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Long-term C-Reactive Protein Variability and Prediction of Metabolic Risk

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Abstract

Purpose—This analysis was undertaken to determine the long-term intraindividual variability, determinants of change, and capacity of the inflammatory marker, C-reactive protein (CRP), to predict metabolic traits and diabetes in a large community-based population.

Methods—Intraindividual CRP variability, predictors of CRP change and metabolic events were evaluated in the Framingham Heart Study Offspring cohort using data from the same 2409 participants with CRP measured by the same methodology at each of 3 exam cycles, spanning 20 years.

Results—Between first and second examinations (averaging 16 years apart), 23–47% of men and 27–49% of women remained within the same quintile of CRP values. An additional 24–51% of men and 24–50% of women occupied an adjacent quintile. Intermediate-term CRP variability (over 4 years) was similar to long-term variability. Both long and intermediate-term variability of CRP was significantly less than that of plasma cholesterol, measured in these same groups. Linear regression models for CRP at the intermediate examination demonstrated that CRP at the initial examination contributed the largest proportion of the variability (partial R-square=0.27) seen in the overall model after adjustment for other covariates known to affect CRP concentrations. Although logistic regression models demonstrated that CRP over the intermediate term did not predict new-onset metabolic syndrome at the final examination, CRP did predict an increase in glucose and new-onset diabetes.

Conclusions—Results of this longitudinal analysis suggest the intraindividual, long-term variability of CRP concentrations is relatively small and over an intermediate-term of 4 years is predictive of new diabetes.

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Keywords

epidemiology; C-reactive protein; metabolic syndrome; diabetes

INTRODUCTION

C-reactive protein (CRP) is a non-specific marker of inflammation that is notably increased in subjects with the pro-inflammatory states of the metabolic syndrome (MetS) and diabetes,¹⁻³ diagnoses that predispose individuals to develop cardiovascular disease.⁴ Whereas the extent to which high blood concentrations of CRP may be an independent predictor of cardiovascular disease is still unclear, it has been demonstrated that higher CRP identifies individuals who may have vascular or metabolic abnormalities, which are often present at early stages of cardiovascular disease.⁵

Unlike the more traditional risk factors for cardiovascular disease such as high cholesterol, high glucose, and high blood pressure (BP), there appears to be little information related to the long-term biological (or intraindividual) variability of CRP measurements. Furthermore, there appear to be no sizable population studies that have assessed the extent to which the long or intermediate-term variability of CRP may be related to other major risk factors for cardiovascular disease, nor the extent to which CRP measured at an earlier time point might be used to predict the development of the MetS or diabetes later in life. Several analyses of CRP variability, using current sensitive CRP analytical methods, have been undertaken in studies of relatively small, ostensibly healthy groups for several months up to one year⁶⁻⁸ and in one case⁹ for 5 years. These studies have shown that CRP concentrations are relatively stable and between-examination variability has ranged from 40-60%, which was comparable to the variability of cholesterol^{7,8} or other major cardiovascular risk factors.⁷

The present analysis was undertaken to examine the intraindividual variability of CRP in the large group of men and women that constitutes the Framingham Offspring cohort over intervals much more prolonged than previously reported; to assess the strength of a number of CRP-related measures to predict future CRP concentrations; and in multivariable analysis, to assess the association of CRP with the development of the MetS or diabetes.

METHODS**Study sample**

Study of the Framingham Offspring cohort was begun in 1971.¹⁰ During the period from 1979-2001, seven examinations of this group were completed, usually at 4-year intervals. Serum CRP concentrations were measured using the same procedure at 3 examination periods: from 1979-83 (Examination 2); from 1995-98 (Examination 6); and from 1998-2001 (Examination 7). The present analysis was limited to participants with CRP measured at each of these 3 examination cycles, and consisted of 1123 men and 1286 women (representing 72.5% of the men and 72.1% of the women who attended the Cycle 7 examination). The study was approved by the Institutional Review Board at Boston University Medicine Center and all participants gave written informed consent.

Clinical measurements

Participants provided a medical history, underwent a physical examination, and had a series of laboratory tests. Subjects were considered to have cardiovascular disease if they had a history of coronary heart disease, death due to coronary heart disease, stroke, transient ischemic attack, intermittent claudication, or heart failure by a panel of three physicians who reviewed medical

and hospital records.¹¹ Fasting glucose concentrations were categorized by 2003 American Diabetes Association criteria. MetS was defined by the NCEP Adult Treatment Panel III criteria, as refined in 2004.¹² For this analysis, the diagnosis of MetS did not include subjects with known diabetes.

Laboratory measurements

Blood was obtained from study participants who had fasted for at least 10 hours. At each of the 3 examinations, total cholesterol, triglycerides, and HDL-C were measured by procedures previously described and modified after examination 2 only by the substitution of the apolipoprotein B-precipitant, dextran-Mg⁺² for heparin-Mn⁺², for the measurement of HDL-C.¹³ LDL-C values were obtained using the Friedewald formula. The intraassay coefficient of variation was less than 5% for all lipid measurements. Glucose was measured using a hexokinase reagent with intraassay variability that was below 3%.

High-sensitivity CRP was measured at all cycles using the same nephelometric method, analytical instrument (Dade-Behring BN 100 nephelometer), and protocol for maintaining quality control over a 2-year period. Analyses were performed to routinely include blinded replicate specimens every 25th sample. Interassay and intraassay coefficients of variation for examination 2 averaged 5.0% and 3.8%, respectively; for examination 6 these averaged 3.4% and 3.8%, respectively; and for examination 7 these averaged 5.1% and 3.2%, respectively. Although measurements were made over a two year period (from 05/2002 to 06/2004), values of CRP re-measured at the beginning and end of this 2-year period were very similar, with mean±SD in 2002 of 2.79±2.56 mg/L and in 2004 of 2.76±2.34 mg/L for 35 randomly chosen samples.

To provide a referent structure for evaluating CRP changes, the intraindividual variability of plasma cholesterol was also compared, long and intermediate-term, in the same Framingham groups used for CRP assessment. Values for cholesterol were those that were measured at the times that subjects were examined, using the Abell Kendall method¹⁴ at examination 2 and an automated cholesterol oxidase-based procedure at examinations 6 and 7.¹⁵ A cross-comparison of methods was conducted to ensure comparable cholesterol results between earlier and later cycles of examinations.

Statistical analysis

All analyses were performed using SAS 8. Intermediate- and long-term intra-individual CRP variability, during average follow-up times of 4 and 16 years were compared. Shift-tables of sex-specific quintiles of CRP were compared for consistency between examinations 2 versus 6 and between examinations 6 versus 7 using weighted Kappa test for symmetry. CRP variability between examinations was examined using sex-specific Spearman correlation coefficients. A comparison of the intermediate and long-term variability of CRP with total cholesterol was undertaken using the McNemar's test, comparing the shift-tables of participants with greater than a one quintile change in CRP distribution to a one quartile change in cholesterol distribution between the same pairs of examinations.

A variety of metabolic variables and cardiovascular risk factors have been associated with CRP concentrations, as previously reviewed.¹⁶ Two multiple linear regression models were constructed to assess which of these covariates, including initial CRP values (CRP at examination 2), best predicted future CRP concentrations (CRP at examination 6). The first model included the covariates at examination 2 of age, sex, body mass index (BMI), systolic BP, diastolic BP, smoking status, prevalent cardiovascular disease, fasting glucose, triglycerides, and the total cholesterol/HDL-C ratio as well as aspirin use, BP therapy, lipid therapy, and hormone replacement therapy. The second multiple linear regression model

utilized those examination 2 covariates and their examination 6 equivalents. A stepwise backwards selection procedure using all examination 2 and 6 covariates was used to select the most parsimonious model.

The association of long-term change in CRP, defined as CRP at examination 6 minus CRP at examination 2, and CRP at examination 6 with incident MetS and diabetes at examination 7 were evaluated using multivariable logistic regression. Models were adjusted for the metabolic parameters and cardiovascular risk factors present at examination 6. Participants with established diagnoses of the MetS and/or diabetes at examination 6 were excluded from analyses with either of these diagnoses as an endpoint. The discriminative ability of the models was assessed using a c-statistic.

RESULTS

The characteristics of the study sample are shown in Table 1 at each of 3 examination cycles for men and women separately. Data are shown as mean values (SD) or percentages for the same individuals at each of 3 examination periods.

Longitudinal, Intraindividual CRP Variability

CRP values at each examination were divided into sex-specific quintiles. The percentage of men and women with the same quintile ranking are shown in Table 2, first comparing examination 2 with examination 6 (for long-term variability), and then examination 6 with examination 7 (for intermediate-term variability). Both long-term and intermediate-term CRP variability showed similar patterns in men and women. The largest percentage of subjects remaining in the same quintile between examinations occurred at the extremes of the quintile distribution, (i.e., at the lowest and highest quintiles) comparing both examination 2 with 6 and examination 6 with 7. A comparison of CRP quintiles at examination 2 with examination 6, showed that a high of 45 to 47% of men and 49% of women stayed in the same quintile of CRP at both examinations. Qualitatively similar results for CRP variability were found in the intermediate follow-up time period between examination 6 and 7. In the intermediate case, at the highest and lowest quintile, 52 to 56% of men and 62 to 65% of women remained within their same quintile at each examination.

CRP measurements at earlier and later cycles of examinations were highly correlated. For men, the Spearman correlation coefficient between CRP quintiles measured at examination 2 and 6 was 0.51, between examination 2 and 7 was 0.48, and between examination 6 and 7 was 0.60. For women, similar values comparing CRP quintiles were obtained between examination 2 and 6 ($r=0.54$), examination 2 and 7 ($r=0.51$), and examination 6 and 7 ($r=0.71$). All correlation coefficients were significant ($P<0.0001$).

Tests of symmetry for each of the sex-specific analyses were not significant ($P>0.10$), indicating that movement of participants into adjacent quintiles between examination cycles was equally likely in both directions. Tests for intraindividual agreement using a weighted Kappa test for symmetry was highly significant at both pairs of examinations compared ($P<0.0001$), indicating that individuals were properly assigned to their respective quintiles.

Cholesterol measurements at earlier and later cycles of examinations were highly correlated and all were significant ($P<0.0001$), comparing examination 2 with examination 6 ($r=0.44$ for men and $r=0.52$ for women) and comparing examination 6 with examination 7 ($r=0.61$ for men and $r=0.57$ for women). As shown in Table 3, results were similar for both sexes. Over the longer interval from examination 2 to 6, 42-48% of the population remained within the highest and 44-46% remained within the lowest quintile designations. Over the intermediate interval between examinations (examination 6 to 7), 51% of men and women remained at the highest

level and 54% at the lowest level of a cholesterol quintile distribution. However, a sex-pooled comparison of the change in quintile distributions between cholesterol and CRP showed that a change of more than one quintile of CRP was significantly less frequent than a change in one quintile of cholesterol ($P=0.0001$) over both long and shorter-term periods of examinations ($P=0.0004$).

Variables predicting long-term CRP changes

Two multiple linear regression models were used to explore the correlates of future CRP concentrations. The first model, predicting concentrations of CRP at examination 6 using examination 2 variables was significant with an overall model R^2 of 0.32 ($P<0.0001$). Parameter estimates for significant covariates at examination 2 are shown in the first part of Table 4 and included CRP at examination 2, sex, age, BMI, systolic and diastolic BP, and smoking status. Baseline (examination 2) factors not selected in the stepwise backwards selection procedure and therefore excluded from the final model were prevalent cardiovascular disease, aspirin use, BP therapy, lipid or hormone therapy, and glucose, triglycerides, and the cholesterol/HDL-C ratio.

In the second model (second part of Table 4), adding examination 6 to examination 2 covariates, increased the overall model R^2 to 0.43 ($P<0.0001$). CRP at examination 2 was significant ($P<0.05$) as were the following other examination 2 covariates (age, BMI, systolic BP, diastolic BP, and smoking status) and examination 6 covariates (BMI, glucose, cholesterol/HDL-C ratio, BP therapy, hormone therapy, and lipid therapy). CRP accounted for 29% of overall variability in the second model with a large extent of variability also related to hormone replacement therapy and sex.

Association of CRP and Related Variables with New-onset MetS or the Development of Diabetes

The extent to which CRP was associated with new-onset MetS or the development of diabetes was assessed by multiple logistic regression in conjunction with a number of other variables related to CRP or to the development of the MetS or diabetes. Over 90% of the participants (2177/2409) had criteria available at examination 6 and 7 to diagnose the MetS. Of these, 38% (831/2177) were excluded from this analysis with a diagnosis of prevalent MetS at examination 6 leaving 1346 participants eligible for an analysis of incidence. Of these 1346 participants, 21% (276/1346) developed MetS by examination 7. As shown in Table 5, neither the change in CRP from examination 2 to 6 nor the CRP value at examination 6 predicted the MetS at examination 7. In contrast to the absence of a significant association of CRP, MetS incidence was associated positively with female sex, age, BMI, diastolic BP, fasting blood glucose, and the ratio of total cholesterol to HDL-C. As additionally shown, the presence of MetS at examination 7 was strongly associated with the use of BP or lipid therapy at examination 6. This model was significant ($P<0.0001$) with high discriminatory power (c-statistic = 0.808).

All 2409 participants had information available at examination 6 and 7 to confirm or exclude the diagnosis of diabetes. From these 2409, 8% (202/2409) had diabetes at examination 6 and were excluded from the analysis of new diabetes at examination 7, leaving 2207 participants. Sixteen percent (352/2207) with glucose <110 mg/dL at examination 6 progressed to either impaired fasting glucose ($n=280$) or diabetes with glucose >125 mg/dL ($n=72$) by examination 7. Sex, BMI, glucose, prevalent cardiovascular disease at examination 6 were significant predictors of impaired glucose or diabetes at examination 7 (OR and 95% confidence intervals shown on Table 5). This model was significant ($P<0.0001$) with high discriminatory power (c-statistic = 0.934).

DISCUSSION

In an assessment of the variability and associations of the inflammatory marker CRP in the Framingham Offspring cohort, we observed that intraindividual variability of CRP was similar when CRP was re-measured over relatively long and intermediate-term periods, averaging 16 and 4 years. After adjusting for major variables known to be related to CRP the strongest predictor of CRP concentrations in this longitudinal analysis were CRP values measured on average 16 years earlier, accounting for 27% of the overall variability of future CRP concentrations. Neither long-term CRP change nor CRP concentrations 4 years earlier were associated with new-onset MetS but were associated with a significant increase in fasting blood glucose and a new diagnosis of diabetes.

The variability of CRP measurements has previously been assessed in smaller samples and for far shorter time intervals than in our present analysis.⁷⁻⁹ In the longest of these, CRP variability was evaluated in a Japanese study of 388 individuals over a 5-year period.⁹ Those investigators reported a 43% correlation between the initial and subsequent mean CRP concentrations, which is similar to the correlations between CRP measurements that we have observed in the Framingham cohort over a much longer interval.

As reported by others in smaller comparative CRP studies,^{7,8} we also have compared the intraindividual variability of CRP to the variability of total plasma cholesterol over the same time periods. In this analysis, we have made the assumption that although there have been large changes in certain variables that are known to influence concentrations of both CRP and cholesterol (most notably, the frequency of lipid therapy), these changes would be distributed in a similar pattern throughout the population so as not to distort a comparison (of percentages) within an ordered distribution of a population between examinations. We have found, contrary to findings in the smaller, shorter-term studies, that the extent of variability of CRP measurements in Framingham was significantly less over both relatively long and intermediate intervals than the variability of cholesterol measurements.

We tested a number of clinical and laboratory variables that have previously been found to influence CRP concentrations and evaluated their relation to future CRP concentrations. Although a relatively large number of measurements in Framingham were significantly related to future CRP values, the strongest single predictor of CRP values appeared to be prior CRP itself. There are well-described sex differences in CRP that appear to be more highly correlated with the use of estrogen therapy than with female sex per se or with a predisposition to inflammation.^{17,18} In any case, hormone replacement therapy which is known to increase concentrations of CRP was found to be strongly related to future CRP measurements as was lipid therapy (predominantly with statins), which has been shown to reduce CRP concentrations¹⁹ as well as other markers of inflammation.²⁰

In the present analysis, we did not find that long-term change or the previous concentration of CRP predicted the development of the MetS. However, we did find that MetS was associated with other variables in our multivariable model that are key components defining the MetS (BMI, glucose, BP, and HDL-C relative to cholesterol) or are therapies used in the treatment of these MetS components (specifically, BP or lipid therapy). In cross-sectional analysis, CRP concentrations have previously been shown to correlate with a number of features of the MetS¹ or add to the prediction of vascular events in individuals with known MetS.^{1,21} However, we know of no studies, including one previously from Framingham,²² in which CRP, when evaluated in conjunction with other proinflammatory biomarkers, has been shown to independently predict the MetS.

In contrast to the MetS, we did find that CRP was associated with an increase in fasting blood glucose and the development of diabetes. Although we have no certain explanation for this

association, it is notable that an increase in CRP concentrations is strongly associated with the presence of insulin resistance²³⁻²⁵ and higher CRP concentrations have been found to be predictive of adult-onset diabetes in at least two other large population studies.^{3,17} In contrast to these results, an earlier study from Framingham has reported that CRP was only of borderline significance in the prediction of new diabetes.²⁶ In that analysis, however, CRP was measured by an older, less sensitive immunologic method than the nephelometric procedure that we have used for this present analysis of trends.

It has been proposed that CRP be measured in clinical practice in addition to more classic risk factors to estimate cardiovascular risk or to better define an inflammatory component of risk that is associated with the MetS or diabetes.²⁷ Our findings suggest that single measurements of CRP spaced several years apart, which may be a good reflection of usual clinical practice, can provide a highly reliable measure of this biomarker in the individual patient. The apparent stability of CRP over relatively long periods irrespective of the potential for CRP change with, for example, seasonal variation and infectious diseases, provides a strong measure of confidence that a single measurement of CRP in the individual patient is a representative CRP value.

Strengths and limitations

We believe our observations have broad applicability to the general population. The Framingham Heart Study is a large longitudinal study with a well-characterized cohort and standardized methods of analysis. Although the Framingham cohort is largely a white population, NHANES III survey data has shown that there is very little difference in CRP concentrations between a variety of ethnic groups living in the United States.²⁸ Furthermore, although there has been a suggestion that CRP concentrations might be higher in Indian Asians than in European whites, this difference can be largely explained by differences in central obesity.²⁹ We believe that the scope of this analysis far exceeds any previous comparative CRP measurements; that analytic variability has been minimized by the use of the same high-sensitivity CRP method and the same laboratory throughout this analysis.

We recognize that our comparison of CRP with cholesterol variability may be faulted for a number of reasons. Most prominently this might include a variable and increasing use of cholesterol-lowering statin therapy in the Framingham cohort (as shown in Table 1). However, statin therapy also lowers CRP, often by percentages that are comparable to those attained for cholesterol reduction.^{19,20} We further recognize that there are measurement issues that might limit a comparison of CRP and cholesterol. Whereas CRP represents a single molecular form, cholesterol is present in the blood as unesterified and esterified molecules that are components in variable proportions of different lipoproteins which are metabolized at different rates. Finally, although our cholesterol measurements were well-standardized by cross-comparisons, cholesterol was measured over longer intervals than was CRP and this might be expected to result in inherently greater analytical variability for cholesterol than for CRP measurements.

Conclusions

Single measurements of CRP from specimens obtained as long as 20 years earlier appear to be more highly predictive of future concentrations of CRP than a variety of other commonly-measured metabolic or cardiovascular risk factors. Although CRP is associated with many features of the MetS, CRP in this sample was not associated with new-onset of the MetS but was positively related to development of higher concentrations of blood glucose and the incidence of diabetes.

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Table 1
Major Characteristics of the Framingham Offspring by Sex and Examination Cycle.

Characteristics	Men (n=1123)				Women (n=1286)			
	Examination				Examination			
	2	6	7		2	6	7	
Age, years	43 (10)	59 (10)	62 (10)		43 (10)	59 (10)	62 (10)	
Body mass index, kg/m ²	26.6 (3.5)	28.6 (4.3)	28.8 (4.5)		24.5 (4.7)	27.3 (5.5)	27.6 (5.7)	
Systolic BP, mm Hg	125 (14)	129 (17)	128 (18)		118 (16)	127 (20)	126 (20)	
Diastolic BP, mm Hg	80 (9)	77 (10)	75 (10)		75 (9)	74 (9)	72 (10)	
Cholesterol/HDL-C	5.0 (2)	4.9 (2)	4.5 (1)		3.9 (1)	3.9 (1)	3.7 (1)	
HDL-C, mg/dL	43 (11)	43 (12)	45 (13)		54 (13)	58 (16)	60 (16)	
Triglycerides, mg/dL	142 (79)	143 (93)	142 (98)		103 (54)	132 (80)	132 (78)	
Glucose, mg/dL	101 (18)	107 (27)	109 (31)		94 (12)	100 (25)	100 (22)	
Current smoker, %	40	55	13		32	47	12	
Prevalent disease								
Hypertension, %	44	61	61		26	51	53	
Diabetes, %	2	11	14		1	7	9	
Obesity, %	15	31	33		11	25	26	
MetS, %	13	44	53		4	34	43	
Cardiovascular disease, %	3	15	19		2	7	9	
Therapy								
BP, %	9	31	38		8	25	32	
Diabetes, %	1	6	8		<1	3	5	
Lipid, %	2	16	25		1	10	18	
Aspirin, %	25	36	40		28	23	26	
Hormone, %	-	-	-		3	27	30	
CRP, mg/L								
Group mean	2.3	3.6	4.3		2.1	4.9	4.6	
Quintile 1 mean	0.3 (0.1)	0.5 (0.2)	0.6 (0.2)		0.2 (0.1)	0.5 (0.2)	0.6 (0.2)	
Quintile 2 mean	0.6 (0.1)	1.0 (0.2)	1.2 (0.2)		0.4 (0.1)	1.2 (0.2)	1.3 (0.3)	
Quintile 3 mean	1.1 (0.2)	1.8 (0.3)	2.0 (0.4)		0.8 (0.2)	2.4 (0.5)	2.7 (0.5)	
Quintile 4 mean	2.1 (0.5)	3.3 (0.6)	3.9 (0.8)		1.9 (0.4)	4.8 (1.1)	5.1 (1.0)	
Quintile 5 mean	7.7 (8.5)	11.2 (12.7)	13.9 (19.9)		7.1 (7.6)	15.4 (18.4)	13.4 (7.9)	

Data shown is given as mean values (SD) or percentages for the same individuals at each of 3 examination periods. Examination 2 was conducted from 1995-98; and examination 7 from 1998 to 2001.

Prevalent disease criteria. Hypertension, by systolic BP>140 mm Hg, diastolic BP >90 mmHg, or history; diabetes by fasting glucose >125 mg/dL or by history; obesity by BMI $\geq$ 30 kg/m²; MetS by presence of $\geq$ 3 NCEP III criteria (Methods).

Abbreviations: BP, blood pressure; HDL-C, HDL-cholesterol; MetS, Metabolic syndrome; CRP, C-reactive protein.

Table 2
Sex-specific Cross Comparisons of the CRP Distribution at Different Framingham Examination Cycles.

A. CRP Quintile Rankings for Men and Women at Examination 2 and 6												
Exam 2 CRP Quintiles	Men Exam 6 CRP Quintiles					Subjects (n)	Women Exam 6 CRP Quintiles					Subjects (n)
	1	2	3	4	5		1	2	3	4	5	
1	47	25	13	9	6	227	49	24	13	9	5	256
2	24	35	22	12	7	223	29	27	24	13	7	255
3	18	19	23	25	15	223	12	26	29	18	15	261
4	6	13	25	28	28	227	7	14	21	34	24	257
5	5	8	16	26	45	223	2	9	14	26	49	257
Subjects (n)	225	225	224	225	224	1123	256	257	259	257	257	1286
B. CRP Quintile Rankings for Men and Women at Examination 6 and 7												
Exam 6 CRP Quintiles	Men Exam 7 CRP Quintiles					Subjects (n)	Women Exam 7 CRP Quintiles					Subjects (n)
	1	2	3	4	5		1	2	3	4	5	
1	56	26	11	4	3	225	65	25	6	2	2	256
2	21	33	27	12	7	225	20	42	25	9	5	257
3	10	22	32	21	15	224	9	19	37	26	9	259
4	8	12	22	33	24	225	2	9	25	41	23	257
5	4	7	8	30	52	224	3	5	7	23	62	257
Subjects (n)	224	225	224	226	224	1123	253	261	258	257	257	1286

Values shown in individual cells are percentages of men and women with the same quintile ranking for CRP at examinations 2 (1979-83) and 6 (1995-98).

For men, a Test of Symmetry (S) = 4.53 ($P=0.92$), Weighted Kappa = 0.37

For women, a Test of Symmetry (S) = 6.77 ($P=0.75$), Weighted Kappa = 0.40

Values shown in individual cells are percentages of men with the same quintile ranking for CRP at examinations 6 (1995-98) and 7 (1998-2001).

For men, a Test of Symmetry (S) = 11.06 ($P=0.35$), Weighted Kappa = 0.46.

For women, a Test of Symmetry (S) = 7.76 ($P=0.65$), Weighted Kappa = 0.57.

Table 3
Sex-specific Cross Comparisons of the Quintile Distribution of Cholesterol at Different Framingham Examination Cycles.

A. Cholesterol Quintile Rankings for Men and Women at Examination 2 and 6.												
Exam 2 Cholesterol Quintiles	Men Exam 6 Cholesterol Quintiles					Subjects (n)	Women Exam 6 Cholesterol Quintiles					Subjects (n)
	1	2	3	4	5		1	2	3	4	5	
1	42	27	15	13	3	222	48	25	17	7	3	255
2	22	25	21	22	8	220	25	25	24	20	7	262
3	17	19	28	21	21	238	13	21	24	24	17	254
4	13	15	22	24	24	222	9	17	23	25	27	259
5	6	15	14	20	44	221	6	13	12	24	46	256
Subjects (n)	226	219	226	227	225	1123	254	261	259	260	252	1286
B. Cholesterol Quintile Rankings for Men and Women at Examination 6 and 7.												
Exam 6 Cholesterol Quintiles	Men Exam 7 Cholesterol Quintiles					Subjects (n)	Women Exam 7 Cholesterol Quintiles					Subjects (n)
	1	2	3	4	5		1	2	3	4	5	
1	51	30	13	4	2	226	51	27	14	5	2	254
2	19	30	25	20	5	219	22	32	26	15	6	261
3	16	20	28	27	9	226	10	19	25	32	15	259
4	8	10	25	31	28	227	7	12	23	33	26	260
5	6	11	10	19	56	225	10	10	12	15	52	252
Subjects (n)	229	217	233	221	223	1123	261	248	260	263	254	1286

Values shown within individual cells are percentages of men and women with the same quintile ranking for CRP at examinations 6 (1995-98) and 7 (1998-2001).

For men, Test of Symmetry (S) = 15.91 (P=0.10), Weighted Kappa = 0.29.

For women, Test of Symmetry (S) = 12.97 (P=0.23), Weighted Kappa = 0.34.

Values shown within individual cells are percentages of men and women with the same quintile ranking for CRP at examinations 6 (1995-98) and 7 (1998-2001).

For men, Test of Symmetry (S) = 30.3 (P=0.0008), Weighted Kappa = 0.43.

For women, Test of Symmetry (S) = 38.23 (P<0.0001), Weighted Kappa = 0.41.

Table 4

CRP-related Variables Predicting Future CRP.

Variables at exam 2	Parameter estimate (SE)	P-value
CRP	0.44 (0.02)	<0.0001
Sex	0.43 (0.04)	<0.0001
Age	0.01 (0.002)	<0.0001
BMI	0.03 (0.006)	<0.0001
Systolic BP	- 0.005 (0.002)	0.01
Diastolic BP	0.008 (0.003)	0.02
Smoking status	0.12 (0.04)	0.006
Variables at exam 2 or exam 6		
CRP at exam 2	0.43 (0.02)	<0.0001
Sex	0.22 (0.04)	<0.0001
Age at exam 2	0.02 (0.002)	<0.0001
BMI at exam 2	- 0.06 (0.008)	<0.0001
BMI at exam 6	0.08 (0.006)	<0.0001
Cholesterol/HDL-C at exam 6	0.11 (0.01)	<0.0001
Smoking status at exam 2	0.08 (0.04)	0.03
BP therapy at exam 6	0.10 (0.04)	0.02
Hormone therapy at exam 6	0.67 (0.06)	<0.0001
Lipid therapy at exam 6	- 0.21 (0.06)	0.0002

Demographic, clinical, and laboratory variables are shown which by linear regression analysis predicted CRP change over an average of 16 years (from examination 2 (1979-83) to examination 6 (1995-98)).

Abbreviations: CRP, C-reactive protein; BMI, body mass index; HDL-C, HDL-cholesterol; BP, blood pressure; exam, examination.

Table 5

Probability of CRP and Related Variables in the Prediction of a New Diagnosis of the Metabolic Syndrome or Diabetes

Covariate	MetS		Diabetes	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
CRP change (exam 2-6)	1.02 (0.88-1.19)	0.78	0.81 (0.60-1.09)	0.16
CRP at exam 6	1.06 (0.89-1.26)	0.53	1.78 (1.29-2.46)	0.0005
Sex	1.67 (1.15-2.43)	0.0073	0.62 (0.31-1.23)	0.17
Age	1.03 (1.01-1.05)	0.0061	0.97 (0.94-1.01)	0.14
BMI	1.17 (1.12-1.22)	<0.0001	1.06 (1.01-1.12)	0.023
Systolic BP	1.001 (0.99-1.01)	0.86	1.01 (0.99-1.03)	0.60
Diastolic BP	1.04 (1.01-1.06)	0.0022	0.98 (0.95-1.02)	0.31
Glucose	1.05 (1.03-1.07)	<0.0001	1.19 (1.15-1.23)	<0.0001
Cholesterol/HDL-C	1.74 (1.47-2.05)	<0.0001	1.02 (0.81-1.29)	0.85
Triglycerides	1.49 (0.96-2.30)	0.074	1.73 (0.88-3.38)	0.11
Smoking	0.82 (0.60-1.12)	0.20	0.95 (0.54-1.68)	0.87
Cardiovascular disease	1.30 (0.73-2.32)	0.37	2.16 (1.00-4.68)	0.05
Aspirin therapy	0.86 (0.59-1.25)	0.44	0.82 (0.43-1.55)	0.54
BP therapy	2.07 (1.39-3.10)	0.0004	0.78 (0.42-1.46)	0.44
Hormone therapy	1.34 (0.82-2.19)	0.25	0.84 (0.28-2.50)	0.76
Lipid therapy	5.09 (2.65-9.77)	<0.0001	1.85 (0.84-4.05)	0.12

All covariates, except for change in CRP from examination 2 (1979-83) to examination 6 (1995-98), were measured at examination 6 and used in logistic regression models to predict a diagnosis of new MetS or diabetes at examination 7 (1998-2001).

Abbreviations: CRP, C-reactive protein; MetS, metabolic syndrome; BMI, body mass index; BP, blood pressure; HDL-C, HDL-cholesterol; exam, examination