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## C-Reactive Protein and Other Circulating Markers of Inflammation in the Prediction of Coronary Heart Disease

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### ABSTRACT

#### BACKGROUND

C-reactive protein is an inflammatory marker believed to be of value in the prediction of coronary events. We report data from a large study of C-reactive protein and other circulating inflammatory markers, as well as updated meta-analyses, to evaluate their relevance to the prediction of coronary heart disease.

#### METHODS

Measurements were made in samples obtained at base line from up to 2459 patients who had a nonfatal myocardial infarction or died of coronary heart disease during the study and from up to 3969 controls without a coronary heart disease event in the Reykjavik prospective study of 18,569 participants. Measurements were made in paired samples obtained an average of 12 years apart from 379 of these participants in order to quantify within-person fluctuations in inflammatory marker levels.

#### RESULTS

The long-term stability of C-reactive protein values (within-person correlation coefficient, 0.59; 95 percent confidence interval, 0.52 to 0.66) was similar to that of both blood pressure and total serum cholesterol. After adjustment for base-line values for established risk factors, the odds ratio for coronary heart disease was 1.45 (95 percent confidence interval, 1.25 to 1.68) in a comparison of participants in the top third of the group with respect to base-line C-reactive protein values with those in the bottom third, and similar overall findings were observed in an updated meta-analysis involving a total of 7068 patients with coronary heart disease. By comparison, the odds ratios in the Reykjavik Study for coronary heart disease were somewhat weaker for the erythrocyte sedimentation rate (1.30; 95 percent confidence interval, 1.13 to 1.51) and the von Willebrand factor concentration (1.11; 95 percent confidence interval, 0.97 to 1.27) but generally stronger for established risk factors, such as an increased total cholesterol concentration (2.35; 95 percent confidence interval, 2.03 to 2.74) and cigarette smoking (1.87; 95 percent confidence interval, 1.62 to 2.16).

#### CONCLUSIONS

C-reactive protein is a relatively moderate predictor of coronary heart disease. Recommendations regarding its use in predicting the likelihood of coronary heart disease may need to be reviewed.

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SINCE ATHEROSCLEROSIS MAY, IN PART, BE an inflammatory disease,<sup>1</sup> circulating factors related to inflammation may be predictors of cardiovascular disease in general populations.<sup>2</sup> A recent statement from the Centers for Disease Control and Prevention and the American Heart Association concluded that it is reasonable to measure C-reactive protein, a sensitive circulating marker of inflammation, as an adjunct to the measurement of established risk factors in order to assess the risk of coronary heart disease.<sup>3</sup> The report acknowledged, however, that the epidemiologic data to support this view were not entirely consistent and recommended that larger prospective studies be conducted to improve the reliability of the evidence.

We measured C-reactive protein concentrations in approximately 2400 patients with coronary heart disease diagnosed since their enrollment in the cohort and approximately 4000 controls nested within the Reykjavik Study, a prospective cohort study of about 19,000 middle-aged men and women without a history of myocardial infarction. The number of cases of coronary heart disease in this cohort was about four times as great as in the largest previous study<sup>4</sup> and should reduce the scope for random error in our estimates. We also assessed the effect of within-person variation in the concentrations of inflammatory markers<sup>5</sup> in serial blood samples obtained over a period of several years in several hundred participants. To compare the predictive value of the C-reactive protein concentration with that of some other inflammatory markers studied in coronary heart disease, we also analyzed the erythrocyte sedimentation rate and circulating concentrations of von Willebrand factor, each of which can also fluctuate considerably in acute-phase inflammatory responses.<sup>6,7</sup> To help put the new data in context, we updated meta-analyses of previous relevant studies of each of these inflammatory markers.

## METHODS

### PATIENTS AND CONTROLS

The Reykjavik Study, initiated in 1967 as a prospective study of cardiovascular disease, has been described in detail previously.<sup>8</sup> All men born between 1907 and 1934 and all women born between 1908 and 1935 who were residents of Reykjavik, Iceland, and its adjacent communities on December 1, 1966, were identified in the national population register and then invited to participate in the study during five stages of recruitment between 1967 and 1991. A total of 8888 men and 9681 women without a his-

tory of myocardial infarction were enrolled, reflecting a response rate of 72 percent.<sup>9</sup>

Nurses administered questionnaires, made physical measurements, performed spirometry and electrocardiography, and collected venous blood samples after an overnight fast for the measurement of the erythrocyte sedimentation rate and to prepare aliquots of serum, which were stored at  $-20^{\circ}\text{C}$  for subsequent analysis. All participants have subsequently been monitored with respect to death from any cause and the occurrence of major cardiovascular conditions, with a total loss to follow-up of only about 0.6 percent of participants.<sup>9</sup>

A total of 2459 men and women with available serum samples had major coronary events between the beginning of follow-up and December 31, 1995, for a mean ( $\pm$ SD) duration of follow-up of  $17.5 \pm 8.7$  years, as compared with  $20.6 \pm 8.2$  years among controls. Among the men, 1073 deaths from coronary heart disease and 701 nonfatal myocardial infarctions were recorded (564 confirmed and 137 possible myocardial infarctions), and among the women, 385 died of coronary heart disease and 300 had a nonfatal myocardial infarction (237 confirmed and 63 possible myocardial infarctions). Deaths from coronary heart disease were ascertained from central registers on the basis of a death certificate listing an *International Classification of Diseases* code of 410 through 414, and the diagnosis of nonfatal myocardial infarction was based on the criteria of the Monitoring Trends and Determinants in Cardiovascular Disease study.

We selected 3969 control subjects from among the participants who had survived to the end of the study period without having a myocardial infarction. The controls were frequency-matched to the patients with respect to the calendar year of recruitment, sex, and age (in five-year increments).<sup>10</sup>

The National Bioethics Committee and the Data Protection Authority of Iceland approved the study protocol. All participants provided informed consent.

### LABORATORY METHODS

Laboratory measurements were made without knowledge of the participants' disease status, and thus samples from patients and controls were randomly distributed among assay plates. Concentrations of C-reactive protein were measured by latex-enhanced immunoturbidimetry, with a lower limit of detection of 0.02 mg per liter (Roche Diagnostics).<sup>11</sup> The variation in C-reactive protein values within runs was less than 1 percent, and the be-

tween-day variability was 1 percent at a concentration of 14 mg per liter and 3.7 percent at a concentration of 3.8 mg per liter. The concentration of von Willebrand factor was determined by means of a sensitive enzyme immunoassay. We also determined the concentration of von Willebrand factor in paired plasma and serum samples from 56 healthy persons from another study and found close agreement between plasma and serum values (correlation coefficient, 0.94).<sup>7</sup> The Wintrobe method was used to measure the erythrocyte sedimentation rate in fresh blood samples obtained at the time of base-line venesection.<sup>6</sup> Other biochemical and hematologic measurements involved the use of standard assays, as previously described.<sup>8</sup> Measurements were made in pairs of samples obtained from 379 participants a mean of about 12 years apart. Data on erythrocyte sedimentation rate from the Reykjavik Study have been reported previously.<sup>12</sup>

#### STATISTICAL ANALYSIS

Comparisons between patients and controls were made by means of unmatched stratified logistic regression fitted according to the unconditional maximum likelihood (Stata software, version 7). To maximize the ability to compare our results with those of previous reports, primary analyses of values of C-reactive protein, erythrocyte sedimentation rate, and von Willebrand factor were prespecified to compare extreme thirds of patients and controls with respect to the distribution of values in the controls. Subsidiary analyses involved other cutoff values. Odds ratios were sequentially adjusted for the following variables: age, sex, calendar year of enrollment, smoking status, systolic blood pressure, total cholesterol level, triglyceride level, body-mass index (the weight in kilograms divided by the square of the height in meters), forced expiratory volume in one second, presence or absence of diabetes, socioeconomic status, and the concentrations of other markers of inflammation.

To estimate the discriminative value of predictive models, we calculated the areas under the receiver-operating-characteristic curve, in order to determine whether the sequential addition of data on inflammatory markers increased the predictive value of major established coronary risk factors, as described previously.<sup>13</sup> We performed meta-analyses of studies published before January 2003 that included essentially general populations (i.e., cohorts not selected on the basis of preexisting disease) with more than a year of follow-up, using search, abstraction, and data-synthesis methods that have

been described previously and using nonfatal myocardial infarction or death from coronary heart disease as end points.<sup>6,7,14</sup> We combined the results of the studies by using inverse variance-weighted averages of logarithmic odds ratios. Heterogeneity was assessed by means of standard  $\chi^2$  tests. Odds ratios are given with 95 percent confidence intervals, and two-sided P values are reported. Since previous studies have reported on the predictive values of single base-line measurements of inflammatory markers with respect to coronary heart disease, odds ratios have not been corrected for regression dilution in the present study, so as to allow direct comparisons with previous work.<sup>5</sup>

## RESULTS

The mean age at the time of the coronary heart disease event was  $70.2 \pm 9.7$  years. There were significant differences between patients and controls with respect to established coronary risk factors, such as smoking status, body-mass index, blood pressure, and serum lipid concentrations (Table 1).

#### BASE-LINE ASSOCIATIONS AND LONG-TERM STABILITY OF INFLAMMATORY MARKERS

The partial correlation coefficients (adjusted for age, sex, calendar year of recruitment, and smoking status) for C-reactive protein, on the one hand, and the erythrocyte sedimentation rate and von Willebrand factor, on the other, were 0.38 and 0.18, respectively ( $P < 0.001$  for each comparison), and the partial correlation coefficient for the erythrocyte sedimentation rate and the von Willebrand factor concentration was 0.17 ( $P < 0.001$ ). A higher C-reactive protein concentration was significantly associated with cigarette smoking ( $P < 0.001$ ), an increased body-mass index ( $P < 0.001$ ), a low forced expiratory volume in one second ( $P < 0.001$ ), and an increased triglyceride concentration ( $P < 0.001$ ) (data not shown). Higher values for the erythrocyte sedimentation rate were significantly associated with older age ( $P < 0.001$ ), female sex ( $P < 0.001$ ), a low hemoglobin value ( $P < 0.001$ ), a low hematocrit ( $P < 0.001$ ), an elevated serum uric acid concentration ( $P < 0.001$ ), a low forced expiratory volume in one second ( $P < 0.001$ ), and smoking ( $P < 0.001$ ). A higher von Willebrand factor concentration was significantly associated with older age ( $P < 0.001$ ) and smoking ( $P < 0.001$ ).

Among 379 participants who provided paired blood samples, the within-person correlation coefficients for C-reactive protein, erythrocyte sedimen-

**Table 1. Base-Line Characteristics of the Patients with Coronary Heart Disease and Controls.\***

Characteristic	Patients (N=2459)	Controls (N=3969)	P Value
Age — yr	55.8±9.3	55.7±9.1	—
Male sex — no. (%)	1774 (72)	2743 (69)	—
Current smoker (including cigarettes, cigars, pipes) — no. (%)	1417 (58)	1941 (49)	<0.001
Current cigarette smoker — no. (%)	962 (39)	1266 (32)	<0.001
History of diabetes — no. (%)	83 (3)	63 (2)	<0.001
Nonmanual occupation — no. (%)†	703 (40)	1227 (42)	0.15
Education beyond high school — no. (%)‡	354 (27)	645 (30)	0.12
Home owner — no. (%)§	1962 (84)	3201 (85)	0.39
Lives in apartment block — no. (%)¶	1186 (53)	1833 (50)	0.09
Height — m	1.71±0.087	1.72±0.087	0.07
Weight — kg	76±14	75±14	<0.001
Body-mass index	26±3.9	25±3.7	<0.001
Systolic blood pressure — mm Hg	146±22	141±20	<0.001
Diastolic blood pressure — mm Hg	89±11	87±11	<0.001
Forced expiratory volume in 1 sec — liters	2.8±0.85	2.9±0.86	0.002
Protein or glucose in urine — no. (%)	112 (5)	102 (3)	<0.001
Blood value			
Total serum cholesterol — mmol/liter	6.82±1.18	6.40±1.14	<0.001
Serum triglycerides — mmol/liter**	1.19±0.79	1.03±0.62	<0.001
Fasting glucose — mmol/liter	4.6±1.1	4.5±0.8	<0.001
Serum creatinine — μmol/liter	77±14	75±13	<0.001
Serum uric acid — μmol/liter	312±73	300±66	<0.001
Hemoglobin — mmol/liter	9.2±0.80	9.1±0.81	<0.001
Hematocrit — %	44.8±3.6	44.2±3.5	<0.001
Inflammatory marker††			
C-reactive protein — mg/liter**	1.75±5.3	1.28±5.2	<0.001
Erythrocyte sedimentation rate — mm/hr**	7.4±10.6	6.3±9.7	<0.001
von Willebrand factor — IU/dl**	107.4±48.1	103.2±46.2	<0.001

\* Plus-minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters.

† Information on occupation was available for 1742 patients and 2888 controls.

‡ Information on education was available for 1292 patients and 2157 controls.

§ Information on home ownership was available for 2323 patients and 3754 controls.

¶ Information on the type of residence was available for 2258 patients and 3646 controls. Other categories included “duplex” and “villa.”

|| To convert values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert values for triglycerides to milligrams per deciliter, divide by 0.01129. To convert values for glucose to milligrams per deciliter, divide by 0.05551. To convert values for creatinine to milligrams per deciliter, divide by 88.4. To convert values for uric acid to milligrams per deciliter, divide by 59.48. To convert values for hemoglobin to grams per deciliter, divide by 0.6206.

\*\* Values were log-transformed for analysis and presented as geometric means ±SD.

†† Information on C-reactive protein, erythrocyte sedimentation rate, and von Willebrand factor was available for 2406, 2440, and 2445 patients, respectively, and 3891, 3942, and 3948 controls, respectively.

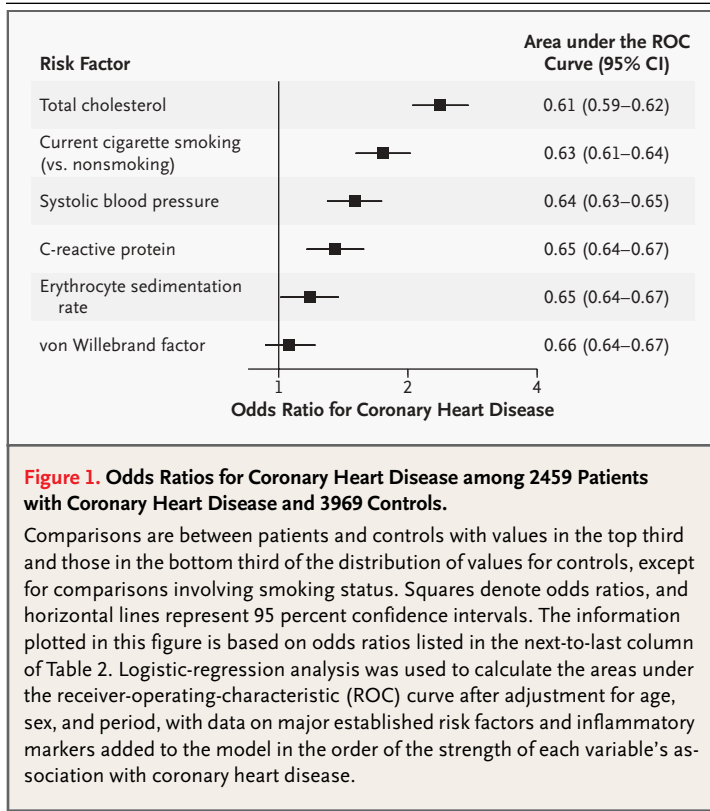
tation rate, and von Willebrand factor were 0.59 (95 percent confidence interval, 0.52 to 0.66), 0.67 (95 percent confidence interval, 0.61 to 0.73), and 0.57 (95 percent confidence interval, 0.50 to 0.64), respectively. These values were similar with respect to long-term consistency to the values for systolic

blood pressure (correlation coefficient, 0.66; 95 percent confidence interval, 0.60 to 0.72), diastolic blood pressure (correlation coefficient, 0.53; 95 percent confidence interval, 0.46 to 0.60), and total serum cholesterol (correlation coefficient, 0.60; 95 percent confidence interval, 0.54 to 0.66).

**Table 2. Relative Odds of Coronary Heart Disease (CHD) among Patients Who Had Levels of Inflammatory Markers in the Top Third of the Distribution of Values for Controls, as Compared with Those Who Had Values in the Bottom Third of This Distribution.**

Factor**	Patients			Controls			Odds Ratio (95% Confidence Interval)†				
	Top Third	Middle Third	Bottom Third	Top Third	Middle Third	Bottom Third	Adjusted for Age, Sex, and Period	Adjusted for Age, Sex, Period, and Smoking Status	Adjusted for Age, Sex, Period, and CHD Risk Factors	Adjusted for Age, Sex, Period, CHD Risk Factors, and Socioeconomic Status	Adjusted for Age, Sex, Period, CHD Risk Factors, Socioeconomic Status, and Levels of Other Inflammatory Markers
<b>Inflammatory markers</b>											
Up to 2459 patients and 3969 controls											
C-reactive protein level (2.0 and 0.78 mg/liter)	1090	742	574	1294	1300	1297	1.92 (1.68–2.18)	1.76 (1.54–2.01)	1.45 (1.25–1.69)‡	1.45 (1.25–1.68)	1.36 (1.16–1.58)
Erythrocyte sedimentation rate (10 and 4 mm during 1st hr)	922	733	785	1220	1201	1521	1.64 (1.44–1.87)	1.55 (1.36–1.78)	1.31 (1.13–1.51)	1.30 (1.13–1.51)	1.18 (1.01–1.38)
von Willebrand factor level (124 and 88 IU/dl)	913	789	743	1310	1316	1322	1.23 (1.09–1.40)	1.19 (1.05–1.35)	1.12 (0.98–1.28)	1.11 (0.97–1.27)	1.06 (0.92–1.22)
Up to 2083 patients without evidence of CHD at base line and 3969 controls§											
C-reactive protein level (2.0 and 0.78 mg/liter)	887	635	520	1294	1300	1297	1.81 (1.58–2.07)	1.65 (1.43–1.89)	1.37 (1.17–1.60)	1.37 (1.17–1.59)	1.30 (1.10–1.52)
Erythrocyte sedimentation rate (10 and 4 mm during 1st hr)	766	633	671	1220	1201	1521	1.53 (1.34–1.77)	1.45 (1.26–1.68)	1.22 (1.05–1.43)	1.22 (1.04–1.42)	1.10 (0.95–1.28)
von Willebrand factor level (124 and 88 IU/dl)	752	675	643	1310	1316	1322	1.25 (1.09–1.43)	1.20 (1.05–1.37)	1.15 (0.99–1.33)	1.14 (0.98–1.31)	1.11 (0.94–1.31)
<b>Some established CHD risk factors</b>											
Up to 2459 patients and 3969 controls											
Total cholesterol level (6.80 and 5.85 mmol/liter)	1150	826	482	1309	1320	1334	2.62 (2.29–3.00)	2.68 (2.30–3.08)	2.33 (2.01–2.70)	2.35 (2.03–2.74)	2.38 (2.05–2.77)
Current smoking (vs. never)¶	1417	544	498	1941	851	1177	1.74 (1.53–1.98)	1.74 (1.53–1.98)	1.87 (1.63–2.22)	1.87 (1.62–2.16)	1.75 (1.51–2.03)
Systolic blood pressure (147 and 131 mm Hg)	1041	742	670	1308	1240	1402	1.72 (1.51–1.96)	1.85 (1.62–2.10)	1.51 (1.32–1.74)	1.50 (1.30–1.73)	1.50 (1.30–1.74)

\* Values in parentheses refer to cutoffs of values for the top and bottom thirds, respectively, of the distribution of values in controls. To convert values for cholesterol to milligrams per deciliter, divide by 88.4.  
 † "Period" refers to the calendar year of recruitment. Markers of socioeconomic status were nonmanual occupation, education beyond high school, home ownership, and type of residence.  
 ‡ The adjusted odds ratios for coronary heart disease for C-reactive protein with the use of alternative comparisons were as follows: 1.55 (95 percent confidence interval, 1.31 to 1.84) for the top quarter as compared with the bottom quarter of distribution, 1.65 (95 percent confidence interval, 1.36 to 2.00) for the top fifth as compared with the bottom fifth of distribution, and 1.20 (95 percent confidence interval, 1.12 to 1.27) per standard deviation (log scale).  
 § These analyses exclude patients with electrocardiographic evidence of coronary heart disease or a history of angina. As described in the Methods section, persons with a history of myocardial infarction were excluded from the base-line survey of the Reykjavik Study.  
 ¶ Smoking status does not reflect thirds of a continuous distribution: frequencies among patients and controls are tabulated for current smokers (top), former smokers (middle), and non-smokers (bottom), and odds ratios compare current smokers with those who never smoked.



#### INFLAMMATORY MARKERS AND INCIDENT CORONARY HEART DISEASE

The odds ratio for coronary heart disease was 1.92 (95 percent confidence interval, 1.68 to 2.18;  $\chi^2=105$ , with 1 df) among patients with values in the top third (cutoff value, 2.0 mg per liter), as compared with the bottom third (cutoff value, 0.78 mg per liter), of base-line C-reactive protein concentrations in the control group. The odds ratio fell to 1.45 (95 percent confidence interval, 1.25 to 1.68;  $\chi^2=28$ , with 1 df) after adjustment for smoking status, other established coronary risk factors, and indicators of socioeconomic status (Table 2). Comparisons between the top and bottom thirds of patients and controls with respect to the other markers gave the following adjusted odds ratios for coronary heart disease: for erythrocyte sedimentation rate (cutoff value of 10 mm in first hour of measurement for the top third and 4 mm in first hour for the bottom third), 1.30 (95 percent confidence interval, 1.13 to 1.51;  $\chi^2=13$ , with 1 df), and for von Willebrand factor (cutoff value of 124 IU per deciliter for the top third and 88 IU per deciliter for the bottom third), 1.11 (95 percent confidence interval, 0.97 to 1.27;  $\chi^2=26$ , with 1 df) (Table 2 and Fig. 1). The

calculated areas under receiver-operating-characteristic curves indicate that information on the C-reactive protein concentration (and the other inflammatory markers that were assessed) provided comparatively little additional predictive value over that provided by assessment of major established risk factors (Fig. 1).

These findings were not materially changed in analyses restricted to the 2083 patients without evidence of coronary heart disease at base line (Table 2), to the 2206 patients with C-reactive protein values who had a confirmed myocardial infarction or died of coronary heart disease, or to the participants without evidence of acute-phase reactions at the baseline examination (i.e., this analysis excluded 132 patients and 152 controls with a C-reactive protein concentration of more than 10 mg per liter<sup>15</sup> or an erythrocyte sedimentation rate of more than 30 mm during the first hour). The findings were also unaffected by changes in the cutoff values (e.g., analyses of quarters or fifths, or according to increases of 1 SD) (Table 2).

Associations between the C-reactive protein concentration and the risk of coronary heart disease did not vary significantly according to established risk factors, such as smoking or increased blood lipid concentrations, blood pressure, or body-mass index (data not shown). An exploratory analysis suggested the possibility of more extreme odds ratios among the 1049 patients who died of coronary heart disease or had a nonfatal myocardial infarction within 10 years after enrollment (odds ratio, 1.84; 95 percent confidence interval, 1.49 to 2.28), as compared with the 1357 patients who had such an event after the first decade (odds ratio, 1.26; 95 percent confidence interval, 1.05 to 1.51). Such a trend, however, was not observed in the updated meta-analysis, described below, which was based on published data from 22 studies<sup>2,4,13,14,16-33</sup> (Fig. 2). Therefore, it requires further examination involving larger numbers of participants with individual data. Such analysis is also required for a reliable characterization of the shape of the association between C-reactive protein and coronary heart disease.

#### UPDATED META-ANALYSIS

Twenty-two prospective studies of C-reactive protein (including the present study) have involved a total of 7068 patients, with a weighted mean age at entry of 57 years and a weighted mean follow-up of 12 years<sup>2,4,13,14,16-33</sup> (Table 3). All studies used high-sensitivity assays, and all but two<sup>19,32</sup> report-



**Table 3. Comparison of Characteristics of Prospective Studies of C-Reactive Protein and Coronary Heart Disease (CHD) in Essentially General Populations.\***

Study	Location	Population/Sampling Method†	Time of Base-Line Survey	No. of Cases of CHD	Total No. of Participants	Age Range	Male %	Sex	Mean Duration of Follow-up	C-Reactive Protein Assay		Plasma or Serum Storage Temperature °C	
										Source	Type‡		Standard
Reykjavik	Iceland	Population register/complete birth cohorts	1967–1991	2406	18,569	33–59	48		20	Roche	LEIA	WHO 85/506	-20
ARIC <sup>4</sup>	U.S.	Listing of households/random	1987–1989	615	15,792	45–64	43		8	United Biotech	ELISA	WHO 85/506	-70
WOSCOPS <sup>20</sup>	Scotland	Coronary screening clinic/complete	1989–1995	580	6,595	45–64	100		6	In-house	ELISA	IFCC CRM470	-70
BRHS <sup>1,4</sup>	U.K.	General practitioners' list/random	1978–1980	506	5,661	40–59	100		16	In-house or Abbott	MEIA	WHO 85/506	-20
Women's Health Study <sup>13</sup>	U.S.	Female health professionals/complete	1992–1995	371	28,345	>45	0		8	In-house	NS	NS	-70
WHIOS <sup>27</sup>	U.S.	Trial screeners/complete	1994–1998	280	93,724	50–79	0		3	In-house	NS	NS	-70
Caerphilly <sup>28</sup>	Wales	Electoral rolls/random	1979–1983	249	2,512	45–59	100		14	In-house	ELISA	NS	-20
MRFIT <sup>2</sup>	U.S.	Industry and government employees/complete	1973–1976	246	12,866	35–57	100		10	In-house	ELISA	WHO 85/506	-50 to -70
Physicians' Health <sup>22</sup>	U.S.	Physicians' register/complete	1982	246	22,071	40–84	100		14	In-house	ELISA	WHO 85/506	-80
Helsinki Heart <sup>32</sup>	Finland	Industry employees/complete	1981–1982	241	4,081	40–55	100		10	Eucardio Laboratory	ELISA	NS	-20
AFCAPS/TEXCAPS <sup>26</sup>	U.S.	Civilian and military clinics/complete	1990–1993	216	6,605	45–73	NS		5	Dade Behring	LEIA	WHO 85/506	NS
Speedwell <sup>23,30</sup>	U.K.	General practitioners' list/complete	1979–1982	165	1,690	47–67	100		6	Dade Behring	LEIA	WHO 85/506	-20
CHS <sup>33</sup>	U.S.	Medicine eligibility lists/complete	1989–1990	150	5,201	≥65	43		3	In-house	ELISA	NS	-70
Helsinki Aging <sup>19</sup>	Finland	Population register/random from birth cohorts	1989	147	651	75–85	28		10	Medix Diacor	EIA (unspecified)	WHO 85/506	-20
RHPP <sup>33</sup>	U.S.	Medicare beneficiaries/complete	1995	145	3,884	65–79	43		3	In-house	ELISA	WHO 85/506	-70
Glostrup <sup>24</sup>	Denmark	Population register/random from birth cohorts	1976–1984	133	5,637	30–50	100		12	In-house	ELISA	Commercial (Behring)	-20
Quebec <sup>29</sup>	Canada	Population register/random	1985	105	2,100	45–77	100		5	Dade Behring	LEIA	WHO 85/506	-80
Kaiser Permanente <sup>31</sup>	U.S.	Insurance-plan enrollees/random	1967–1979	100	261	NS	NS		5	In-house	ELISA	NS	NS
Iowa 65+ <sup>17</sup>	U.S.	Population register/complete for those >65 yr of age	1982	74	3,673	>65	41		4	In-house	ELISA	WHO 85/506	-70

MONICA Augsburg <sup>25</sup>	Germany	Population register/random	1984-1992	53	5,069	25-74	100	7	In-house	IRMA	WHO 85/506	-70
Hoorn <sup>18</sup>	Netherlands	Population register/random	1989-1992	24	2,484	50-75	48	5	In-house	ELISA	Commercial (Behring)	-70
Göteborg Intervention <sup>21</sup>	Sweden	Hypertension screening clinic/random	1993	16	508	50-72	100	3	Dade Behring	LEIA	WHO 85/506	-80

\* EIA denotes enzyme immunoassay, ELISA enzyme-linked immunosorbent assay, IRMA immunoradiometric assay, LEIA latex-enhanced immunoassay, MEIA microparticle capture enzyme immunoassay, NS not specified, ARIC Atherosclerosis Risk in Communities, WOSCOPS West of Scotland Coronary Prevention Study, BRHS British Regional Heart Study, U.K. United Kingdom, WHIOS Women's Health Initiative Observational Study, MRFIT Multiple Risk Factor Intervention Trial, AFCAPS/TEXCAPS Air Force/Texas Coronary Atherosclerosis Prevention Study, CHS Cardiovascular Health Study, RHPP Rural Health Promotion Project, MONICA Monitoring Trends and Determinants in Cardiovascular Disease.

† A random sampling method was one in which a randomly selected subgroup of eligible persons was invited to participate. A complete sampling method was one in which all eligible persons in the study population were invited to participate.

‡ Eligibility was based on more restrictive criteria in the following studies: WOSCOPS (persons with a low-density lipoprotein level of 174 to 232 mg per deciliter [4.5 to 6.0 μmol per liter]), WHIOS (women ineligible for a randomized trial of hormone-replacement therapy and dietary modification), MRFIT (persons with a high risk of coronary heart disease on the basis of blood pressure, cholesterol concentration, and smoking status), Helsinki Heart Study (persons with high levels of non-high-density lipoprotein cholesterol), AFCAPS/TEXCAPS (persons with below-average levels of high-density lipoprotein cholesterol), and the Göteborg Intervention Study (persons with hypertension).

ed adjustment for at least smoking status and some other established risk factors for coronary heart disease. There was evidence of heterogeneity between these studies ( $\chi^2=46$ , with 21 df;  $P=0.001$ ), but with the exception of the date of publication ( $\chi^2=15$ , with 2 df;  $P<0.001$ ), characteristics such as sample size ( $\chi^2=4.0$ , with 1 df;  $P=0.04$ ), location ( $\chi^2=0.3$ , with 1 df;  $P=0.58$ ), sampling method ( $\chi^2=5.2$ , with 1 df;  $P=0.02$ ), sex of participants ( $\chi^2=3.4$ , with 2 df;  $P=0.18$ ), mean duration of follow-up ( $\chi^2=1.6$ , with 1 df;  $P=0.20$ ), and sample storage temperature ( $\chi^2=0.1$ , with 1 df;  $P=0.77$ ) did not account for much of the overall heterogeneity (Fig. 2).

The tendency toward more extreme findings in studies published before 2000 is consistent with the preferential publication of positive results in earlier studies. Restriction of analyses to the four studies involving more than 500 patients,<sup>4,14,20</sup> comprising 4107 cases of coronary heart disease, should limit any such bias, and yielded a combined odds ratio of 1.49 (95 percent confidence interval, 1.37 to 1.62;  $\chi^2=10.6$ , with 3 df;  $P=0.01$ ). This value is somewhat smaller than the overall odds ratio of 1.58 (95 percent confidence interval, 1.48 to 1.68) derived from combining all 22 studies.

A previous meta-analysis<sup>6</sup> of prospective studies of the effect of the erythrocyte sedimentation rate (based on 1703 cases of coronary heart disease) reported an odds ratio for coronary heart disease of about 1.3 (95 percent confidence interval, 1.2 to 1.5), and this estimate is reinforced by the odds ratio of 1.33 (95 percent confidence interval, 1.22 to 1.44) that we calculated in our updated meta-analysis (which involved an additional 2683 cases from a further two studies<sup>34</sup>). The present updated meta-analysis of prospective studies of von Willebrand factor (which adds 2445 cases of coronary heart disease to the previous total of 1524 cases) yielded an odds ratio of 1.23 (95 percent confidence interval, 1.14 to 1.33), which is probably weaker than the previous estimate of about 1.5 (95 percent confidence interval, 1.1 to 2.0).<sup>7</sup>

## DISCUSSION

We found that the decade-to-decade consistency of values for C-reactive protein, the erythrocyte sedimentation rate, and von Willebrand factor is similar to that of values for blood pressure and total serum cholesterol concentration, suggesting that these inflammatory markers are sufficiently stable for

potential use in the long-term prediction of coronary heart disease. Our findings — reinforced by an updated meta-analysis — indicate, however, that the odds ratio for coronary heart disease in people with elevated C-reactive protein values is lower than that reported recently. Whereas a previous meta-analysis<sup>14</sup> of studies published before 2000 (based on 1953 cases of coronary heart disease) reported an odds ratio for coronary heart disease of about 2.0 (95 percent confidence interval, 1.6 to 2.5), our updated meta-analysis, which adds 5115 cases of coronary heart disease from a further 12 studies, yielded an odds ratio of about 1.5 in a comparison of people with base-line values in the top third with those with base-line values in the bottom third for the population. Moreover, in comparison with major established risk factors (such as an increased total serum cholesterol concentration and cigarette smoking), the C-reactive protein concentration was a relatively moderate predictor of the risk of coronary heart disease and added only marginally to the predictive value of established risk factors for coronary heart disease. These findings suggest that recent recommendations regarding the use of measurements of C-reactive protein in the prediction of coronary heart disease may need to be reviewed.<sup>3</sup>

The potential limitations of our study merit careful consideration. The validity of our measurements is demonstrated by the reasonably high decade-to-decade consistency of C-reactive protein values recorded in paired samples from 379 participants (a level of stability that was at least as high as those recorded in previous studies with sampling intervals of just one to five years<sup>35-38</sup>). Further validation is suggested by the finding of the expected base-line associations of C-reactive protein with other inflammatory markers and with established coronary risk factors.

The mean values and the distributions of several established coronary risk factors (and the strength of their associations with the risk of coronary heart disease) in our study were generally similar to those reported in other western European populations.<sup>8</sup> Therefore, although the relative homogeneity of the Reykjavik population should have minimized certain residual biases (such as that due to differences in socioeconomic status), the present findings should have wider relevance. Only total serum cholesterol concentrations were measured in the pres-

ent study (rather than those of its subfractions, which have opposing effects on the risk of coronary heart disease), thereby underestimating the predictive ability of lipid concentrations (and potentially overestimating the adjusted predictive value of the C-reactive protein concentration).

No information was recorded on the use of aspirin and statins, which, like hormone-replacement treatment, may alter C-reactive protein values. However, fewer than 5 percent of the women in this study reported the use of such hormonal treatment during recruitment, and the use of aspirin and of statins was similarly uncommon in the general middle-aged population of Reykjavik between 1967 and 1991. We did not address the separate issues of the predictive value of inflammatory markers with respect to the risk of cardiac complications among patients recently hospitalized for acute coronary syndromes<sup>39</sup> or the long-term risk of coronary heart disease in patients with a history of cardiovascular disease.<sup>14</sup>

As suggested by the statement of the Centers for Disease Control and Prevention and the American Heart Association,<sup>3</sup> further clarification of the predictive value of C-reactive protein in coronary heart disease in general populations will require the pooling of studies on the basis of data for individual participants from each of the available prospective studies. Such a strategy will permit more complete adjustment for other risk factors and for within-person fluctuations of C-reactive protein levels, more precise quantification of the associations in particular subgroups (such as age-, sex-, and duration-specific associations as well as assessments of combinations of inflammatory markers), more reliable characterization of the shape of any dose-response relation, and more detailed investigation of potential sources of heterogeneity.

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