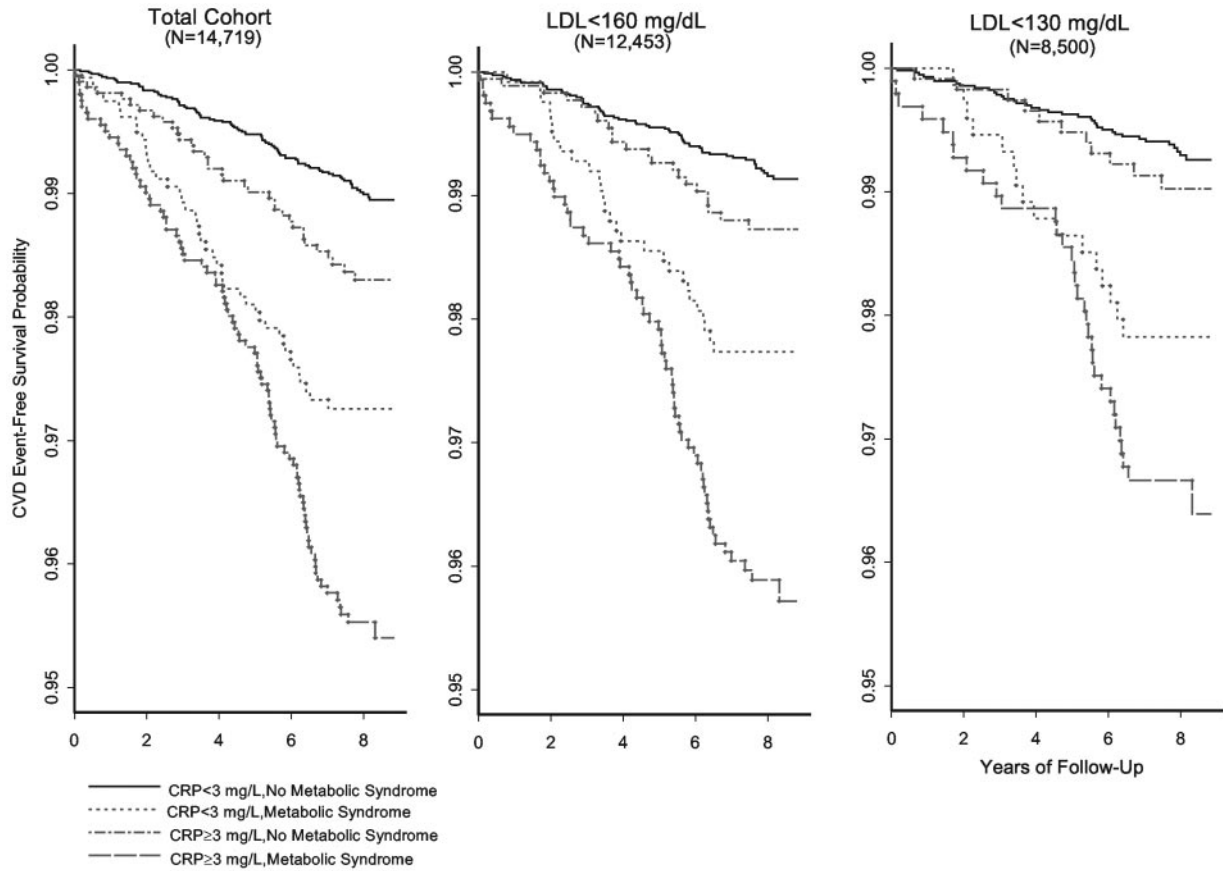


Figure 4. Cardiovascular event-free survival in analyses stratified by both CRP and metabolic syndrome. CVD indicates cardiovascular disease.

the development of cardiovascular disease.⁴ The present prospective cohort of 14 719 initially healthy women confirms this association, because those with the metabolic syndrome had significantly worse cardiovascular event-free survival than did those without the metabolic syndrome. However, the present data also demonstrate that at all levels of severity of the metabolic syndrome, CRP added important and independent prognostic information in terms of future cardiovascular risk. This additive effect was present in all study groups evaluated and was robust to the several methods used to define the metabolic syndrome.

That CRP levels correspond with individual components of the metabolic is consistent with work of other investiga-

tors^{15–20} and the hypothesized role of inflammation in several processes critical to the development of both diabetes and atherothrombosis.^{24,25} Indeed, in this cohort, we have previously shown baseline CRP levels to be a strong predictor not only of myocardial infarction and stroke^{8,10} but also of incident type 2 diabetes.⁵ Rapidly evolving work now demonstrates that in addition to being a marker of innate immunity, CRP also has several direct effects at the level of the vessel wall.^{26,27} These observations, along with basic research into the inflammatory mechanisms of both diabetes and vascular dysfunction, provide strong evidence that insulin resistance and atherosclerosis share a common inflammatory basis.²⁸ CRP, however, is also associated with several aspects

TABLE 3. Relative Risks (95% CIs) of Future Cardiovascular Events According to CRP Levels Greater Than or Less Than 3.0 mg/L and According to the Presence or Absence of the Metabolic Syndrome

	All Cardiovascular Events			
	Total Cohort (n=14 719)	LDL <160 mg/dL (n=12 453)	LDL <130 mg/dL (n=8500)	Coronary Events Total Cohort (n=14 719)
CRP <3 mg/L, no metabolic syndrome	1.0	1.0	1.0	1.0
CRP >3 mg/L, no metabolic syndrome	1.5 (1.0–2.2)	1.3 (0.8–2.2)	1.2 (0.6–2.3)	1.6 (0.9–2.7)
CRP <3 mg/L, yes metabolic syndrome	2.3 (1.6–3.3)	2.2 (1.4–3.5)	2.5 (1.4–4.4)	3.1 (2.0–4.9)
CRP >3 mg/L, yes metabolic syndrome	4.0 (3.0–5.4)	4.4 (3.1–6.3)	4.4 (2.8–7.1)	5.5 (3.8–8.0)

Data are shown for all cardiovascular events (n=255) and for coronary events only (n=163).

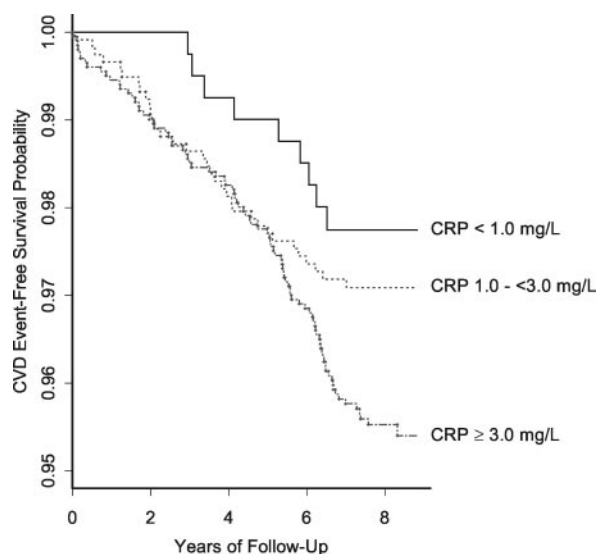


Figure 5. Cardiovascular event-free survival in analyses stratified by CRP levels <1, 1 to 3, and ≥ 3 mg/L. Data are shown for 3597 study participants with metabolic syndrome at study entry. CVD indicates cardiovascular disease.

of the metabolic syndrome not easily ascertained in usual clinical practice, including fasting insulin, hypofibrinolysis, and microalbuminuria.^{15–20} Our finding that CRP measurement adds important prognostic information to clinical definitions of the metabolic syndrome is thus consistent with this hypothesis.

Limitations of this study must be considered. First, the study included only women. We believe, however, that these data are likely to generalize to men because other studies have linked markers of inflammation to individual components of the metabolic syndrome in men, and many cohort studies have already shown CRP to independently predict vascular events in men.^{7,11–14} Second, because we did not have fasting glucose levels in all participants, we elected instead to use the diagnosis of incident diabetes during follow-up as a surrogate for abnormal baseline glucose metabolism. We believe this choice to be valid because other work has shown CRP levels to correlate with fasting glucose level²⁹ and predict incident type 2 diabetes.^{5,6} Moreover, as shown in Table 1, this choice was, if anything, conservative, because it resulted in only 1.2% of the present cohort being defined as having all 5 characteristics of the metabolic syndrome versus 2.9% in the NHANES survey. We also believe it unlikely that this decision affected validity, because elevated fasting glucose is by far the least common abnormality used to define those with the metabolic syndrome. Finally, these analyses do not make adjustment for other factors that may affect CRP levels, such as smoking status.

We recognize that these data have broad implications for the development of therapies targeting insulin resistance, diabetes, and atherothrombosis. We have previously shown that aspirin and statins are relatively more effective in reducing vascular risk among those with elevated CRP levels,^{7,9,30} and we have hypothesized on that basis that CRP is likely to have utility in the targeting of therapies for the primary prevention of cardiovascular disease. At the same

time, weight reduction and exercise, the first-line therapies stressed by ATP-III for the management of the metabolic syndrome, also reduce CRP levels. Furthermore, a recent report suggests that rosiglitazone directly reduces CRP levels, an intriguing observation because this PPAR- γ inhibitor is already established as standard therapy for those with type II diabetes.³¹

In sum, these data provide clear evidence that the presence of at least 3 of 5 components of the metabolic syndrome predicts incident cardiovascular events in apparently healthy women. However, these data also indicate that among those with and without the metabolic syndrome, baseline CRP levels add clinically relevant prognostic information concerning future vascular risk.

Acknowledgments

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